Protocol Title: Phase 1 Dose Escalation Study of the Agonist Redirected Checkpoint, SL-172154 (SIRPα-Fc-CD40L) Administered Intravenously in Subjects with Ovarian Cancer

Short Title: Phase 1 Study of SL-172154 (SIRPα-Fc-CD40L) in Subjects with Ovarian Cancer

Protocol Identifying Number: SL03-OHD-101

Version Number: v6.0

Compound Number: SL-172154

Study Phase: Phase 1

Investigational New Drug (IND) Sponsor: Shattuck Labs

Legal Registered Address:

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Regulatory Agency Identifier Number(s)

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Shattuck Labs Document Number	Date	Version
SL03-OHD-01_00	24 January 2020	Original
SL03-OHD-01_01	03 March 2020	Amendment No. 1

Rationale for Amendment Changes

The protocol is amended to address corrections to instructions and information provided on the drug product in Section 5.

Summary of Changes (new text denoted in italics font)

1. Investigational Product Description Section 5.1.1 was updated as follows:
   Unit Dose strength(s)/Dose Level(s): SL-172154 10 mg/mL; ~~1 mL in a 5 mL sized glass vial~~ (Refer to Section 3.3 for dose levels)
   Physical Description: SL-172154 *10 mg/mL* ~~for infusion is 10 mg of SL172154 per single dose vial at a concentration of 10 mg/mL~~ in a 5mL glass vial closed with a in a 5 mL glass vial closed with a FluroTec® rubber stopper and sealed with a flip-off aluminium seal. *See the Study Pharmacy Manual (SPM) for additional detail.*
   Route/Administration/Duration: Delivered as IV solution via a syringe pump or IV infusion pump. See the Study Pharmacy Manual (SPM) for additional details. Duration of infusion depends on the dose. See Table 1: SL-172154 Dose Escalation Plan in Section 3.3 of the protocol.
2. In Section 5.1.2.1:
   a) Removed text: ~~DO NOT USE a filter for drug preparation.~~ Instructions for preparation of doses will be included in the Study Pharmacy Manual.
   b) The dosing solution of SL-172154 can be held up to 24 hours under refrigerated conditions or 8 hours at room temperature (diluted drug product in bag or syringe) from a stability perspective; but should be used as soon as possible as the product does not contain an antimicrobial preservative. *Preparation (e.g., dilution) and administration of study drug may occur at room temperature without protection from light.* See the SPM for details.

Shattuck Labs Document Number	Date	Version
SL03-OHD-01_01	03 March 2020	Amendment No. 1
SL03-OHD-01_02	24 April 2020	Amendment No. 2

Rationale for Amendment Changes

The protocol is amended to address comments by the United States FDA during review of the IND for SL-172154.

Summary of Changes (Details outlined in Appendix 16.6)

1. Homologous recombinant deficiency (HRD) status will be collected for all subjects including BRCA status
2. Inclusion criteria revised to allow enrollment of subjects who fulfill the definitions below:
   a) all subjects with primary ovarian, peritoneal and fallopian cancers are required to have received platinum-based therapies.b) HRD positive subjects if they have failed prior PARP inhibitor therapy given with or without bevacizumab and,
   c) refractory or intolerant to existing therapy(ies) known to provide clinical benefit for their condition.
3. Treatment beyond progression per iRECIST requires that subjects have no decline in their ECOG performance status.
4. The DLT assessment period for assessment of AEs that inform dose escalation decisions is 28 days (not 21 days as originally proposed).
5. Provided further clarification of the intent to monitor subjects for adverse events for 90 days after SL-172154 treatment is permanently discontinued.
6. Revised the DLT criteria to include any deaths that are not clearly due to the underlying disease or extraneous causes.
7. Clarified that subjects eligible for dose escalation must have tolerated SL-172154 therapy well and experienced AEs < or = Grade 1 in severity on the most recent cycle of study treatment.
8. Clarified that all AEs that occur in subjects enrolled in this study will be collected starting from the time subject consents to participate until they are discontinued from the study.
9. Minor Editorial changes

Shattuck Labs Document Number	Date	Version
SL03-OHD-01_02	24 April 2020	Amendment No. 2
SL03-OHD-01_03	05 May 2020	Amendment No. 3

Rationale for Amendment Changes

Additional test results now indicate that SL-172154 binds to red cells and may obscure the assessment of ABO red blood cell phenotyping. The protocol is amended to address the possibility that treatment with SL-172154 may interfere with compatibility tests including the antibody screen and crossmatch that are a part of a routine pre-transfusion work up should subjects on this study require a blood transfusion for supportive care.

This amendment also addresses a comment provided by the FDA during review of the IND application for SL-172154 on allowable storage condition limits for diluted drug product at room temperature and under refrigerated conditions.

In addition, assessment of C reactive protein will now be collected at baseline during the screening and post treatment follow up visits. Minor editorial changes were also made to the text.

The Summary of Changes are outlined in Appendix 16.7

Shattuck Labs Document Number	Date	Version
SL03-OHD-01_03	05 May 2020	Amendment No. 3
SL03-OHD-01_04	28 September 2020	Amendment No. 4

Rationale for Changes in Amendment 04

The protocol is amended to include exploration of a once weekly dosing schedule of SL-172154 in dose escalation to determine a recommended phase 2 dose for further study. Minor editorial changes and clarifications (e.g., NCT number added to the title page) are also included.

The Summary of Changes are outlined in Appendix 16.8

Administrative Changes (7 October 2020)

1. Corrected typographical errors replacing SL-279252 with SL-172154 as noted
   a. **Evaluation of an Alternative Dosing Schedule Section 3.3** (5th sentence) including Summary of Changes in Appendix 16.8 denoting new text in Section 3.3: During dosing on Schedule 2, ~~SL-279252~~ SL-172154 will be administered once weekly (D1, D8, D15, and D22) every 28 days.
   b. **Schedule of Assessments Table Section 6.2:** ~~SL-279252~~ SL-172154 administration[o]

Shattuck Labs Document Number	Date	Version
SL03-OHD-01_04	28 September 2020	Amendment No. 4
SL03-OHD-01_05	12 July 2021	Amendment No. 5

Rationale for Changes in Amendment 05

The protocol is amended to include infusion pre-medication instructions (Section 5), and additions of a C1D8 pre-dose PK/ADA sample and C1D3 immunophenotyping, receptor occupancy and cytokine sample. Minor editorial and clarifying changes were made as well.

The Summary of Changes are outlined in Appendix 16.9

Shattuck Labs Document Number	Date	Version
SL03-OHD-01_05	12 July 2021	Amendment No. 5
SL03-OHD-01_06	24 August 2021	Amendment No. 6

Rationale for Changes in Amendment 06

The protocol is amended to revise the eligibility criteria required for study participation. The investigational product information in Section 5.1 has been updated to reflect the current program level description of SL-172154 (additional details are provided in the Study Pharmacy Manual). In addition, a minor editorial change was made to the Schedule of Assessments Table for Schedule 1 (Section 6.1) to include weight on C1D1 to reflect this assessment described in Section 5.1.4.

The Summary of Changes are outlined in Appendix 16.10

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LIST OF ABBREVIATIONS

Ab	Antibody
ADA	Anti-drug antibodies
ADCC	Antibody dependent cell-mediated cytotoxicity
ADCP	Antibody dependent cellular phagocytosis
ADL	Activities of daily living
AE	Adverse event
AIMV	Alstroemeria-Mosaic Virus
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
APTT	Activated partial thromboplastin time
APC	Antigen presenting cell
AR	Adverse reaction
ARC	Agonist redirected checkpoint
AST	Aspartate aminotransferase
AUC	Area under the serum concentration time curve
$AUC_{0\text{-last}}$	Area under the serum concentration time curve, time 0 to the last quantifiable concentration
$AUC_{0\text{-inf}}$	Area under the serum concentration time curve from time 0 extrapolated to infinity
$AUC_{0\text{-t}}$	Area under the serum concentration time curve, time 0 to time = t
$\%AUC_{ext}$	Percentage of AUC0-inf due to extrapolation from Tlast to infinity
AUCtau	The area under the serum concentration time curve, over the dosing interval
β-hCG	Beta- human chorionic gonadotropin
BP	Blood pressure
BRCA	Breast cancer gene
°C	Degrees Celsius
CBC	Complete blood count
CBR	Clinical benefit rate
CD	Cluster of differentiation
CD40L	Cluster of differentiation 40 ligand
C1D1	Cycle 1, day 1
CFR	Code of Federal Regulations
cGAS	Cyclic guanine monophosphate-adenosine monophosphate synthase
CL	Clearance
Cm	Centimeters
Cmax	Maximum observed concentration
Cmin	Minimum observed concentration
CMP	Clinical monitoring plan
CO_2	Bicarbonate
CR	Complete response
CrCl	Creatinine clearance
CRF	Case report form
CRS	Cytokine release syndrome
CT	Computed tomography
CTCAE	Common terminology criteria for adverse event
CTLA-4	Cytotoxic T cell lymphocyte-associated antigen 4
CXCL	Chemokine ligand
CYP450	Cytochrome P450
DAT	Direct antiglobulin test
DC	Dendritic cells
DLT(s)	Dose-limiting toxicity(ies)
DOR	Duration of response
DRF	Dose-range-finding

EC	Effective concentration
ECD	Extracellular domain
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOI	End of infusion
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FIH	First in human
FP	Fusion protein
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GITR	Glucocorticoid-induced tumor necrosis factor receptor
GLP	Good Laboratory Practice
H1/H2	Histamine 1/ Histamine 2
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HED	Human equivalent dose
Hgb	Hemoglobin
HNSTD	Highest non-severely toxic dose
hr (time)	Hour(s)
HR	Heart rate
HRD	Homologous recombination deficiency
HSR(s)	Hypersensitivity reaction(s)
Hu5F9-G4	5F9 (i.e., anti-CD47 monoclonal antibody)
IB	Investigator brochure
ICF	Informed consent
ICH	International Conference of Harmonisation
iCPD	Immune confirmed progression of disease
iCR	Immune complete response
IEC	Institutional Ethics Committee
IFNγ	Interferon gamma
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukin
IND	Investigational new drug
INR	International normalized ratio
IP	Investigational product
iPR	Immune partial response
irAE	Immune-related adverse event
IRB	Institutional Review Board
iRECIST	Immune response evaluation criteria in solid tumors
IRR(s)	Infusion-related reaction(s)
irSAE	Immune-related serious adverse event
iSD	Immune stable disease
iUPD	Immune unconfirmed progression of disease
IV (i.v.)	Intravenous
Kd	Receptor off-rate constant
Kg	Kilogram
LDH	Lactate dehydrogenase

LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
m^2	Square meter
mAb(s)	Monoclonal antibody(ies)
MABEL	Minimum anticipated biological effect level
MAD	Maximum administered dose
MDS	Myelodysplastic syndrome
mg	Milligrams
mg/dL	Milligrams per deciliter
mg/kg	Milligrams per kilogram
Min	Minutes
mL	milliliter
mm	millimeter
MMF	Mycophenolate mofetil
Mmol	Millimole
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mTPI-2	Modified toxicity probability interval 2
NCI	National Cancer Institute
NHP	Non-human primate
NF-kB	Nuclear factor kappa B
Ng	Nanogram
NK	Natural killer
NL(s)	New lesion(s)
NLNT	New lesions non-target
NLT	New lesions target
nM	Nanomolar
NOAEL	No observed adverse effect level
ORR	Objective response rate
PARP	Polyadenosine diphosphate polymerase
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Progressive Disease
PD-1	Programmed cell death protein 1
PD-L1 / PD-L2	Programmed cell death ligand 1 / Programmed cell death ligand 2
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/pharmacodynamic
pM	Picomolar
PR	Partial response
PSPD	Pseudo-progression of disease
PT	Prothrombin time
QTc	Corrected QT interval
RBC	Red blood cell
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic acid
RP2D	Recommended phase 2 dose
RR	Respiratory rate
SAE	Serious Adverse Event
SAP	Statistical analysis plan
scFv	Single-chain variable fragment
SD	Stable disease
SL-172154	SIRPα-Fc-CD40L agonist redirected checkpoint
SLM	Study Lab Manual

SMC	Safety Monitoring Committee
SOA	Schedule of Assessments
SOI	Start of infusion
SOM	Sum of measurements
SPM	Study Pharmacy Manual
STING	Stimulator of interferon genes
SUSAR	Suspected, unexpected serious adverse reaction
T	Temperature
T4	Thyroxine 4
t½	terminal elimination half-life
SIRPα	Signal regulatory protein alpha
TK	Toxicokinetic
T_{last}	Time of last observed quantifiable concentration
TLS	Tumor lysis syndrome
T_{max}	Time of maximum observed concentration
TMDD	Target-mediated drug disposition
TME	Tumor microenvironment
TNF-α	Tumor necrosis factor alpha
TRAF	TNF receptor associated factor
TSH	Thyroid stimulating hormone
TXT	Treatment
µg	Microgram
ULN	Upper limit of normal
UP	Unanticipated problems
Vz	Volume of distribution
WBC	White blood cell
Wk	Week
λz	Terminal elimination rate constant
~	Approximately
º	Degree

Trademark Information

Trademarks of Shattuck Labs, Inc.	**Trademarks not owned by Shattuck Labs, Inc.**
Agonist Redirected Checkpoint (ARC™)	FluroTec®

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the protocol and the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, and applicable Federal Regulations on the Protection of Human Subjects, and consistent with the consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Institutional Review Board (IRB)/Institutional Ethics Committee (IEC), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator:

_____ _____

Print/Type Name Signature

Date: _____

KEY TRIAL CONTACTS

Medical Monitor Name and Contact Information is provided in the Study Contact List.

Sponsor Signatory:

[redacted]

Chief Medical Officer, Shattuck Labs

[redacted]

Date

STUDY SCHEMA

Study Design: Phase 1 Study of SL-172154 (SIRPα-Fc-CD40L)

Primary objectives: Safety and tolerability of SL-172154

Secondary objectives: RP2D, PK, immunogenicity and anti-tumor activity / **Exploratory objectives**: PD markers in blood and tumor

Tumor type: platinum-ineligible ovarian, fallopian tube and primary peritoneal cancers

Dose Escalation and Dose Expansion Study (N~33-54 Subjects)

Dose Escalation Rules: mTPI-2

DLT Assessment Period: 28 days

Subjects per Cohort: ≥ 3

Dose Level	SL-172154 IV Dose (mg/kg)*
Start: 1	0.1
2	0.3
3	1.0
4	3.0
5	10.0

Dose Expansion

Further assessment of SL-172154 on a schedule at select dose(s)

PD Cohort

RP2D Decision

Based on totality of data

Safety, PK, PD and anti-tumor activity

***Evaluation of SL-172154 Dosing on Two Potential Schedules:**

Schedule 1: once weekly (D1, D8, D15) q28 days in cycle 1,then q2wks thereafter (D1, D15) q28 days in cycle 2 and beyond

Schedule 2: once weekly (D1, D8, D15, D22) q28 days in each cycle

Abbreviations: D = day; DLT = dose limiting toxicity; IV = intravenous; mTPI-2 = modified toxicity probability interval-2; PD = pharmacodynamic; PK = pharmacokinetics; q2wks = once every 2 weeks; RP2D = recommended phase 2 dose

PROTOCOL SYNOPSIS

Sponsor	Shattuck Labs
Product Name	SL-172154
Other Names	SIRPα-Fc-CD40L recombinant fusion glycoprotein
Protocol Title	Phase 1 Dose Escalation Study of the Agonist Redirected Checkpoint, SL-172154 (SIRPα-Fc-CD40L) Administered Intravenously in Subjects with Ovarian Cancer
Protocol Number	SL03-DEL-101
Clinical Phase	Phase 1
Planned Sample Size	Approximately 33-54 subjects
Planned Number of Sites & Countries	Approximately 6-10 clinical sites; United States
Recruitment Duration	25 months (~2 years)
Study Duration	39 months (~ 3 years)

Background and Rationale

The investigational product, SL-172154, is a novel fusion protein consisting of human SIRPα and CD40L (SIRPα -Fc-CD40L) linked via a human Fc. Fusion of the extracellular domains of SIRPα, a type 1 membrane protein, with CD40L, a type 2 membrane protein, generated a single molecule with dual specificity that retained individual target avidity. The mechanism of action of SL-172154 is designed to pair the increased phagocytic activity of macrophages through CD47-SIRPα binding with the costimulatory role of CD40L in augmenting the antigen cross-presenting ability of dendritic cells. In vitro, SL-172154 was shown to bind to its cognate targets, CD47 and CD40, both individually and simultaneously. High binding affinity for CD47 and CD40 was noted as well as a slow off-rate (K_D values of 0.628 nM and 4.74 nM, respectively), indicating a longer on-target resident time. This longer resident time could be of benefit in the tumor microenvironment (TME) where CD47 is known to be expressed. CD40-mediated activity by SL-172154 was demonstrated in a NFkB reporter system in which CD40-dependent signaling was stimulated in the absence of Fc receptor cross-linking, and in cultured human peripheral blood mononuclear cells (PBMCs) in which dose-dependent proliferation, an increase in the number of interleukin (IL)-2 secreting PBMCs, and the secretion of multiple cytokines were observed.

The anti-tumor activity of mSIRPα-Fc-CD40L was studied in established syngeneic CT26 colorectal murine tumor models. The performance of intraperitoneal administration of mSIRPα-Fc-CD40L was compared to treatment with CD47 blocking antibodies, CD40 agonist antibodies, the combination of the two antibodies and vehicle control. These experiments demonstrated that administration of mSIRPα-Fc-CD40L led to higher rates of primary tumor rejection (63%) than either antibody given as monotherapy (anti-CD40, 0% and anti-CD47, 0%), or the antibody combination treatment group (33%). To assess the durability of an immune response without re-treatment, mice that rejected the initial tumor were re-challenged with a second CT26 tumor on the opposite flank on day 40. Of the 2 mice initially cured with the antibody combination, 0 mice rejected the tumor challenge. In the mSIRPα-Fc-CD40L group, 3 of 5 (60%) mice rejected the tumor re-challenge suggesting that a memory response was generated against the tumor, which led to protection against a subsequent tumor challenge. This memory response correlated with a robust increase in AH1 tetramer +/CD8+ cells in the spleen and the tumor for both the anti-CD40/CD47 combination and the mSIRPα-Fc-CD40L treated mice in comparison to vehicle controls. The preclinical data package demonstrates that SL-172154 selectively and specifically binds to its intended targets, CD47 and CD40, with high affinity. Furthermore, both targets exhibit functional activity in a variety of in vitro assays and anti-tumor models.

Background and Rationale (continued)

In the non-human primate (NHP) studies, dose dependent infusion-related toxicity was observed with repeat dosing. The infusion-related reactions (IRRs) are believed to be the result of exacerbated pharmacology of SL-172154 in the presence of anti-drug antibodies (ADA). SL-172154 is a pharmacologically active molecule: a dose dependent postdose decrease in lymphocyte counts and an increase in a number of serum cytokines was observed; with cytokine elevations tending to increase with repeated dosing. The emergence of ADA in all animals by Day 15 was expected given that SL-172154 is based on human amino acid sequences which have 82% identity to the corresponding cynomolgus sequences. The activation of complement was coincident with the emergence of ADA. Overall, the nonclinical safety studies support the administration of SL-172154 as an intravenous (IV) infusion in the proposed first-in-human (FIH) clinical study SL03-OHD-101.

This Phase 1 trial will evaluate the safety, tolerability, pharmacokinetics, anti-tumor and pharmacodynamic effects of SL-172154 and identify the dose and schedule i.e., recommended Phase 2 dose for future development. Subjects eligible for enrollment are required to have platinum-ineligible ovarian, fallopian tube, and primary peritoneal cancers. Ovarian and related cancers were selected for investigation in this Phase 1 study of SL-172154 due to the fact that a high percentage of tumors have detectable CD47 expression [Wang, 2015; Brightwell, 2016]. Furthermore, CD47 is a tumor associated antigen in ovarian cancer with high levels of expression in epithelial ovarian cancer cells compared with normal ovarian cells [Li, 2017]. Finally, tumor-associated macrophages constitute over 50% of cells within the peritoneal TME and malignant ascites and are potential targets for therapy [Gupta, 2018]. Given that the antigen-presenting cell is hypothesized to be the primary target of SL-172154, the unique immune contexture of ovarian cancers makes this histology particularly suitable for investigation.

Study Objectives

Primary Objective(s)	**Outcome Measures**
To evaluate the safety and tolerability of SL-172154 and to identify the maximum tolerated dose (MTD) or maximum administered dose (MAD) of SL-172154 in subjects with platinum-ineligible ovarian, fallopian tube, and primary peritoneal cancers	▪ Safety/tolerability outcomes include: incidence of all adverse events (AEs) and immune-related adverse events (irAE), serious adverse events (SAEs), fatal SAEs, dose limiting toxicity (DLT), AEs and irAEs leading to discontinuation, and changes in safety assessments (e.g., laboratory para-meters, vital signs etc.) per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE – version 5.0). ▪ The MTD is defined based on the rate of DLTs and the MAD is the highest dose administered
Secondary Objectives	**Outcome Measures**
To select the recommended Phase 2 dose (RP2D) for SL-172154.	▪ Based on review of all data collected during dose escalation, dose expansion, and pharmacodynamic cohorts including safety, tolerability, pharmacokinetics (PK), anti-tumor activity, and pharmacodynamic effects

Secondary Objectives	**Outcome Measures**
To assess preliminary evidence of anti-tumor activity of SL-172154	Disease assessment per investigator assessment according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). ▪ Objective response rate (ORR) (proportion of subjects whose best response is a complete response [CR] or partial response [PR]) ▪ Clinical benefit rate (CBR): proportion of subjects whose best overall response is a CR, PR or stable disease (SD) ≥ 16 weeks ▪ Time to response (TTR): time from the first dose until the first response (CR or PR, whichever is recorded first) that is subsequently confirmed ▪ Duration of response (DOR): time between first response (CR or PR, whichever is recorded first) that is subsequently confirmed and date of disease progression
To evaluate immunogenicity to SL-172154 during and after treatment.	▪ Number/proportion of subjects with positive anti-drug antibody (ADA) titer ▪ ADA duration ▪ Transient vs. persistent ADA
To characterize the PK of SL-172154.	▪ Maximum observed concentration (Cmax) and time at which the maximum concentration is observed (Tmax) and minimum observed concentration (Cmin) following single and multiple doses of SL-172154 ▪ Area under the serum concentration-time curve (AUC) ▪ Terminal elimination half-life (t½), Clearance (CL) and Volume of Distribution (Vz)
Exploratory Objectives	**Outcome Measures**
To assess target engagement of cluster of differentiation 40 (CD40) on peripheral blood mononuclear cells (PBMCs) prior to and following SL-172154 administration.	▪ Free/total receptor occupancy of CD40
To assess target engagement of CD47 on red blood cells (RBCs) and PBMCs prior to and following SL-172154 administration.	▪ Free/total receptor occupancy of CD47
To assess pharmacodynamic biomarkers in blood prior to, on-treatment and following SL-172154 administration.	Pharmacodynamic biomarkers in blood: ▪ Changes from baseline in cytokine/chemokine levels potentially including (but not confined to) interleukin (IL)-17α, interferon alpha (IFN□), tumor necrosis factor alpha (TNFα), IL-7, IL-8, IL-15, IL-10, IL-12p70, chemokine ligand CXCL9, CXCL10 ▪ Changes from baseline in cell counts and percentages of circulating immune cells including T cell subsets, B cell subsets, and myeloid cells ▪ Circulating immunoglobulin (Ig) levels ▪ Complement activation by assessment of SC5b-9 terminal fragment

Exploratory Objectives	Outcome Measures
To assess pharmacodynamic biomarkers in tumor tissue prior to, on-treatment and following SL-172154 administration.	Pharmacodynamic biomarkers in tumor tissue including: ▪ Changes in T cells subsets, B cell subsets and myeloid cells. ▪ CD47 and CD40 expression ▪ Programmed cell death ligand 1 (PD-L1) expression
To evaluate binding of SL-172154 to RBCs	▪ Presence of SL-172154 on RBCs
To estimate progression-free survival (PFS) and overall survival (OS)	▪ PFS based on investigator assessment: time from first dose to progression by RECIST v1.1 or death, whichever comes first ▪ OS: time from first dose to death
To evaluate efficacy using immune-related response criteria.	▪ ORR, CBR, TTR, DOR and PFS based on investigator assessment per immune Response Evaluation Criteria (iRECIST)

Study Design

This clinical trial is a FIH, open label, multi-center, dose escalation Phase 1 study of SL-172154 designed to evaluate the safety, PK, pharmacodynamic effects, and anti-tumor activity of SL-172154 monotherapy administered as an IV infusion. The planned total sample size is approximately 33 -54 subjects. If only Schedule 1 is evaluated, the planned total sample size for dose escalation is 21 subjects. If Schedule 1 and Schedule 2 are both fully evaluated across 5 dose levels in dose escalation, the maximum planned sample size for dose escalation is 42. Approximately 6 subjects may be enrolled in an optional pharmacodynamic cohort; and approximately 6 subjects in the dose expansion cohort at the dose and schedule selected for further evaluation. Dose escalation will utilize the modified Toxicity Probability Interval (mTPI-2) design [Guo, 2017] with a target dose limiting toxicity (DLT) rate of 30% for the MTD. Subjects will be enrolled in cohorts of approximately 3 subjects into sequential dose levels of SL-172154 and evaluated for DLT during the 28-day DLT evaluation period starting from the first dose of SL-172154. At each dose level, a minimum 3-day stagger between dosing the first and second subject is required. The planned dose escalation is in half-log increments as outlined in the table below under the Treatment Schedules Section. The study may also enroll a pharmacodynamic cohort to obtain additional pharmacodynamic data from a total of approximately 6 additional subjects at one or more dose levels that have completed evaluation for safety without exceeding the MTD. Subjects enrolled in the pharmacodynamic cohort will not inform dose escalation decisions. Approximately 6 subjects may be enrolled in a dose expansion cohort to further characterize safety, tolerability, PK, anti-tumor activity, and pharmacodynamic data to inform the selection of a RP2D. The goal is to enroll approximately 6-12 subjects at the potential RP2D, including subjects in dose escalation, pharmacodynamic cohort, and dose expansion.

Treatment Schedules

- **Schedule 1**: SL-172154 will be administered IV on days 1, 8, 15 of a 28-day cycle in cycle 1 and then every 2 weeks thereafter (on days 1 and 15 in cycles ≥ 2).
- **Schedule 2**: SL-172154 will be administered IV once weekly on days 1, 8, 15, and 22 every 28 days in every cycle. The starting dose on schedule 2 would be instituted at a dose level that has completed evaluation for safety on schedule 1 and then continue dose escalation as defined by the mTPI-2 design. Alternative schedules may be explored if emerging data indicate less frequent dosing of SL-172154 should be evaluated. In this case, SL-172154 may be administered once every two weeks, once every three weeks or once every four weeks. The starting dose on these alternate schedules would be instituted at a dose level that has completed evaluation for safety and then continue dose escalation as defined by

the mTPI-2 design, emerging safety data and as recommended by the Safety Monitoring Committee (SMC).

Dose Escalation Scheme – Phase 1

Dose escalation will begin at the starting dose of 0.1 milligrams per kilogram (mg/kg) as outlined below. Intermediate or higher dose levels not shown may be explored based on emerging data (e.g., safety and pharmacodynamic data).

Dose Level	IV Dose of SL-172154 (mg/kg)[a,b,c, d, e]	Duration of Infusion[d]
Level 1 - starting dose	0.1	30 minutes (+/- 10 minutes)
Level 2	0.3	30 minutes (+/- 10 minutes)
Level 3	1.0	30 minutes (+/- 10 minutes)
Level 4	3.0	60 minutes (+/- 15 minutes)
Level 5	10.0	60 minutes (+/- 15 minutes)

a) Dosing will begin on Schedule 1 with SL-172154 administered in 28-day cycles on days 1, 8, and 15 in cycle 1 and then on days 1 and 15 in cycles ≥ 2.

b) Dose escalation on Schedule 2 may be tested. If Schedule 2 is opened, SL-172154 may be administered once weekly on days 1, 8, 15, and 22 of each 28-day cycle.

c) Intermediate or higher dose levels may be tested based on emerging safety and pharmacodynamic data.

d) The actual body in kilograms (kg) will be used for dose calculation in all subjects who body weight is ≤100 kg. For subjects with body weight >100 kg, the dose to be administered should be the same as that calculated for a subject weighing 100 kg.

e) Infusion time may change based on final drug volume needed for administration, safety and tolerability of the infusion for the subject and/or observed safety findings during the study. Please refer to the Study Pharmacy Manual (SPM) for details.

Intrasubject dose escalation(s) may be considered on a case-by-case basis, provided that the subject has completed at least 2 cycles at the originally assigned dose, has tolerated treatment well, and experienced ≤ Grade 1 toxicity on the most recent cycle of SL-172154 therapy. A subject's dose may be increased to a dose level that has completed evaluation for safety and has not exceeded the MTD.

Definition of Dose Limiting Toxicity

DLTs are as defined in the bulleted points below. Toxicities will be graded as per National Cancer Institute Common Terminology Criteria for Adverse Events version 5 (NCI CTCAE v5). The determinate period for DLT is the first 28 days of SL-172154 dosing on Schedule 1 or Schedule 2.
Note: AEs clearly related to disease progression or intercurrent illness are not considered DLTs. Inflammatory reactions attributable to local anti-tumor responses (e.g., severe pain) are not considered DLTs.

- Any death not clearly due to underlying disease or extraneous causes
- Any ≥ Grade 4 AE
- Elevations in liver transaminases (aspartate aminotransferase [AST], alanine aminotransferase [ALT]) and/or total bilirubin:
  - In subjects who enroll with AST/ALT/total bilirubin ≤ upper limit of normal (ULN); AST or ALT elevation of >8 x ULN or total bilirubin > 5 x ULN
  - In subjects who enroll with AST/ALT/total bilirubin > ULN; AST or ALT elevation of >8 x baseline or total bilirubin > 5 x baseline
  - Evidence of Hy's Law (AST or ALT > 3 x ULN [or baseline*] with concurrent increase in total bilirubin > 2 x ULN [or baseline*] without evidence of cholestasis or alternative explanation such as disease progression or viral hepatitis; *ULN or baseline dependent on value at enrollment as described above.
- Any AE that requires permanent discontinuation of SL-172154
- Any Grade 3 or greater AE **except** for those listed below:
  - Grade 3 fatigue lasting ≤ 7 days
  - Grade 3 anemia
  - Grade 3 or 4 neutropenia not associated with fever that improves to Grade 2 within 7 days.
  - Grade 3 or 4 lymphopenia
  - Grade 3 thrombocytopenia not associated with clinically significant bleeding and does not require medical intervention
  - Grade 3 electrolyte abnormalities that are not associated with clinical signs/symptoms and are reversed with appropriate medical intervention
  - Grade 3 laboratory abnormalities that are not deemed clinically significant by the SMC.
  - Indirect/unconjugated hyperbilirubinemia without significant clinical consequences
  - Grade 3 or 4 amylase and/or lipase abnormalities that are not associated with clinical signs/symptoms or findings on imaging consistent with pancreatitis
  - Grade 3 vomiting and/or Grade 3 nausea that resolves within 72 hours with appropriate clinical management
  - Grade 3 hypertension that can be controlled (i.e., systolic BP < 140 mmHg and diastolic BP < 90 mmHg) with medical therapy.
  - Grade 3 endocrine disorder (thyroid, pituitary, hyperglycemia and/or adrenal insufficiency) that is managed with treatment with resolution of symptoms within 14 days after treatment onset.
  - Grade 3 diarrhea with no evidence of colitis that resolves within 72 hours with appropriate clinical management
  - Vitiligo or alopecia of any grade
- Other AEs may be considered a DLT as determined by the investigator in conjunction with the SMC.

A Grade ≥ 3 AE(s) that occurs beyond the DLT period or Grade 2 events that require continuous interruption of SL-172154 for more than 6 weeks or AEs that result in subjects not receiving at least 2 of the 3 scheduled doses of SL-172154 on Schedule 1 (or at least 2 of the 4 scheduled doses of SL-172154 on Schedule 2) during the DLT assessment period due to AE(s) may be taken into consideration when assessing the totality of the data in determining DLT and the RP2D.

Eligibility Criteria

Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply.

1. Subject has voluntarily agreed to participate by giving written informed consent in accordance with ICH/GCP guidelines and applicable local regulations.
2. Subject must have a histologically confirmed diagnosis of an unresectable, locally advanced or metastatic ovarian cancer, or primary peritoneal cancer or fallopian tube cancer.
3. Subjects must be refractory or intolerant to existing therapy(ies) known to provide clinical benefit for their condition. Subject must have received platinum-based therapies, and should not be eligible for further platinum therapy, or should be intolerant to such therapy. Subjects with known HRD positive disease may participate if they have received prior polyadenosine diphosphate ribose polymerase (PARP) inhibitor therapy given alone or with bevacizumab. NOTE: HRD testing is not required per protocol.
4. Subjects should not be primary platinum refractory as defined by progressing during or within 1 month of upfront platinum therapy.
5. Has measurable disease by RECIST v1.1 using radiologic assessment.
6. Subject age is 18 years and older.
7. Has an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
8. Has life expectancy of greater than 12 weeks.
9. Laboratory values must meet the following criteria (see table below).

Laboratory parameter	Threshold value
Absolute neutrophil count (ANC)	$\geq 1.5 \times 10^9$/L without growth factor support
Platelet count	$\geq 75 \times 10^9$/L
Hemoglobin (Hgb)	> 9.0 g/dL with no blood transfusions for at least 5 days prior to D1 of IP.
Creatinine clearance (CrCl)	≥ 30 milliliter (mL)/min (using modified Cockcroft-Gault formula; Appendix Section 16.4)
ALT/AST	≤ 3 x ULN
Total bilirubin	≤ 1.5 x ULN; subjects with isolated indirect hyperbilirubinemia are permitted if direct bilirubin ratio is <35% and total bilirubin is ≤ 3.0 x ULN
Left ventricular ejection fraction (LVEF) by echocardiogram (ECHO)	≥ Lower limit of normal (LLN) per institutional threshold If LLN is not defined for a given institution, then ejection fraction must be ≥50 %

10. Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test within 72 hours of D1 of IP. **NOTE**: FCBP - A female subject who is not sterile due to surgery (i.e., from bilateral tubal ligation/occlusion, bilateral oophorectomy, bilateral salpingectomy or complete hysterectomy) or who does not have a congenital or acquired condition that prevents childbearing or who is not naturally post-menopausal for at least 12 consecutive months (see Appendix Section 16.3 for additional details). Documentation of postmenopausal status must be provided. FCBP should use an acceptable method of contraception (see Appendix Section 16.3) to avoid pregnancy during

treatment and for 30 days (which is expected to exceed 5 half-lives) after the last dose of IP. FCBP must start using acceptable contraception at least 14 days prior to D1 of IP.

11. Recovery from prior anti-cancer treatments including surgery, radiotherapy, chemotherapy or any other anti-cancer therapy to baseline or ≤ Grade 1. (**NOTE**: Low-grade or controlled toxicities such as alopecia, ≤ Grade 2 hypomagnesemia, ≤ Grade 2 neuropathy, ≤ Grade 2 hypothyroidism on supplementation may be allowed upon agreement by the Sponsor Medical Monitor).
12. Willing to consent to mandatory pre-treatment and on-treatment tumor biopsy(ies), unless there is excessive risk as determined by the investigator.

Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Prior treatment with an anti-CD47 or anti-SIRPα targeting agent or a CD40 agonist.
2. Any anti-cancer therapy within the time intervals noted below prior to first dose (D1) of SL-172154.

Therapy	Washout period
Chemotherapy	3 weeks
Hormonal therapy	3 weeks
PD-1/L1 inhibitor and other immunotherapies not otherwise specified	3 weeks
Tumor vaccine	4 weeks
Cell-based therapy	8 weeks
Other mAbs or biologic therapies	3 weeks
Other investigational agents not covered above	4 weeks or 5 half-lives whichever is shorter
Major surgery	2 weeks
Radiation (except palliative intent which does not require washout)	2 weeks

3. Concurrent chemotherapy, immunotherapy, biologic or hormonal/hormonal suppression therapy for cancer treatment is prohibited. Concurrent use of hormones for non-cancer related conditions is acceptable.
4. Use of corticosteroids or other immunosuppressive medication, current or within 14 days of D1 of SL-172154 treatment with the following exceptions (i.e., the following are allowed with or within 14 days of D1 of IP):
    - Topical, intranasal, inhaled, ocular, intraarticular corticosteroids
    - Physiological doses of replacement steroid (e.g., for adrenal insufficiency) not to exceed 10 mg/day of prednisone or equivalent
    - Steroid premedication for reaction to IV contrast
5. Receipt of live attenuated vaccine within 28 days of D1 of IP.
6. Active or documented history of autoimmune disease. Exceptions include controlled Type I diabetes, vitiligo, alopecia areata or hypo/hyperthyroidism.

Exclusion Criteria (continued)

7. Hypersensitivity to the active drug substance or to any of the excipients for the agent to be administered or subjects with known hypersensitivity to Chinese hamster ovary cell products.
8. Active pneumonitis (i.e. drug-induced, idiopathic pulmonary fibrosis, radiation-induced, etc.).
9. Ongoing or active infection (e.g., no systemic antimicrobial therapy for treatment of infection within 5 days of D1 of IP).
10. Symptomatic peptic ulcer disease or gastritis, active diverticulitis, other serious gastrointestinal disease associated with diarrhea within 6 months of D1 of IP.
11. Clinically significant or uncontrolled cardiac/thromboembolic disease including any of the following:
    - Myocarditis
    - Unstable angina within 6 months from D1 of IP
    - Acute myocardial infarction within 6 months from D1 of IP
    - Uncontrolled hypertension
    - New York Heart Association Class II, III or IV congestive heart failure
    - Clinically significant (symptomatic) cardiac arrhythmias (e.g., sustained ventricular tachycardia, second- or third- degree atrioventricular block without a pacemaker, circulatory collapse requiring vasopressor or inotropic support, or arrhythmia that is not stabilized on therapy)
    - Clinically symptomatic thromboembolism on stable anticoagulation for less than three months
12. Untreated central nervous system or leptomeningeal metastases. Subjects with treated central nervous system metastases must have completed definitive treatment (radiotherapy and/or surgery) > 2 weeks prior to D1 of IP and no longer require steroids.
13. Women who are breast feeding.
14. Psychiatric illness/social circumstances that would limit compliance with study requirements and substantially increase the risk of AEs or compromised ability to provide written informed consent.
15. Another malignancy that requires active therapy and that in the opinion of the investigator and Sponsor would interfere with monitoring of radiologic assessments of response to IP.
16. Has undergone allogeneic stem cell transplantation or organ transplantation.
17. Known history or positive test for human immunodeficiency virus, or positive test for hepatitis B (positive for hepatitis B surface antigen [HBsAg]) or hepatitis C virus ([HCV]; if HCV antibody (Ab) test is positive check for HCV ribonucleic acid [RNA]).

(**NOTE**: *Hepatitis B virus (HBV)*: Subjects who are hepatitis B core antibody positive, but HBsAg negative are eligible for enrollment. *HCV*: Subjects who are HCV Ab positive, but HCV ribonucleic acid (RNA) negative are eligible for enrollment).

Safety Oversight
During the study while subjects are receiving treatment with SL-172154, SMC meetings will be held to review relevant data with the investigators or delegates. These meetings will be held once a month (or more frequently if required) during dose escalation to share safety data and communicate results of ongoing analyses. All available safety, PK, pharmacodynamic, and clinical outcome data for all subjects at the time of the scheduled SMC Meeting will be reviewed and summarized. Attendees of SMC meetings will include but not be limited to clinical investigators (or designees), the Sponsor Medical Monitor and Statistician. The SMC will operate in accordance with the SMC charter which will define roles and accountabilities and the process for safety review. The Sponsor will remain in constant contact with the clinical sites during the enrollment period to ensure that cohort enrollment during the dose escalation of this study is completed as per protocol. All dose escalation or safety decisions made by the SMC will be documented in writing with copies maintained at each site and the Trial Master File at the Contract Research Organization.
Statistical Analyses
The safety evaluation will be based on the All Treated Population defined as all subjects who received at least one dose of study treatment. Frequency tables will be used to describe safety and tolerability parameters AEs, irAEs, SAEs, fatal SAEs and AEs leading to discontinuation of SL-172154. Changes in toxicity grade for clinical chemistry and hematology will also be summarized. AEs will be mapped to a Medical Dictionary for Regulatory Activities preferred term and system organ classification. Laboratory abnormalities will be graded according to the NCI CTCTAE v5., if applicable. The DLT evaluation will be based on the DLT evaluable population (defined as All Treated subjects enrolled in the dose escalation cohorts 1) who have received ≥2 of the 3 scheduled doses of IP during cycle 1 on Schedule 1 (or at least 2 of the 4 scheduled doses of SL-172154 on Schedule 2) and complete the safety follow-up through the 28-day DLT evaluation period; or 2) who experience any DLT during the DLT evaluation period). DLTs will be summarized by dose level. The MTD will be estimated using isotonic regression. Anti-tumor activity data will be summarized by dose level and overall in the All Treated population and Response Evaluable population (defined as Subjects in the All Treated Population who have a baseline disease assessment and have at least one post-baseline disease assessment or have progressed or died before the first post-baseline disease assessment). The primary analysis of anti-tumor activity assessment is based on RECIST v1.1 and exploratory analysis of anti-tumor activity assessment is based on iRECIST. The PK serum concentrations and PK parameters will be summarized and analyzed using appropriate statistical methods. The pharmacodynamic biomarkers values will be summarized descriptively by dose level and visit.

1. INTRODUCTION, BACKGROUND AND STUDY RATIONALE

1.1 Background Information

An essential element for increasing the immunogenicity of a tumor involves the processing of tumor antigens released from dead or dying tumor cells, and the subsequent presentation of tumor antigens on major histocompatibility complex (MHC) molecules expressed by activated antigen presenting cells (APCs). Cluster of differentiation (CD)47 is expressed by many somatic and hematopoietic tissues and is an important protective mechanism to prevent red blood cell (RBC) and platelet destruction by macrophages and splenic CD4+ dendritic cells (DCs) [Oldenborg, 2000; Blazar, 2001; Yamao, 2002; Olsson, 2005; Yi, 2015]. The anti-phagocytic activity of CD47/SIRPα led to the description of this axis as the macrophage 'do not eat me' signal. The 'eat me' signal which ultimately leads to RBC destruction by splenic dendritic cells (DCs) is dependent upon a second activating signal, including CD18 containing integrins [Yi, 2015]. Uncoupling of the 'do not eat me' and 'eat me' signals likely increased the fitness of the host by providing improved regulation for erythrocyte homeostasis and should be considered in the therapeutic application of CD47/SIRPα inhibitors.

Abundant expression of CD47 in many solid and hematogenous tumors led to investigation of whether tumor cells had co-opted this pathway as a protective mechanism against immune mediated destruction. Early studies hypothesized that the role of CD47 as a 'do not eat me' signal by macrophages for erythrocyte homeostasis would also explain the observed anti-tumor benefit in preclinical studies with CD47 blocking antibodies or SIRPα-Fc fusion proteins [Chao, 2012; Willingham, 2012; Weiskopf, 2013]. More recent studies, however, have clarified that DCs are also an important target of CD47/SIRPα inhibition in the context of tumor immunotherapy [Liu, 2015]. Specifically, inhibition of SIRPα signaling in CD8α+ DCs has been shown to enhance sensing of phagocytosed tumor mitochondrial deoxyribonucleic acid, which initiates a cyclic guanine monophosphate – adenosine monophosphate synthase/stimulator of interferon genes (cGAS/STING) mediated type I interferon response that facilitates cross-presentation of tumor antigens to CD8+ T cells [Liu, 2015; Xu, 2018]. Increased antigen priming of CD8α+ DC in the presence of CD47/SIRPα inhibition dramatically enhances tumor rejection in multiple pre-clinical tumor models, demonstrating that the CD47/SIRPα axis is capable of bridging innate and adaptive immunity.

CD8α+ DCs expressing the transcription factor batf3 have previously been reported to be essential for anti-tumor immunity [Hildner, 2008]. The essential role of CD8α+ DCs in anti-tumor immunity is due to the specialized ability of these APCs to cross-present exogenous tumor antigens. Following phagocytosis, these tumor antigens gain entry to the DC cytosol and then are cross-presented to CD8+ T cells. CD40 ligation by CD40 ligand (CD40L), expressed by resting CD8α+ (but not CD8α-) DCs, is an important signal for enhancing the antigen cross-presenting activity of exogenous antigen by DCs to CD8+ T cells [O'Connell, 2000; Delamarre, 2003; Yasumi, 2004; de Silva, 2019]. Interestingly, activation of tumor necrosis factor receptor-associated factor (TRAF) signaling downstream of CD40 ligation has also been shown to facilitate a type I interferon response via STING activation, but STING activation does not appear to be essential for the anti-tumor immune response to CD40 stimulation [Byrne, 2016; Yao, 2016]. Despite the potentially context-dependent role of a type I interferon response, anti-tumor immunity to CD40 agonists remained dependent upon batf3 positive DCs and CD8+ T cells [Byrne, 2016]. These data indicate that, like CD47/SIRPα, the CD40/CD40L axis appears capable of bridging innate and

adaptive immunity, however the two pathways appear to have distinct dependence upon a type I interferon response.

SIRPα-Fc fusion proteins and anti-CD47 antibodies, as well as CD40L-Fc fusion proteins and CD40 agonist antibodies are being investigated in clinical trials and have demonstrated preliminary evidence of anti-tumor activity [Vonderheide, 2007; Kornbluth, 2012; Ingram, 2017; Lin, 2017; Petrova, 2017; R. Advani, 2018; Kauder, 2018; Merz, 2018; Sikic, 2019; Vitale, 2019]. The roles of CD47/SIRPα and CD40/CD40L in bridging innate and adaptive immune response suggests that the two pathways could be complimentary or synergistic in combination and have the potential to improve anti-tumor activity in cancer patients.

In an attempt to improve upon current paradigms, Shattuck Labs has developed a bifunctional fusion protein (FP) platform, capable of simultaneously blocking 'checkpoints' while activating tumor necrosis factor (TNF) receptor superfamily co-stimulators. Shattuck's Agonist Redirected Checkpoint (ARC™) platform adjoins the extracellular domain (ECD) of a select type 1 membrane protein to the ECD of a select type 2 membrane protein, via a central Fc domain. Using this approach, combination immunotherapy can be achieved by a single fusion protein (FP). Superior preclinical activity has been observed compared to the separate administration of two individual antibodies against identical targets [de Silva, 2019]. As a result, we sought to develop a SIRPα-Fc-CD40L ARC™ fusion protein as a means to target these pathways with a single compound.

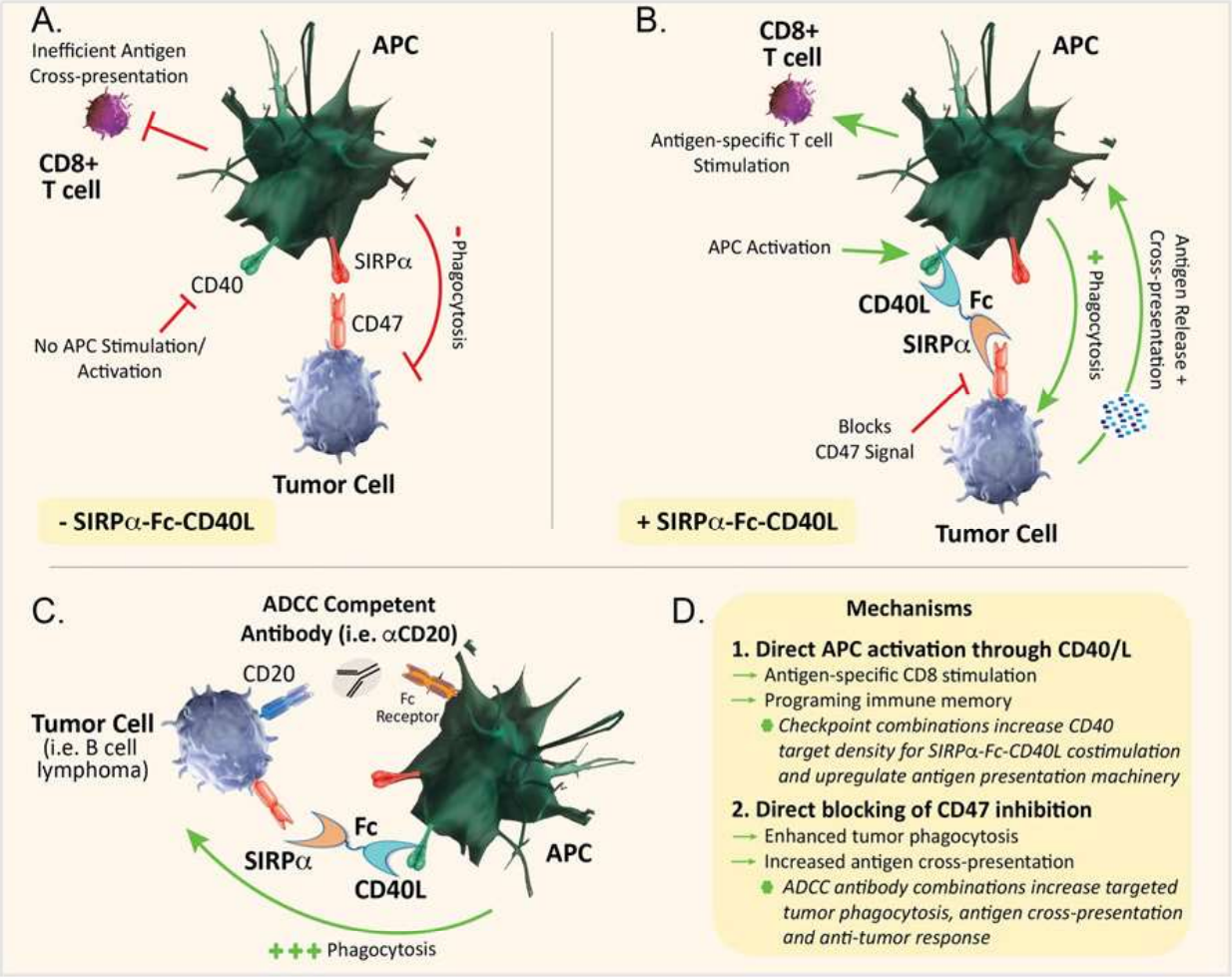
1.2 Investigational Product, SL-172154

The investigational product (IP), SL-172154, is a novel FP consisting of human SIRPα and CD40L (SIRPα -Fc-CD40L) linked via a human Fc. Fusion of the ECDs of SIRPα, a type 1 membrane protein, with CD40L, a type 2 membrane protein, generated a single molecule with dual specificity that retained individual target avidity.

1.2.1 Mechanism of Action

The mechanism of action of SL-172154 is designed to pair the costimulatory role of CD40 ligand (CD40L) in augmenting the antigen cross-presenting ability of DCs with the increased phagocytic activity of macrophages through CD47-SIRPα binding (Figure 1A and Figure 1B). Importantly, because the ECDs of SIRPα and CD40L are physically linked to one another and localized to the tumor microenvironment (TME), APCs and tumor cells receive these signals in a spatiotemporally coordinated manner.

Figure 1: Mechanism of Action of SL-172154 Alone or Combined with an ADCC-competent mAb



(A) Tumor expressed CD47 binds SIRPα on the APCs and suppresses APC (i.e. macrophages and DCs) activities including tumor phagocytosis and cross-presentation to CD8+ T-cells.

(B) SIRPα-Fc-CD40L directly induces APC activation. The CD40L end of the molecule engages CD40 on the APC resulting in APC stimulation and promoting an antigen-specific CD8+ T-cell response. The SIRPα domain of the ARC™ blocks CD47 on the tumor cell thus directly enhancing APC-mediated phagocytosis of tumor cells.

(C) Macrophage-mediated tumor phagocytosis can be further enhanced by combining SIRPα-Fc-CD40L with a tumor-targeted ADCC competent antibody via engagement of the Fc-receptor on the APC.

(D) Direct APC activation through CD40L and direct blocking of CD47 'do not eat me' signals enhance tumor phagocytosis, increase antigen cross presentation and anti-tumor response when SL-172154 is administered alone. The combination of SIRPα-Fc-CD40L with checkpoint blocking agents increases CD40 target density and may stimulate a more potent and durable anti-tumor response. CD47-SIRPα-mediated tumor phagocytosis is further enhanced when SIRPα-Fc-CD40L is combined with an ADCC-competent antibody.

SL-172154, or its mouse surrogate, mSIRPα-Fc-CD40L, has demonstrated functional activity in in vitro and in vivo nonclinical test systems. The nonclinical data supporting the translational study of SL-172154 in human subjects with cancer is described in detail in the Investigator's Brochure (IB) [Report_SL2020IB001]. The mechanism of action, information from the nonclinical in vitro and in vivo pharmacology, toxicokinetics (TK), and toxicity evaluations and the rationale for investigation are briefly summarized.

1.2.2 In Vitro Pharmacology

In vitro, SL-172154 was shown to bind to its cognate targets, CD47 and CD40, both individually and simultaneously. High binding affinity for CD47 and CD40 was noted as well as a slow off-rate (K_D values of 0.628 nM and 4.74 nM, respectively), indicating a longer on-target resident time. This longer resident time could be of benefit in the tumor microenvironment (TME) where CD47 is known to be expressed. CD40-mediated activity by SL-172154 was demonstrated in a NFkB reporter system in which CD40-dependent signaling was stimulated in the absence of Fc receptor cross-linking, and in cultured human peripheral blood mononuclear cells (PBMCs) in which dose-dependent proliferation, an increase in the number of interleukin (IL)-2 secreting PBMCs, and the secretion of multiple cytokines were observed. In addition, SIRPα/CD47 axis-mediated activity was demonstrated by SL-172154 increasing human macrophage-mediated phagocytosis of tumor cells in vitro, which was further enhanced when SL-172154 was combined with a tumor-targeted ADCP/ADCC-competent antibody (rituximab, cetuximab, or trastuzumab).

1.2.3 In Vivo Pharmacology

Treatment of mice with mSIRPα-Fc-CD40L leads to a significant early and sustained activation of murine DCs (CD8+ and CD4+ DC) which matched the duration of activation observed with murine CD40 antibodies. This finding confirmed a previous report that CD47 blockade in vivo leads to rapid upregulation of CD86 and MHC-II on splenic CD8α+ DCs [Yi, 2015].

In vivo, the anti-tumor activity of mSIRPα-Fc-CD40L was studied in established syngeneic CT26 colorectal murine tumor models. The performance of intraperitoneal administration of mSIRPα-Fc-CD40L was compared to treatment with CD47 blocking antibodies, CD40 agonist antibodies, the combination of the two antibodies and vehicle control. These experiments demonstrated that administration of mSIRPα-Fc-CD40L led to higher rates of primary tumor rejection (63%) than either antibody given as monotherapy (anti-CD40, 0% and anti-CD47, 0%), or the antibody combination treatment group (33%). To assess the durability of an immune response without re-treatment, mice that rejected the initial tumor were re-challenged with a second CT26 tumor on the opposite flank on day 40. Of the 2 mice initially cured with the antibody combination, 0 mice rejected the tumor challenge. In the mSIRPα-Fc-CD40L group, 3 of 5 (60%) mice rejected the tumor re-challenge suggesting that a memory response was generated against the tumor, which led to protection against a subsequent tumor challenge. This memory response correlated with a robust increase in AH1 tetramer +/CD8+ cells in the spleen and the tumor for both the anti-CD40/CD47 combination and the mSIRPα-Fc-CD40L treated mice in comparison to vehicle controls.

1.2.3.1 SL-172154 anti-tumor activity with anti-CTLA-4, anti-PD-1 or ADCC-competent antibodies

To assess the effect of combining mSIRPα-Fc-CD40L with checkpoint inhibitors, mice were treated with the following two combinations: mSIRPα-Fc-CD40L + murine anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) antibody or murine or anti-programmed cell death 1 (anti-PD1) antibody. In these combination experiments, the baseline tumor volume was increased by approximately 2-3-fold compared to the monotherapy studies, in order to create a more stringent environment to observe potential synergistic or additive relationships. Both combinations improved anti-tumor response and overall tumor rejection in comparison to the monotherapy controls. Anti-CTLA-4 in combination with concurrent mSIRPα-Fc-CD40L resulted in a potent memory response (57% primary tumor rejection and 100% secondary tumor rejection in

comparison to 0% primary tumor rejection for the monotherapy controls). Similar results were noted with anti-PD-1+ mSIRPα-Fc-CD40L with 43% primary tumor rejection and 100% secondary tumor rejection. These synergistic relationships were noted when anti-PD-1 or anti-CTLA-4 was administered first or concurrently with the mSIRPα-Fc-CD40L. The effect was lost if the mSIRPα-Fc-CD40L treatment preceded treatment with anti-CTLA-4 or anti-PD-1.

Other anti-CD47 agents have demonstrated that tumor phagocytosis is augmented via combinations with tumor-targeting antibodies such as rituximab [Chao, 2012]. Rituximab induces complement and natural killer (NK) cell–mediated, antibody-dependent, cell-mediated cytotoxicity (ADCC) effects by means of its active Fc effector function. In addition, the Fc region of rituximab provides a potent prophagocytic signal for macrophages by stimulating antibody-dependent cellular phagocytosis.

Since SL-172154 was observed to potentiate the activity of rituximab in vitro, the combination of mSIRPα-Fc-CD40L with a murine surrogate for rituximab (murine anti-CD20) was investigated in two CD20+ mouse tumor models, WEHI3 and A20, that were subcutaneously implanted. In both tumor models, similar control of established tumor growth was observed when anti-CD20 antibodies or mSIRPα-Fc-CD40L were tested as monotherapy. In keeping with the in vitro phagocytosis data, the combination of mSIRPα-Fc-CD40L + anti-CD20 resulted in a further decrease in tumor volume. In the WEHI3 model, the combination of mSIRPα-Fc-CD40L + anti-CD20 resulted in 33% of the mice rejecting the tumor, while 17% of mice rejected the tumor when treated with anti-CD20 as monotherapy. There was no tumor rejection in the A20 model, regardless of treatment. These data indicate that mSIRPα-Fc-CD40L induced significant anti-tumor efficacy in both CD20+ hematological tumors models which was enhanced by combination with anti-CD20.

Collectively, these data demonstrate that SL-172154 has a dual mechanism of action (Figure 1A and Figure 1B). Tumor cells expressing CD47 normally bind SIRPα and suppress APCs including macrophages and DCs. One mechanism of action of SL-172154 is direct enhancement of APC-mediated phagocytosis of tumor cells, through blockade of CD47 with the SIRPα domain of the ARC™. SL-172154-mediated tumor phagocytosis can be enhanced through combination with a targeted ADCC competent antibody (Figure 1C and Figure 1D). A second mechanism of action of SL-172154 is induction of APC activation through CD40 which stimulates an antigen-specific CD8+ T cell response. Combination treatment of SL-172154 with checkpoint blocking agents increases CD40 target density which may stimulate a more potent and durable anti-tumor response.

1.2.4 Toxicology and Toxicokinetics

The cynomolgus monkey was selected for the nonclinical toxicology studies due to the cross-reactivity of SL-172154 binding to the respective targets in this species and *in vitro* activity. The anatomical, physiological, and biochemical similarities of cynomolgus monkeys to humans facilitate extrapolation of potential effects to human.

Two, repeat intravenous (IV) dose studies, utilizing once-weekly administration, of up to 5 weeks in duration, have been conducted in cynomolgus monkeys. In both the dose range finding (DRF) study and Good Laboratory Practice (GLP) definitive study, the evaluated SL-172154 doses were 0.1, 1, 10, and 40 mg/kg. The GLP study also included recovery groups to evaluate the reversibility, progression, or delayed appearance of any observed findings following a 4-week off-dose period. Additionally, SL-172154 was evaluated in vitro for potential hemolysis.

In the DRF study, SL-172154 was well tolerated with no incidence of infusion related reactions. Generally, dose-proportional postdose decreases in lymphocytes (0.1 to 40 mg/kg) and platelets (10 and 40 mg/kg) were observed during the study with both parameters trending toward, or returning, to baseline after a 7-day recovery period. A number of serum cytokines were increased with the elevations being generally dose-dependent and tending to increase with repeated dosing. Anti-drug antibodies (ADA) were present in all SL-172154-treated monkeys by Day 15 (Dose 3) and may have contributed to reduced serum SL-172154 levels on Day 29. Plasma complement split products were increased coincident with the emergence of ADA. In the DRF study, 40 mg/kg was designated as the HNSTD and corresponded with mean Cmax and $AUC_{0\text{-last}}$ values of 727,000 ng/mL and 1,670,000 ng*h/mL, respectively, on Day 1 (Dose 1), and 594,000 ng/mL and 1,060,000 ng*h/mL, respectively, on Day 29 (Dose 5).

In the GLP study, the occurrence of dose-dependent infusion-related reactions (IRRs) at 10 and 40 mg/kg (Days 15 or 22) resulted in early termination of dosing in these two dose groups with 2 monkeys in the 40 mg/kg group euthanized in extremis [a female on Day 15 (Dose 3) and a male on Day 22 (Dose 4)]. Minimally to moderately decreased platelets occurred at ≥10 mg/kg (Days 16 and 23) and transient, mild decreases in lymphocytes were seen in the 40 mg/kg group (both sexes on Days 2 and 16; 2 of 4 males on Day 23). Dose-dependent increases in splenic weight and increased lymphoid cellularity in the spleen and lymph node were noted and attributed to SL-172154 administration. These findings were reversed after a 4-week recovery period. Assessment of pharmacodynamic biomarkers showed that SL-172154 occupied CD40 and CD47 receptors on circulating blood cells and caused elevations in a number of serum cytokines. Transient and reversible complement activation was coincident with the production of ADA to SL-172154. Additionally, the presence of ADA from at least Day 15 (Dose 3) onward likely contributed to low or non-quantifiable plasma SL-172154 concentrations on Day 29. At the 1.0 mg/kg dose level, there were no clinical observations, abnormalities in clinical pathology parameters, or non-reversible pathology findings, thus 1.0 mg/kg was considered to be the no-observed-adverse-effect level (NOAEL) for intravenous infusion doses of SL-172154. The 1.0 mg/kg dose corresponded with mean Cmax and $AUC_{0\text{-last}}$ values of 1230 ng/mL and 518 ng*h/mL on Day 1. The mean terminal elimination half-life ($t_{½}$) on Day 1 was approximately 0.4 hours following a 1 mg/kg dose and was higher with mean values of approximately 1.1 and 0.9 hours for the 10 mg/kg and 40 mg/kg dose groups, respectively.

In contrast to the DRF study, there was evidence of toxicity in the GLP study that manifested as dose-dependent infusion-related reactions. The GLP study was a larger study than the DRF study. The GLP study was conducted with study drug that is representative of the Good Manufacturing Process used for clinical drug supplies. The acute clinical observations that were noted in the GLP study were paleness and decreased activity; the severity of signs and symptoms during dose administration resulted in 2 monkeys dosed at 40 mg/kg being euthanized in extremis. Pharmacodynamic analyses performed on the samples from the cynomolgus monkeys in both the DRF and GLP studies demonstrated similar, dose-dependent, on-target pharmacological effects.

The on-target pharmacological effects that were noted in the DRF and GLP study included post-dose changes in peripheral blood lymphocytes and elevations in serum cytokines. In the GLP study, on Day 1 (Dose 1), SL-172154 readily bound to its intended targets, in a dose-dependent manner, achieving >90% CD40 receptor occupancy on PBMCs and ~80% CD47 receptor occupancy on RBCs in the 10 and 40 mg/kg groups. Furthermore, in the GLP study, SL-172154-related increases in serum cytokines levels occurred at ≥1 mg/kg. Most cytokine increases were

observed after repeated administration, generally increased with repeated dosing, and were coincident with emergence of ADA which may have exacerbated the cytokine response. Cytokine levels returned to or were near control levels prior to the next dose. The cytokines with the largest increases in the GLP study were: IL-1 receptor antagonist, monocyte chemoattractant protein-1, IL-6, CD40-ligand, IL-8, macrophage inflammatory protein-1β, stromal cell-derived factor-1α, and vascular endothelial growth factor-A.

RBC hemolysis was investigated and ultimately ruled out as a potential causal or contributory factor to the IRRs. In vitro incubation of SL-172154 with human whole blood did not result in any detectable hemolysis. While SL-172154 was shown to bind to CD47 receptors on RBCs in the monkey GLP study, there were no changes in erythrocyte count, hemoglobin, or hematocrit in the study which were not also observed in control animals. Furthermore, analysis of laboratory values from the GLP study, including lactate dehydrogenase, total bilirubin, hemoglobin and hematocrit demonstrated no evidence of anemia or hemolysis.

ADA developed in both the DRF and GLP studies with a similar time course. The emergence of ADA in cynomolgus monkeys was not unexpected because SL-172154 is based on human amino acid sequences which have 82% identity to the cynomolgus. Across both studies, pretreatment samples from all monkeys in the study were negative. In the GLP study, prior to receiving Dose 2 on Day 8 (168 hours following Dose 1), an ADA response was detected in only 1 animal in each of the 10 and 40 mg/kg groups. On Day 15, prior to Dose 3, all animals in the SL-172154 treatment groups had a positive ADA titer, and remained positive at subsequent time points, including at necropsy of the 10 and 40 mg/kg recovery groups (4 weeks after their last SL-172154 dose). Complement activation, as evidenced by increased plasma C5b-9 concentrations, was only noted after the emergence of ADA.

In summary, the repeat IV dose toxicity studies in cynomolgus monkeys demonstrated on-target pharmacological activity of SL-172154. The onset of ADA, elevations in serum cytokines, activation of complement, and postdose changes in lymphocyte counts were similar between the DRF and GLP studies. Dose-dependent, infusion-related toxicity was observed with repeat dosing in the GLP study, a finding that is attributable to exaggerated pharmacology and immunogenicity. Thus, the IRRs are believed to be the result of exacerbated pharmacology of SL-172154 in the presence of ADA. Overall, the nonclinical safety assessment program supports the administration of SL-172154 as an intravenous infusion in the first-in-human (FIH) clinical study SL03-OHD-101.

1.3 Rationale for Investigation of SL-172154

The preclinical data package provided in the IB [Report_SL2020IB001] demonstrates that SL-172154 selectively and specifically binds to its intended targets, CD47 and CD40, with high affinity. Furthermore, both targets exhibit functional activity in a variety of in vitro assays and anti-tumor models.

SL-172154 is designed to pair the costimulatory role of CD40L in augmenting the antigen cross-presenting ability of DCs with the increased phagocytic activity of macrophages through CD47-SIRPα binding. Binding of the SIRPα side of SL-172154 to CD47 in the tumor for an extended period of time may block this important checkpoint axis and provide a larger window of opportunity for increased tumor phagocytosis, CD40L co-stimulation, and greater antigen-processing and presentation. Furthermore, both the CD47/SIRPα and the CD40/CD40L axes

appear capable of bridging innate and adaptive immunity, suggesting that the two pathways could be complimentary or synergistic in combination. The data also suggest that the tethering of SIRPα to CD40L using an ARC™ provides a mechanistic advantage over the separate administration of two antibodies that have different PK properties, distribute separately, and may compete for Fc receptor binding. We hypothesize that co-localization and co-stimulation is critical for combination immunotherapy and will result in superior clinical activity in comparison to the separate administration of two individual antibodies targeting CD40 and CD47.

SL-172154 overcomes several major functional limitations seen with existing bifunctional technologies (i.e., bispecific antibodies or linked single-chain variable fragment [scFv] molecules). The active unit of SL-172154 exists as a glycosylated multimer, thereby retaining high target avidity, and inducing CD40 receptor clustering and active signaling. The TNF superfamily receptors (i.e., CD40, OX40, GITR, 4-1BB) require clustering on a cell membrane and coordinated binding of multiple receptors for signal activation. With bispecific antibodies or linked scFv molecules, one of the two target binding domains is replaced to bind a second molecule thus resulting in a loss of target avidity. The monovalent binding interaction with each of these two targets is incapable of activating receptors that require clustering on a cell membrane. For this reason, there is not a current example of a bispecific antibody or linked scFv that is able to simultaneously block a checkpoint ligand while stimulating a TNF costimulatory receptor.

This FIH Phase 1 study will evaluate the safety, tolerability, PK, anti-tumor and pharmacodynamic effects of SL-172154 to identify the dose and schedule i.e., recommended Phase 2 dose (RP2D) for future development. The trial will enroll patients with platinum-ineligible ovarian, fallopian tube, and primary peritoneal cancers (Section 4.1). Ovarian and related cancers were selected for investigation in the Phase 1 study of SL-172154 due to the fact that these histologies have a high percentage of tumors with detectable CD47 expression (TCGA data; [Wang, 2015; Brightwell, 2016]. A tissue microarray of 265 tissues from patients with ovarian, primary peritoneal and fallopian tube cancers were analyzed by immunohistochemical analysis for CD47 expression and expression was detected in 210 of 265 cases (79%). Furthermore, CD47 is a tumor associated antigen in ovarian cancer with high levels of expression in epithelial ovarian cancer cells compared with normal ovarian cells [Li, 2017]. Finally, ovarian cancer is characterized by peritoneal metastases which are facilitated by a crosstalk between tumor cells and other cells in the TME. Tumor-associated macrophages constitute over 50% of cells within the peritoneal TME and malignant ascites and are potential targets for therapy [Gupta, 2018]. Given that the APC is hypothesized to be the primary target of SL-172154, the unique immune contexture of ovarian cancers makes this histology particularly suitable for investigation. These hypotheses are supported by the results of a Phase 1 study of an anti-CD47 antibody, Hu5F9-G4, in which monotherapy activity was reported in 2 (partial responses) out of 13 patients with ovarian cancer [Sikic, 2019].

1.4 Potential Risks and Benefits of SL-172154

1.4.1 Potential Risks

Potential risks to subjects are addressed by safety guidelines and vigilant monitoring of participants as outlined below. Potential safety concerns are based on preclinical safety toxicology findings in cynomolgus monkeys dosed with SL-172154 and other in vivo or in vitro studies of SL-172154 summarized in the IB, as well as established clinical management guidelines.

SL-172154 is a pharmacologically active molecule [Report_SL2020IB001]. The risks (evaluation of safety and tolerability) and potential benefits (evaluation of anti-tumor activity) of SL-172154 in humans will be assessed for the first time in this Phase 1 clinical trial. In the absence of data in humans, an assessment of potential safety risks is based on (1) the results of nonclinical studies with SL-172154 (e.g., non-human primate (NHP) studies in cynomolgus monkeys); and (2) the adverse event (AE) profile of other CD40 agonists and CD47-SIRPα targeting agents.

Based on a thorough review of the totality of the NHP data (including clinical findings, laboratory studies, cytokine analysis, TK, immunogenicity studies, complement split product levels, and anatomical pathology), the underlying etiology of the SL-172154-related effects is most likely due to a combination of both the pharmacologic activity of the molecule and to immunologic reactions to SL-172154 administration. The following are potential contributory factors to the dose dependent IRRs: (1) elevations in serum cytokines; (2) postdose changes in lymphocyte number; (3) development of ADA and downstream complement activation.

Adverse events that have been observed following administration of other CD40 agonists agents include infusion related reactions (most common symptoms associated with infusion related reactions are chills, nausea, vomiting, hypotension, pyrexia, pruritus, rash), cytokine release syndrome (CRS), fatigue, rash, elevation of hepatic transaminases, lymphopenia, anemia, thrombocytopenia, neutropenia, thromboembolism, and inflammatory eye disorders (conjunctivitis and ocular hyperemia). Immune mediated events, including dermatitis, colitis, hypophysitis and thyroiditis, have not been seen with CD40 antibodies but remain a potential concern [Vonderheide, 2001; Calvo, 2019].

Adverse events that have been observed following administration of agents that target the CD47-SIRPα axis include anemia, hemagglutination, hyperbilirubinemia, lymphopenia, thrombocytopenia, neutropenia, elevation of hepatic transaminases, fatigue, headache, fever, and infusion related reactions [Ansell, 2016; Chow, 2019; Sikic, 2019].

Implications for monotherapy dosing of SL-172154 in this FIH clinical trial [Report_SL2020IB001]:

1) The data indicate a potential risk for IRRs and CRS in humans. The IRRs that were noted in the NHP studies were potentially cytokine-mediated as they demonstrated dose- and time-dependence. In contrast, antibody-mediated type 1 or type 3 hypersensitivity reactions (HSRs) would not be expected to demonstrate dose-dependence. Furthermore, CRS is to be expected given the mechanism of action of SL-172154. The steps taken to minimize these risks include low starting dose, decreased dose frequency in comparison to the weekly dosing schedule for the NHP studies, administration in an outpatient oncology clinic or inpatient setting, management guidelines (e.g., rescue treatments, prophylaxis), and extended monitoring when indicated. The steps taken to minimize the risks are outlined in the Toxicity Management Guidelines section of the protocol (Section 3.6). This section is based on robust management guidelines that are available for managing CRS in the context of treatment with adoptive T-cell therapies, bispecific antibodies, and agonist antibodies.
2) Immunogenicity Risk and Complement Activation: ADA did emerge in the non-human primate studies as expected given that SL-172154 is based on human amino acid sequences which have 82% identity to the corresponding cynomolgus sequences. However, SL-172154 has >99% identity to the corresponding human proteins and hence SL-172154 is considered to

have a low risk of immunogenicity in humans. Subjects in the clinical trial will, nevertheless, be monitored starting at baseline and serially for ADA and complement activation. In the event of a positive ADA response, antibody titer will be measured, and antibody isotype will be characterized. A guideline for monitoring and management of HSRs is included in the protocol (Section 3.6.1).

3) Hemolysis and Anemia: SL-172154 does bind RBCs in vivo but was not shown to cause hemolysis in NHPs. The lack of hemolysis is likely due to the fact that the Fc domain of SL-172154 is inactive [Chow, 2019]. Regardless, subjects will be monitored serially for evidence of hemolysis and anemia. Another potential risk is that treatment with SL-172154 may result in interference with pre-transfusion testing due to SL-172154 binding of CD47 on RBC and platelet membranes [Report_SL2020IB001]. To investigate this possible risk, blood phenotyping, type and screen (ABO/Rh), and direct antiglobulin test (DAT) will be performed before and following exposure to SL-172154.

4) Immune-Related Adverse Events (irAEs): As with other checkpoint inhibitors and costimulatory molecules, irAEs resulting from a breakdown of self-tolerance remain a potential concern associated with SL-172154 administration. As experience using checkpoint inhibitor therapies has grown, the list of toxicities has increased, and the types of AEs observed span essentially every organ class. Extensive knowledge in managing immune-related toxicities has developed over the years and led to the publication of consensus guidelines in peer reviewed journals [Haanen, 2017; Puzanov, 2017; Brahmer, 2018]. Moreover, clinical trial sites familiar with these therapeutic agents have developed institutional guidelines to ensure effective management of these toxicities. Monitoring and management of irAEs as outlined in protocol section 3.6 follow these consensus guidelines in this FIH study.

In summary, this Phase 1 study has taken the following precautions to minimize the potential for adverse outcome: (1) the study is being conducted at centers that have extensive experience with this class of agents and the management of associated toxicities; (2) the starting dose of SL-172154 is estimated based on minimum anticipated biological effect level (MABEL) and is 10x lower than the NOAEL observed in the NHP studies (Section 3.2). Therefore, the starting dose is expected to be lower than doses associated with AEs in humans; (3) staggered enrollment between dose cohorts and within cohorts allows for the monitoring of acute toxicities in one subject before treating another; (4) administration of SL-172154 in an outpatient oncology treatment center/hospital allows for close monitoring of subjects for AEs and for timely action; (5) guidelines for management of AEs based on established guidelines [Haanen, 2017; Puzanov, 2017; Rosello, 2017; Brahmer, 2018; Porter, 2018] are provided in the clinical trial protocol (Section 3.6); (6) a Safety Monitoring Committee (SMC) will meet monthly and on an ad hoc basis to review emerging toxicities, and assess the impact of these toxicities on study conduct.

1.4.2 Potential Benefits

The clinical benefits of SL-172154 are unknown: no clinical trials in human subjects have been conducted to date. SL-172154 targets both the CD40/CD40L and the SIRPα/CD47 axes. Monoclonal antibodies and fusion proteins targeting each of these axes have been extensively evaluated in clinical trials [Beatty, 2017; Uger, 2020] but there are no current regulatory approvals for agents targeting either axis. There are currently no reported multitargeted agents or trials for CD47 inhibitors in combination with CD40 agonists.

Encouraging preliminary anti-tumor activity has been observed in patients with hematologic malignancies and solid tumors receiving CD47 blockade alone as well as in combination with agents that provide additional 'eat me' signals (rituximab, trastuzumab, azacitidine) and the T-cell checkpoint inhibitor pembrolizumab [Uger, 2020]. The most advanced development program is for Hu5F9-G4 (5F9), a high affinity humanized IgG4 anti-CD47 antibody, that is administered IV with a 1 mg/kg priming dose followed by weekly maintenance doses up to 45 mg/kg [Sikic, 2019]. The unique dosing regimen minimizes red blood cell (RBC) toxicity by selectively clearing aging RBCs, which results in a mild and transient anemia. Pooled efficacy results from Phase 1b/2 of 5F9 and rituximab (n = 75) indicate an objective response rate (ORR) of 49% and a complete response (CR) rate of 21% [R. Advani, 2018; R. Bartlett Advani, N.L. Smith, S.M. et al. , 2019]. These response rates are likely higher than those achievable with rituximab alone in this patient population as the majority have previously failed a prior rituximab-containing regimen. 5F9 in combination with azacitidine, a demethylating agent that upregulates calreticulin expression on tumor cells, is also showing clinical promise, with an ORR of 100% in untreated myelodysplastic syndromes (MDS) patients (n = 11, 55% CR rate), and 64% in untreated acute myeloid leukemia (AML) patients (n = 14) [Sallman, 2019]. The combination appears to compare favorably with historical data from azacitidine monotherapy. As a monotherapy, 5F9 has shown relatively low response rates: 10% in relapsed/refractory AML/MDS patients and 5% in solid tumors.

Several different CD40 agonistic antibodies have been studied in early phase trials [Beatty, 2017]. Sporadic responses in solid and hematologic malignancies including renal cell cancer, melanoma, diffuse large B cell lymphoma and Hodgkin's lymphoma have been noted with monotherapy CD40 agonists. However, a critical component that is believed to mediate the anti-tumor effect is the presence of tumor antigen, which is necessary for CD40-activated APCs to induce antigen-specific T cell adaptive immunity. This is the hypothesis for several other ongoing clinical trials combining CD40 agonists with vaccines and chemotherapy.

The mechanism of action of SL-172154 is designed to pair the costimulatory role of CD40L in augmenting the antigen cross-presenting ability of DCs with the increased phagocytic activity of macrophages through CD47-SIRPα binding. Importantly, because the ECDs of SIRPα and CD40L are physically linked to one another and localized to the TME, APCs and tumor cells receive these signals in a spatiotemporally coordinated manner, potentially leading to more potent and durable anti-tumor response. This FIH, Phase 1 clinical trial of SL-172154 is designed to evaluate the safety and tolerability of SL-172154 monotherapy. Secondary endpoint measures include determination of a RP2D and schedule for monotherapy dosing, assessment of the PK and pharmacodynamic effects of SL-172154, and a preliminary description of anti-tumor activity. Subjects with platinum-ineligible ovarian, fallopian tube, and primary peritoneal cancers are eligible for enrollment.

2. STUDY OBJECTIVES AND OUTCOME MEASURES

Primary Objective(s)	Outcome Measures
To evaluate the safety and tolerability of SL-172154 and to identify the maximum tolerated dose (MTD) or maximum administered dose (MAD) of SL-172154 in subjects with platinum-ineligible ovarian, fallopian tube, and primary peritoneal cancers	▪ Safety/tolerability outcomes include: incidence of all adverse events (AEs) and immune-related adverse events (irAE), serious adverse events (SAEs), fatal SAEs, dose limiting toxicity (DLT), AEs and irAEs leading to discontinuation, and changes in safety assessments (e.g., laboratory parameters, vital signs etc.) per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE – version 5.0). ▪ The MTD is defined based on the rate of DLTs and the MAD is the highest dose administered.
Secondary Objectives	**Outcome Measures**
To select the recommended Phase 2 dose (RP2D) for SL-172154.	▪ Based on review of all data collected during dose escalation, dose expansion, and pharmacodynamic cohorts including safety, tolerability, pharmacokinetics (PK), anti-tumor activity, and pharmacodynamic effects.
To assess preliminary evidence of anti-tumor activity of SL-172154	Disease assessment per investigator assessment according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). ▪ Objective response rate (ORR) (proportion of subjects whose best response is a complete response [CR] or partial response [PR]) ▪ Clinical benefit rate (CBR): proportion of subjects whose best overall response is a CR, PR or stable disease (SD) ≥ 16 weeks ▪ Time to response (TTR): time from the first dose until the first response (CR or PR, whichever is recorded first) that is subsequently confirmed ▪ Duration of response (DOR): time between first response (CR or PR, whichever is recorded first) that is subsequently confirmed and date of disease progression

Secondary Objectives	Outcome Measures
To evaluate immunogenicity to SL-172154 during and after treatment.	▪ Number/proportion of subjects with positive anti-drug antibody (ADA) titer ▪ ADA duration ▪ Transient vs. persistent ADA
To characterize the PK of SL-172154.	▪ Maximum observed concentration (Cmax) and time at which the maximum concentration is observed (Tmax) and minimum observed concentration (Cmin) following single and multiple doses of SL-172154 ▪ Area under the serum concentration-time curve (AUC) ▪ Terminal elimination half-life ($t_{½}$), Clearance (CL) and Volume of Distribution (Vz)
Exploratory Objectives	**Outcome Measures**
To assess target engagement of cluster of differentiation 40 (CD40) on peripheral blood mononuclear cells (PBMCs) prior to and following SL-172154 administration.	▪ Free/total receptor occupancy of CD40
To assess target engagement of CD47 on red blood cells (RBCs) and PBMCs prior to and following SL-172154 administration.	▪ Free/total receptor occupancy of CD47
To assess pharmacodynamic biomarkers in blood prior to, on-treatment and following SL-172154 administration.	Pharmacodynamic biomarkers in blood: ▪ Changes from baseline in cytokine/chemokine levels potentially including (but not confined to) interleukin (IL)-17α, interferon alpha (IFNα), tumor necrosis factor alpha (TNFα), IL-7, IL-8, IL-15, IL-10, IL-12p70, chemokine ligand CXCL9, CXCL10 ▪ Changes from baseline in cell counts and percentages of circulating immune cells including T cell subsets, B cell subsets, and myeloid cells ▪ Circulating immunoglobulin (Ig) levels ▪ Complement activation by assessment of SC5b-9 terminal fragment

Exploratory Objectives	Outcome Measures
To assess pharmacodynamic biomarkers in tumor tissue prior to, on-treatment and following SL-172154 administration.	Pharmacodynamic biomarkers in tumor tissue including: ▪ Changes in T cells subsets, B cell subsets and myeloid cells. ▪ CD47 and CD40 expression ▪ Programmed cell death ligand 1 (PD-L1) expression
To evaluate binding of SL-172154 to RBCs	▪ Presence of SL-172154 on RBCs
To estimate progression-free survival (PFS) and overall survival (OS)	▪ PFS based on investigator assessment: time from first dose to progression by RECIST v1.1 or death, whichever comes first ▪ OS: time from first dose to death
To evaluate efficacy using immune related response criteria.	▪ ORR, CBR, TTR, DOR and PFS based on investigator assessment per immune Response Evaluation Criteria (iRECIST)

3. STUDY DESIGN

3.1 Description of Study Design

This clinical trial is a FIH, open label, multi-center, dose escalation Phase 1 study of SL-172154 (see SCHEMA).

This Phase 1 trial is designed to evaluate the safety, PK, pharmacodynamic effects, and anti-tumor activity of SL-172154 monotherapy. Subjects with platinum-ineligible ovarian, fallopian tube, and primary peritoneal cancers (Section 4.1) are eligible for treatment.

Dose Escalation

Dose escalation will utilize the modified Toxicity Probability Interval (mTPI-2) design [Guo, 2017] with target DLT rate of 30% for the MTD. The dose escalation decision rules are outlined in Table 7 in Section 9.1. Subjects will be enrolled in cohorts of approximately 3 subjects into sequential dose levels of SL-172154 and evaluated for DLT (see Section 3.4 for Definition of DLT) during the 28-day DLT evaluation period starting from the first dose of SL-172154. At each dose level, a minimum 3-day stagger between dosing the first and second subject is required. The planned dose escalation is in half-log increments as outlined in Table 1 and Section 3.3. During dose escalation, two possible schedules (Schedule 1 and Schedule 2) for administration of SL-172154 may be explored as outlined in Section 3.3. Schedule 1 will be evaluated first. A transition to Schedule 2 may be implemented for reasons outlined in Section 3.2.1. If Schedule 2 is opened for enrollment, then enrollment on Schedule 1 will be halted. If Schedule 2 is opened, the Sponsor may also elect to stop enrollment in Schedule 2 early (e.g., based on safety) and resume enrollment in Schedule 1. The MTD or MAD may be determined for either Schedule 1 or Schedule 2. Alternatively, a less intensive dosing schedule may be instituted if safety, pharmacokinetic and/or pharmacodynamic data on Schedule 1 support less frequent dosing of SL-172154.

For each dose level evaluated on Schedule 1 or Schedule 2, the minimum number of subjects evaluable for DLT (see Section 9.2.1 for definition of DLT evaluable subject) will be 3 unless unacceptable toxicity is observed prior to enrollment of 3 subjects (e.g., the first 2 subjects experience a DLT before the third subject enrolls). The maximum number of subjects evaluable for DLT at a dose level will be 12 (e.g., this may be reached by sequential enrollment of 4 cohorts of 3 subjects) assuming the dose decision is to stay at the current dose from the first 3 cohorts. If the maximum of 12 DLT evaluable subjects at a given dose level is reached, a dose escalation decision will be made if ≤3 subjects experience a DLT (DLT rate ≤25%); and a dose de-escalation decision will be made if ≥4 subjects experience a DLT (DLT rate >=33%).

Note: Example scenarios for dose escalation per mTPI-2 dose decision rules are provided in Appendix 16.1.

During dose escalation, a review of available safety data for all subjects at a given dose level will be undertaken by the SMC approximately every four weeks and a decision made regarding the safety profile of that dose level.

Pharmacodynamic Cohorts
The Sponsor, in consultation with the SMC, may elect to open a pharmacodynamic cohort to obtain additional pharmacodynamic data from a total of approximately 6 additional subjects at one or more dose levels that have completed evaluation for safety without exceeding the MTD on the selected schedule. Subjects in the pharmacodynamic cohort must have tumor accessible for biopsy without excessive safety risk and must consent to providing paired biopsies for translational research. Subjects enrolled in the pharmacodynamic cohort will not inform dose escalation decisions but the pharmacodynamic information gathered from these additional subjects will inform selection of doses for further evaluation and the RP2D determination. Subjects in the pharmacodynamic cohort will be followed per the Schedule of Assessment (SOA) table provided in Section 6.

Dose Expansion
Approximately 6 subjects may be enrolled in the dose expansion cohort on a selected schedule. Subjects may be enrolled at one or more dose levels to further characterize safety, tolerability, PK, anti-tumor activity, and pharmacodynamic data to inform the selection of a RP2D. The number of subjects in dose expansion will vary depending on the number of subjects enrolled in both dose escalation and the pharmacodynamic cohort at a potential RP2D. The goal is to enroll approximately 6-12 subjects at the potential RP2D, including subjects in dose escalation, pharmacodynamic cohort, and dose expansion. Subjects enrolled in the dose expansion cohort(s) will be followed per the Schedule of Assessment (SOA) table provided in Section 6.

3.1.1 Selection of the Recommended Phase 2 dose

Selection of the RP2D and schedule for SL-172154 monotherapy will be based upon the totality of the data in subjects treated in dose escalation, dose expansion and pharmacodynamic cohorts. Approximately 6-12 subjects (inclusive of the subjects enrolled at this dose in the Dose Escalation, Pharmacodynamic cohort, and Dose Expansion) may be treated at the RP2D.

3.1.2 Sample Size

If only Schedule 1 is evaluated, the planned total sample size is 21 for dose escalation. If Schedule 1 and Schedule 2 are both fully evaluated in dose escalation, the maximum planned sample size for dose escalation is 42 This sample size assumes evaluation of approximately 21 subjects across 5 dose levels in dose escalation on Schedule 1 and 21 subjects across 5 dose levels on Schedule 2. Approximately 6 subjects may be enrolled in an optional pharmacodynamic cohort. After a dose and schedule are selected, approximately 6 subjects will be included in the dose expansion cohort. The number of subjects in dose expansion will vary depending on the number of subjects enrolled in both the dose escalation and pharmacodynamic cohorts at a potential RP2D. The goal is to enroll approximately 6-12 subjects at the potential RP2D, including subjects in the dose escalation, pharmacodynamic, and dose expansion cohorts. Overall, the total sample size estimate for this study is 33 subjects assuming only Schedule 1 is evaluated, and 54 subjects if both Schedule 1 and Schedule 2 are fully evaluated. See Section 9.1 for more details.

3.2 Justification for Starting Dose and Schedule of SL-172154

Analysis of available data support a starting dose of 0.1 mg/kg for the administration of SL-172154 to humans via IV infusion. The starting dose for the FIH clinical study of SL-172154 was determined based on MABEL principles, taking into account available preclinical pharmacology, toxicology, and pharmacokinetic data. The most sensitive in vitro measure of biological activity in response to SL-172154 exposure was the PBMC proliferation assay conducted in AIMV medium. Additional key data to support selection of the starting dose for the FIH study is data from cynomolgus monkey toxicology studies, including identifying the NOAEL, and the pharmacokinetic results.

The *in vitro* potency of SL-172154 in human PBMCs was estimated using the AIMV (Alstroemeria-Mosaic Virus) proliferation assay. PBMCs from humans and cynomolgus monkeys (9 donors/species) were exposed to increasing concentrations of SL-172154 (0 to 100 nM) for 7 days after which absorbance of each sample was measured at 490 nm as an index of cell proliferation. This study demonstrated a dose-dependent increase in proliferation in both humans and cynomolgus monkeys PBMCs. While human PBMCs were overall more sensitive, there was similarity in the degree of SL-172154-stimulated proliferation in humans and cynomolgus monkeys at both EC_{20} and EC_{50}. An EC_{20} value of 5.18 nM was calculated for human PBMC proliferation using a baseline Emax model. The human EC_{20} has been chosen as the target Cmax concentration benchmark for systemic exposure, consistent with the conclusion by Saber et al. that a starting dose of 10 to 30% pharmacologic activity was acceptable for CD3 targeted bispecific constructs [Saber, 2017].

In vivo monkey PK data from the GLP toxicology study [Report_SL2020IB001] were used to convert the target Cmax to a human equivalent dose (HED). In the monkey GLP toxicology study, a dose of 1 mg/kg was associated with a mean Cmax of 1230 ng/mL (13.96 nM, n=6 monkeys). Note that the lowest dose studied in the GLP study was 0.1 mg/kg; however, the Cmax was not well characterized as only two animals had measurable concentrations at this dose level. The non-quantifiable concentrations were likely due to the rapid clearance of SL-172154 from the serum. Potential explanations for rapid drug clearance include an antigen sink due to the ubiquitous expression of CD47 on peripheral blood cells (i.e., RBC, platelets, PBMC) and target-mediated uptake at early time points with trafficking of cells (e.g., PBMC) and bound drug to peripheral tissues. From Day 15 onwards, the removal of drug by anti-drug antibodies results in rapid

clearance. Assuming dose-proportionality, a dose of 0.4 mg/kg in the monkey is predicted to achieve the preliminary human target Cmax (5.18 nM). The 0.4 mg/kg dose level in monkeys was converted to a HED using a standard conversion factor of 0.32 [FDA, 2005]. The resultant preliminary starting dose for IV infusion of SL-172154 in humans is 0.1 mg/kg (0.4 mg/kg x 0.32).

The GLP study concluded that 1.0 mg/kg was considered to be NOAEL for IV infusion doses of SL-172154. Thus, the proposed SL-172154 starting dose of 0.1 mg/kg is $1/10^{th}$ the NOAEL dose of 1 mg/kg observed in cynomolgus monkeys and provides an appropriate safety margin for the FIH starting dose.

Justification for Schedule: A weekly dosing schedule for 5 consecutive weeks was implemented in the NHP studies. Toxicity was dose-dependent (only at the higher doses) and occurred at the third and subsequent doses. Receptor occupancy data from Day 1 (Dose 1) demonstrated that SL-172154 readily bound to its intended target in a dose-dependent manner, attaining >90% CD40 receptor occupancy on PBMCs and ~80% CD47 receptor occupancy on RBCs in the 10 and 40 mg/kg groups. Maximal occupancy for the CD47 receptor on RBCs was attained by 1 hour post-infusion and persisted through at least 168 hours. CD40 receptor occupancy was transient, likely influenced by endocytosis and migration of CD40+ cells to tissues including the spleen.

Based upon the durability of binding for SL-172154 to CD47, dosing for the clinical trial will begin by incorporating administration of SL-172154 on Schedule 1 on Day 1, 8, 15, and then every 2 weeks thereafter. The Day 8 dose was retained as no toxicity was observed at this time point, minimal pharmacodynamic effects were noted, and this dose may have contributed to the pharmacodynamic effect on day 15. In NHPs, multiple factors may have contributed to the onset of reactions at Day 15 including ADA, complement activation, margination of lymphocytes and cytokine elevations. It is unknown if these contributing factors would be observed in humans at the doses studied. Therefore, dosing on Day 1, 8, 15 is considered acceptable. The 2-week treatment free interval beyond Day 15 may allow for pharmacodynamic effects to subside between subsequent doses and to mitigate toxicity. A more or less intensive dosing schedule may be instituted if safety and pharmacodynamic data support more or less frequent dosing of SL-172154 (e.g., one dose given weekly on Schedule 2 or every two weeks or every 3 weeks or every 4 weeks).

3.2.1 Criteria for Decision to Transition from Schedule 1 to Schedule 2

Schedule 1 may be safe and tolerable, but pharmacodynamic effects may not be present or detectable, or pharmacokinetic parameters may suggest that a more frequent dosing schedule is warranted. In this event an alternative dosing schedule (i.e., Schedule 2; once weekly dosing over 28 days in each cycle) will be explored in lieu of Schedule 1. During dose escalation pharmacokinetic parameters will be analyzed by dose level and subjects will be monitored for pharmacodynamic effects pre- and post-dose. Dynamic changes that are anticipated following administration of pharmacologically active doses of SL-172154 include:

- Changes from baseline in cell counts and percentages of circulating immune cells including T cell subsets, B cell subsets, and myeloid cells
- Increase in cytokines/chemokines
- Changes in circulating immunoglobulins

- Free/Total receptor occupancy of CD47 and CD40
- Appearance of activation markers on the surface of CD4 lymphocytes and macrophages in the peripheral blood

The anticipated timing of pharmacodynamic effects based on NHP studies is at cycle 1, day 15 (C1D15) and beyond, although these effects may be observed as early as C1D1 and C1D8.

3.3 SL-172154 Dose Escalation Plan

Dose escalation will begin on Schedule 1 at the starting dose of 0.1 milligrams per kilogram (mg/kg) as outlined in Table 1 below. Intermediate or higher dose levels not shown may be explored based on emerging data (e.g., safety and pharmacodynamic data). Dose escalation of SL-172154 will not exceed half-log increments. The DLT assessment period is 28 days in length and ends 14 days after the last dose is administered in the first cycle on Schedule 1 and 7 days after the last dose is administered on Schedule 2. Dose escalation will follow the mTPI-2 decision rules outlined in Table 7 in Section 9.1.

- **Schedule 1 administration for SL-172154**: Given on days 1, 8, and 15 in cycle 1 over 28 days and then every two weeks thereafter on days 1 and day 15 in cycles ≥ 2 every 28 days.
- **Schedule 2 administration for SL-172154**: Given on days 1, 8, 15 and 22 of each 28-day cycle
- **Cycle length for Schedules 1 and 2**: 28 days
- **DLT assessment period for Schedules 1 and 2**: 28 days

Table 1: SL-172154 Dose Escalation Plan in Phase 1

Dose Level	IV Dose of SL-172154 (mg/kg)[a,b,c,d,e]	Duration of Infusion[d]
Level 1 - starting dose	0.1	30 minutes (+/- 10 minutes)
Level 2	0.3	30 minutes (+/- 10 minutes)
Level 3	1.0	30 minutes(+/- 10 minutes)
Level 4	3.0	60 minutes (+/- 15 minutes)
Level 5	10.0	60 minutes (+/- 15 minutes)

a) Dosing will begin on Schedule 1 with SL-172154 administered in 28-day cycles on days 1, 8, and 15 in cycle 1 and then on days 1 and 15 in cycles ≥ 2.

b) Dose escalation on Schedule 2 may be tested: If Schedule 2 is opened, SL-172154 may be administered once weekly on days 1, 8, 15, and 22 of each 28-day cycle.

c) Intermediate or higher dose levels may be tested based on emerging safety and pharmacodynamic data.

d) The actual body in kilograms (kg) will be used for dose calculation in all subjects who body weight is ≤100 kg. For subjects with body weight >100 kg, the dose to be administered should be the same as that calculated for a subject weighing 100 kg (see Section 5.1.4).

e) Infusion time may change based on final drug volume needed for administration, safety and tolerability of the infusion for the subject and/or observed safety findings during the study. Please refer to the Study Pharmacy Manual (SPM) for details.

Evaluation of an Alternative Dosing Schedule: Safety, pharmacokinetic and/or pharmacodynamic data from the dose escalation cohorts and pharmacodynamic cohorts, if available, may support exploration of a more or less intensive dosing schedule for SL-172154. If these data from Schedule 1 support exploration of more frequent dosing (see Section 3.2.1 for criteria needed to transition to Schedule 2), then cohort enrollment on Schedule 2 will be instituted in lieu of Schedule 1. The starting dose on Schedule 2 will be at a dose level that has completed evaluation for safety on Schedule 1 as defined by the mTPI-2 design. Dose escalation (or de-escalation) may then proceed on schedule 2 as shown in Table 1. During dosing on Schedule 2, SL-172154 will be administered once weekly (D1, D8, D15, and D22) every 28 days. If less frequent dosing is supported by safety, pharmacokinetic and/or pharmacodynamic data, SL-172154 may be administered once every two weeks, once every three weeks or once every four weeks. The starting dose on a less frequent schedule would be instituted at a dose level that has completed evaluation for safety as defined by the mTPI-2 design, emerging safety data and as recommended by the SMC.

3.3.1 Intrasubject Dose Escalation

Intrasubject dose escalation(s) may be considered on a case-by-case basis, provided that the subject has completed at least 2 cycles at the originally assigned dose, has tolerated treatment well, and experienced ≤ Grade 1 toxicity on the most recent cycle of SL-172154 therapy. A subject's dose may be increased to a dose level that has completed evaluation for safety and has not exceeded the MTD. Approval for intrasubject dose escalation must be obtained from the Sponsor Medical Monitor and must be documented on an Intrasubject Dose Escalation Decision Form provided by the Sponsor.

3.4 Definition of Dose-Limiting Toxicity

DLTs are as defined in the bulleted points below. Toxicities will be graded as per National Cancer Institute Common Terminology Criteria for Adverse Events version 5 (NCI CTCAE v5). The determinate period for DLT is the first 28 days of SL-172154 dosing on Schedule 1 or Schedule 2. **Note**: AEs clearly related to disease progression or intercurrent illness are not considered DLTs. Inflammatory reactions attributable to local anti-tumor responses (e.g., severe pain) are not considered DLTs.

- Any death not clearly related to underlying disease or extraneous causes
- Any ≥ Grade 4 AE
- Elevations in liver transaminases (aspartate aminotransferase [AST], alanine aminotransferase [ALT]) and/or total bilirubin:
    - In subjects who enroll with AST/ALT/total bilirubin ≤ upper limit of normal (ULN); AST or ALT elevation of >8 x ULN **or** total bilirubin > 5 x ULN
    - In subjects who enroll with AST/ALT/total bilirubin > ULN; AST or ALT elevation of >8 x baseline **or** total bilirubin > 5 x baseline
    - Evidence of Hy's Law (AST or ALT > 3 x ULN [or baseline*] with concurrent increase in total bilirubin > 2 x ULN [or baseline*] without evidence of cholestasis or alternative explanation such as disease progression or viral hepatitis; *ULN or baseline dependent on value at enrollment as described above.
- Any AE that requires permanent discontinuation of SL-172154
- Any Grade 3 or greater AE **except** for those listed below:
    - Grade 3 fatigue lasting ≤ 7 days
    - Grade 3 anemia
    - Grade 3 or 4 neutropenia not associated with fever that improves to Grade 2 within 7 days.
    - Grade 3 or 4 lymphopenia
    - Grade 3 thrombocytopenia not associated with clinically significant bleeding and does not require medical intervention
    - Grade 3 electrolyte abnormalities that are not associated with clinical signs/symptoms and are reversed with appropriate medical intervention
    - Grade 3 laboratory abnormalities that are not deemed clinically significant by the SMC.
    - Indirect/unconjugated hyperbilirubinemia without significant clinical consequences
    - Grade 3 or 4 amylase and/or lipase abnormalities that are not associated with clinical signs/symptoms or findings on imaging consistent with pancreatitis
    - Grade 3 vomiting and/or Grade 3 nausea that resolves within 72 hours with appropriate clinical management
    - Grade 3 hypertension that can be controlled (i.e., systolic BP < 140 mmHg and diastolic BP < 90 mmHg) with medical therapy.
    - Grade 3 endocrine disorder (thyroid, pituitary, hyperglycemia and/or adrenal insufficiency) that is managed with treatment with resolution of symptoms within 14 days after treatment onset.
    - Grade 3 diarrhea with no evidence of colitis that resolves within 72 hours with appropriate clinical management
    - Vitiligo or alopecia of any grade
- Other AEs may be considered a DLT as determined by the investigator in conjunction with the SMC.

A Grade ≥ 3 AE(s) that occurs beyond the DLT period or Grade 2 events that require continuous interruption of SL-172154 for more than 6 weeks or AEs that result in subjects not receiving at least 2 of the 3 scheduled doses of SL-172154 on Schedule 1 (or at least 2 of the 4 scheduled doses of SL-172154 on Schedule 2) during the DLT assessment period due to AE(s) may be taken into consideration when assessing the totality of the data in determining DLT and the RP2D.

3.5 Concomitant Medications, Treatments, and Procedures

Investigators may prescribe concomitant medications or treatments deemed necessary to provide supportive care except for prohibited medications (see Section 3.5.1). Best supportive care should be provided when necessary for all subjects (including antibiotics, bisphosphonates, receptor activator of nuclear factor kappa B ligand (RANKL) inhibitors, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management including palliative radiotherapy after consultation with the Sponsor Medical Monitor.

Use of inhaled, topical, intranasal corticosteroids or local steroid injections (e.g., intra-articular injection) is permitted. Temporary use of corticosteroids (e.g., prior to computed tomography [CT] to prevent contrast allergies) is acceptable after consultation with the Sponsor Medical Monitor.

3.5.1 Prohibited Medications/Treatments

Subjects must be instructed not to take any medications, including over-the-counter products without first consulting with the investigator. The following medications are prohibited during SL-172154 therapy:

- Any investigational anti-cancer therapy not described in this protocol
- Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy after consultation with the Sponsor Medical Monitor), hormonal or hormonal suppression therapy for anti-cancer intent, immunotherapy, or biologic therapy for cancer treatment
- Immunosuppressive medications for primary prophylaxis against IRRs are not permitted. Subjects who require immunosuppressive medications (e.g., corticosteroids) for management of irAEs or IRRs should be managed per Toxicity Management Guidelines in Section 3.6.
- Live attenuated vaccines during the study through 30 days after the last dose of SL-172154

3.5.2 Medications to be used with Caution

SL-172154 is a therapeutic protein that may induce the transient release of cytokines including IL-6 which in turn, may inhibit the activity of cytochrome P450 (CYP450) enzymes including CYP3A4 activity [Evers, 2013]. Although not tested clinically, a drug-drug interaction may occur with the coadministration of medications that are CYP450 substrates. Drugs metabolized by CYP450 enzymes may have reduced clearance or an increase in half-life or peak plasma concentration and should be used with caution. There may be an increased risk of side effects for drugs that are CYP450 substrates. Where possible consider substitutions for these medicinal products if therapeutic effects cannot be monitored.

A complete list of drugs that are CYP450 substrates including CYP3A4 substrates is available at: https://drug-interactions.medicine.iu.edu/Main-Table.aspx (Flockhart Table).

3.6 Toxicity Management Guidelines Dosing Delays/Dose Modifications

No dose reductions are permitted for SL-172154. The toxicity guidelines provided in this section represent general guidance for AEs that are considered by the investigator to be related to treatment with SL-172154. All AEs should be assessed using NCI-CTCAE v5.0 criteria. These guidelines are not meant to be prescriptive and investigators should always use clinical judgement in the determination of dosing. Investigators should always err on the side of caution if treatment-related toxicity is suspected. Subjects should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections). In the absence of a clear alternative etiology, all events should be considered potentially immune related.

Please see Section 5.1.5 Monitoring Dose Administration for further information on SL-172154.

NOTE: Hereafter in this section and in subsequent sections, SL-172154 monotherapy may be referred to as SL-172154 or as IP.

Differentiating between IRRs that are due to either the common non-allergic hypersensitivity reactions [HSRs (e.g., CRS)] or the rarer allergic HSRs can be challenging due to overlapping clinical manifestations. There are no specific clinical features (including symptoms and timing of reaction) that can absolutely distinguish between these two entities. General guidance is provided below for IRRs secondary to both allergic and non-allergic HSRs e.g., CRS. These guidelines are not meant to be prescriptive. Established institutional guidelines should be followed where appropriate. At the resolution of the event, the entirety of the data including clinical symptoms, response to treatment and laboratory studies should be re-evaluated to determine the final etiology of the event. For purposes of standardized reporting, utilize terms based on best medical judgement of the AE/SAE and the definition found in NCI-CTCAE v5.0 for IRR, allergic reaction, anaphylaxis, and CRS.

Discretionary use of primary prophylaxis for IRR prevention for subjects enrolled at 3 mg/kg or less is permitted. However, as noted in Section 3.6.1, secondary prophylaxis (i.e., prevention of IRRs following an initial episode) for these subjects is appropriate and permitted at the discretion of the investigator for all dose levels. Primary prophylaxis for IRR prevention is required with each SL-172154 administration for subjects enrolled at 10mg/kg or higher dose levels. See Section 5.1.2.3 for details regarding the primary prophylaxis medications.

NOTE: In the event of a Grade ≥ 2 IRR, subjects will be observed on-site or hospitalized for close observation until resolution of symptoms as per Table 3.6.1.

3.6.1 Management of Infusion-related Reactions

<table>
<tr><th>Adverse Event</th><th colspan="2">General Guidance for Infusion-related Reactions (IRRs) [Rosello, 2017; Porter, 2018]</th></tr>
<tr><td rowspan="5">Infusion or Hypersensitivity Reactions</td><td colspan="2">Acute reactions to the IV administration of biologic agents are not uncommon. Reactions are either allergic reactions to foreign proteins or non-immune reactions. The term HSR is used to describe objectively reproducible signs or symptoms initiated by exposure to a defined stimulus at dose tolerated by a normal person. Allergy is an HSR initiated by specific immunological mechanisms. Anaphylaxis is a severe, life threatening HSR. CRS consists of a non-allergic, cytokine mediated HSR. Differentiation between the common non-allergic HSR reactions and the rarer allergic HSR reactions can be challenging due to overlapping clinical manifestations. Fever, chills, rigors, headache, arthralgias, back pain, abdominal pain, nausea, vomiting, diarrhea, dyspnea, flushing, pruritus, and changes in heart rate and blood pressure are manifestations of common acute infusion reactions. Proinflammatory cytokines such as TNF-α and IL-6 may play a role in these reactions. Symptoms more suggestive of allergic HSR include generalized pruritus, urticaria, wheezing, frequent coughing, and anaphylactic symptoms. Subjects must be monitored for signs and symptoms of IRRs with prompt institution of treatment. Subjects should be notified that symptoms may occur during the first infusion and for up to several hours afterwards or with subsequent infusions. Instruct subjects to contact their physician if symptoms or signs of an IRR occur.</td></tr>
<tr><td>Severity (Symptoms)</td><td>Management</td></tr>
<tr><td>Grade 1</td><td>• Infusion interruption not indicated.
• Monitor subjects with close observation in an outpatient or inpatient setting for a minimum of 12 hours or until recovery from symptoms
• Consider pre-medication (antipyretics, histamine (H1 and H2 antihistamines), leukotriene inhibitors, corticosteroids) for subsequent infusions per investigator/institutional guidelines if pre-medications are not already required.</td></tr>
<tr><td>Grade 2</td><td>• Temporarily interrupt SL-172154 or decrease the rate of the infusion by 50%.
• Begin IV infusion of normal saline and treat with antipyretics, histamine 1 and 2 (H1 and H2) antihistamines, and leukotriene inhibitor. Corticosteroids and/or bronchodilator therapy may also be administered as appropriate. Consider opioids (e.g., meperidine) for rigors.
• Monitor subjects with close observation in an outpatient or inpatient setting for a minimum of 12 hours or until recovery from symptoms. Consider admission to hospital.
• If the infusion is interrupted, then restart the infusion at no more than 50% of the rate at which the reaction symptoms occurred. For subsequent infusions, consider starting infusion at 50% rate at which the symptoms occurred and titrate to tolerance.
• If symptoms recur, then no further SL-172154 will be administered at this visit.
• The following prophylactic pre-medications are recommended for future infusions: antipyretics, antihistamines with/without corticosteroids per institutional guidelines</td></tr>
<tr><td>Grade 3</td><td>• Immediately discontinue infusion of SL-172154
• Begin IV infusion of normal saline and treat with epinephrine, bronchodilators, diphenhydramine, ranitidine, corticosteroids, oxygen, fluids, vasopressors, etc. and consider opioids (e.g., meperidine) for rigors. as indicated and per institutional guidelines. Epinephrine is the drug of choice in an anaphylactic reaction and its administration should not be delayed.
• Monitor subjects with close observation in an outpatient or inpatient setting for a minimum of 12 hours or until recovery from symptoms. Consider admission to hospital.
• Rechallenge should not be attempted in cases of true anaphylaxis. In other cases, once subject has completely recovered, carefully consider if it is safe for the subject to receive SL-172154 at the next scheduled dose with pre-medication (e.g., corticosteroids, antihistamines, antipyretics) and slow infusion (≤ 50% of the rate at which the reaction occurred). The next two subsequent infusions of SL-172154 (after an event of grade 3 event of infusion-related reaction) must be administered in an inpatient or outpatient setting with prolonged observation for a minimum of 12 hours after the completion of the infusion. Start infusion at 50% rate at which the symptoms occurred. If no further symptoms, rate may be escalated at intervals and increments as clinically appropriate. If symptoms recur, permanently discontinue SL-172154.</td></tr>
</table>

Infusion or hypersensitivity reactions (continued from previous page)	**Severity (Symptoms)**	**Management**
	Grade 4	• Permanently discontinue SL-172154. • Admit to hospital for close observation until resolution of symptoms • Manage severe IRRs per institutional standards (e.g., epinephrine, diphenhydramine, ranitidine, corticosteroids, bronchodilators, oxygen, fluids, etc. and consider opioids (e.g., meperidine) for rigors. Epinephrine is the drug of choice in an anaphylactic reaction and its administration should not be delayed
Adverse Event	**General Guidance for Cytokine Release Syndrome (CRS)** [Rosello, 2017; Porter, 2018]	
Cytokine-release Syndrome	CRS is a non-antigen specific, systemic inflammatory response that occurs as result of high-level immune activation with concomitant elevations of cytokines (e.g., IL-6, IL-10, TNF-α, IL-2, IFNɣ). Clinical features of the syndrome include (but are not confined to) fever, flu-like symptoms, rash, nausea, vomiting, diarrhea, hypotension, tachypnea, transaminitis, hypofibrinogenemia, elevation in D-dimer, hyperbilirubinemia, azotemia, neurologic manifestations. The syndrome can progress to life-threatening capillary leak, hypoxic respiratory failure, vasodilatory shock and end-organ dysfunction. **NOTE:** CRS may have a similar presentation to a type 1 HSR and may be clinically indistinguishable.	
	Severity (symptoms)	**Management**
	Grade 1	• Consider decreasing the rate of the infusion of SL-172154 by 50%, until resolution of the event • Monitor subjects with close observation in an outpatient or inpatient setting for a minimum of 12 hours or until recovery from symptoms. • Maintain IV access. Symptomatic treatment with antipyretics, antiemetics, analgesics, histamine 1/histamine 2 (H1/H2) antihistamines as needed; monitor fluid balance; assess for infection. Consider opioids (e.g., meperidine) for rigors. Regularly evaluate for signs of further deterioration • For subsequent infusions, consider pre-medication (e.g., antipyretics, antihistamines) per institutional guidelines
	Grade 2	• Interrupt SL-172154 • Start IV infusion with normal saline. Administer oxygen if needed. Treat with antipyretics, H1/H2 antagonists (diphenhydramine 50 mg IV plus ranitidine 50 mg IV), and/or methylprednisolone 1-2 mg/kg or equivalent dose of corticosteroid every 6 hours and manage per institutional guidelines. Consider opioids (e.g., meperidine) for rigors. Closely monitor cardiac and other organ functions. • Monitor subjects with close observation in an outpatient or inpatient setting for a minimum of 12 hours or until recovery from symptoms. Consider admission to hospital for management of symptoms, organ dysfunction or administration of therapy • The next two subsequent infusions of SL-172154 (after an event of grade 2 CRS) must be administered in an inpatient or outpatient setting with prolonged observation for a minimum of 12 hours after the completion of the infusion. • For subsequent infusions, start infusion at 50% rate at which the symptoms occurred and titrate to tolerance. Pre-medicate with dexamethasone 20 mg, antipyretics, H1/H2 antihistamines, and manage per institutional guidelines. • Subjects with extensive comorbidities or those of older age should be treated as for Grade 3. Subjects with worsening symptoms should be treated as for Grade 3

Adverse Event	Severity (Symptoms)	Management
Cytokine-release Syndrome (continued from previous page)	Grade 3 or 4	• Interrupt SL-172154 • Hospitalization required for management of symptoms related to organ dysfunction: admit to the hospital and potentially the intensive care unit or equivalent for close monitoring and management • Treat hypotension with IV fluid for blood pressure support and/or pressers. Administer oxygen for treatment of hypoxia. Cryoprecipitate or fresh frozen plasma may be required for coagulopathy. Manage per institutional guidelines. • Manage severe IRRs and CRS per institutional standards (e.g., epinephrine, diphenhydramine, ranitidine, corticosteroids, bronchodilators, oxygen, fluids, meperidine for rigors, etc.). Epinephrine is the drug of choice in an anaphylactic reaction and its administration should not be delayed • Administer tocilizumab at a dose of 8 mg/kg. If clinical improvement does not occur within 24 hours, administer a second dose of tocilizumab. • Second-line therapies: o Methylprednisolone 2 mg/kg/day IV tapered over several days. For subjects with severe neurologic symptoms, consider using dexamethasone due to more efficient penetration of the blood-brain barrier. o anti-TNF-α mAbs (infliximab) or soluble TNF-α receptor (etanercept), or IL-1R-based inhibitors (anakinra). • For Grade 3 CRS, may consider rechallenge after consultation with medical monitor. If rechallenge is given: o The next two subsequent infusions of SL-172154 (after an event of grade 2 CRS) must be administered in an inpatient or outpatient setting with prolonged observation for a minimum of 12 hours after the completion of the infusion. o Start infusion at 50% rate at which the symptoms occurred. If no further symptoms, rate may be escalated at intervals and increments as clinically appropriate. o After a Grade 3 CRS event, subjects must be premedicated with high dose steroids prior to the next infusion of SL-172154. o If there is no evidence of CRS with the subsequent infusion, premedication with high dose steroids may be omitted for subsequent infusions. o Any patient that experiences recurrence of Grade 3 CRS following re-treatment must be permanently discontinued from study treatment. • For Grade 4 CRS, permanently discontinue SL-172154.

3.6.2 Management of Immune-related Reactions

<table>
<tr><th>Adverse Event</th><th colspan="2">General Guidance for Management of Immune-related Adverse Events (irAEs) [Haanen, 2017; Puzanov, 2017; Brahmer, 2018]</th></tr>
<tr><td rowspan="5">irAEs - General</td><td colspan="2">Guidelines for management of irAEs across body systems are outlined in this section. These guidelines are not meant to be prescriptive. Established institutional guidelines should be followed where appropriate. Severity of irAE are categorized according to NCI CTCAEv5. Limitations of classification and grading by CTCAEv5 for specific irAEs may be encountered. Based on the severity of the irAE, SL-172154 may either be continued, held or permanently discontinued. Management relies heavily on corticosteroids and other immunomodulatory agents. Generally, the decision on IP and institution of immunosuppressive therapy (corticosteroid therapy) can be approached as noted below. However, treatment should be individualized depending on the subject's medical history, the nature and severity of the AE, co-morbidities, and ability to tolerate corticosteroids. When starting corticosteroid therapy, consider initiating proton pump inhibitors for gastrointestinal (GI) toxicity prophylaxis. Once toxicity has improved to ≤ Grade 1 AE, start tapering corticosteroid therapy over a 4 to 6-week period. Add pneumocystis pneumonia prophylaxis (cotrimoxazole or inhaled pentamidine if cotrimoxazole allergy) if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent). Consider calcium & vitamin D supplementation as per local guidelines.</td></tr>
<tr><td>Severity (Symptoms)</td><td>Management</td></tr>
<tr><td>Grade 1</td><td>• SL-172154 is continued, and treatment with corticosteroids is usually not indicated</td></tr>
<tr><td>Grade 2</td><td>• SL-172154 may be continued.
• Depending on the nature of the AE, corticosteroids may be indicated.
• Start with oral prednisone 0.5-1 mg/kg/day. SL-172154 is generally held during corticosteroid therapy and until irAE has resolved to ≤ Grade 1 and corticosteroids have been tapered to ≤ prednisone 10 mg/day (or equivalent) or discontinued.
• If IV therapy is required, use methylprednisolone 0.5 – 1 mg/kg/day. If no improvement in symptoms, the dose may be increased to 2 mg/kg/day.</td></tr>
<tr><td>Grade 3</td><td>• Hold SL-172154.
• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone).
• If no improvement, consider adding alternative immune suppressant therapy.</td></tr>
<tr><td>Grade 4</td><td>• Permanently discontinue SL-172154 and start IV methylprednisolone 1-2 mg/kg/day.
• If no improvement, consider adding alternative immunosuppressant.</td></tr>
</table>

Adverse Event	General Guidance for Hepatotoxicity	
Hepatotoxicity	Monitor signs, symptoms and laboratory evidence of liver dysfunction. Evaluate alternative etiologies: review medications for hepatotoxic drugs and alcohol history; perform liver screen: hepatitis A, B, C serology, hepatitis E PCR, antinuclear antibody (ANA)/smooth muscle antibody/liver kidney microsomal antibodies /soluble liver antibody/liver-pancreas antigen/liver cytosol iatrogene antibodies, iron studies. Consider imaging for progressive disease/thrombosis. Guidelines are based on elevations in ALT, AST and bilirubin per CTCAEv5. Discontinue SL-172154 for Hy's law as follows: in subjects who enroll with AST/ALT/total bilirubin≤ ULN who experience concomitant AST or ALT > 3 x ULN and total bilirubin > 2 x ULN; or in subjects who enroll with AST/ALT/total bilirubin > ULN who experience concomitant AST or ALT > 3 x baseline and total bilirubin > 2 x baseline.	
	Severity (Symptoms)	**Management**
	Grade 1	• Continue SL-172154 with close monitoring. • Monitor liver function at least weekly; if liver function is stable, reduce frequency of blood tests.
	Grade 2	• Hold SL-172154. • Assessments as above; monitor liver function ~every 3 days • Consider hepatology consult and liver biopsy is optional. • If persistent or rising liver chemistries or significant clinical symptoms and an immune etiology is suspected, start oral prednisone 0.5-1 mg/kg/day (or equivalent of methylprednisolone) with 4-week taper. • Resume SL-172154 when toxicity ≤ G1 and corticosteroid taper to ≤ 10 mg/day prednisone or equivalent.
	Grade 3	• Grade 3: hold SL-172154. • Permanently discontinue SL-172154 for liver function test abnormality that meets following criteria in subjects who enroll with AST/ALT/total bilirubin ≤ ULN: AST or ALT > 8 x ULN **or** total bilirubin > 5 x ULN • Permanently discontinue SL-172154 for liver function test abnormality that meets following criteria in subjects who enroll with AST/ALT/total bilirubin > ULN: AST or ALT > 8 x baseline **or** total bilirubin > 5 x baseline. • If persistent or rising liver chemistries, or significant clinical symptoms and an immune etiology is suspected, start oral prednisone 0.5-1 mg/kg/day (or equivalent of methylprednisolone) with 4-week taper. Obtain hepatology consult and assessments as above, monitor liver function daily; consider liver biopsy. • Other Grade 3 laboratory abnormalities: re-challenge may be considered only after consultation with hepatologist.
	Grade 4	• Grade 4: permanently discontinue SL-172154. • Consider hospitalization; obtain hepatology consult; assessments as above; monitor liver function daily; consider liver biopsy. • If an immune etiology is suspected, immediately start methylprednisolone 1-2 mg/kg (start with 2 mg/kg for Grade 4) or equivalent. • If refractory after 3 days, consider mycophenolate mofetil (MMF). Avoid the use of infliximab in immune mediated hepatitis.

Adverse Event	General Guidance for Hematologic Toxicity	
Anemia	Subjects with cancer can have multiple causes of cytopenias and thus blood counts must be monitored carefully. SL-172154 does exhibit binding to white blood cells (WBCs), red blood cells (RBCs) and platelets in non-human primate studies, but there was no evidence of neutropenia, anemia, hemagglutination, RBC destruction or clinically significant thrombocytopenia. However, in the event of anemia, it is important to use physical exams, complete blood counts (CBCs), serum chemistries, D-dimer testing and review of peripheral smears to look for evidence of RBC agglutination, microangiopathy, spherocytosis, and evidence of RBC destruction (e.g., schistocytosis, fragments). A hematologic AE needs to be distinguished from transient changes in laboratory values that can occur during initiation of an immune response (e.g., lymphopenia, lymphocytosis, eosinophilia, neutrophilia, monocytosis can be observed following treatment). Development of persistent or progressive cytopenias should prompt evaluation of potential causes. In cases where an obvious cause cannot be identified, an autoimmune cause should be considered and investigated accordingly. Since the CTCAE definition of thrombocytopenia describes absolute platelet levels rather than a change in cell number, it is not a reliable tool for evaluating potentially life-threatening cytopenias. Drug binding to CD47 on RBCs may result in interference with standard serologic techniques for blood compatibility testing (Section 6.4.6.3).	
	Severity (Symptoms)	**Management**
	Grade 1	• Continue SL-172154 with close clinical follow-up and laboratory evaluation
	Grade 2	• Consider holding SL-172154 until AE has reverted to Grade 1 or baseline. • Consider hematology consult • Repeat type and screen and DAT • Transfusion per existing guidelines (minimum number of units to relieve symptoms of anemia or to return subject to safe hemoglobin (Hgb) range), folic acid supplementation.
	Grade 3	• Hold SL-172154 until AE has reverted to Grade 1 or baseline. • Repeat type and screen and DAT • Hematology consult, consider hospitalization, transfusion per existing guidelines (minimum number of units to relieve symptoms of anemia or to return subject to safe Hgb range), folic acid supplementation.
	Grade 4	• Permanently discontinue SL-172154. • If evidence of an immune-mediated etiology, give prednisone 1-2 mg/kg/day; if no improvement on or if worsening on corticosteroids or severe symptoms on presentation, initiate other immunosuppressive drugs, such as rituximab, IVIG, cyclosporine, infliximab, MMF, anti-thymocyte globulin. • Hospitalize; hematology consult; transfuse per existing guidelines.
Thrombocytopenia	**Severity (Symptoms)**	**Management**
	Grade 1	• Continue SL-172154 with close clinical follow-up and laboratory evaluation.
	Grade 2	• Consider holding SL-172154 until AE has reverted to Grade 1 or baseline. • Consider Hematology Consult

	Severity (Symptoms)	Management
Thrombocytopenia (continued from previous page)	Grade 3 or 4	• Hold SL-172154 until AE has reverted to Grade 1 or baseline. • Hematology consult. • If evidence of an immune-mediated etiology, give prednisone 1-2 mg/kg/day or equivalent. • IVIG 1 g/kg may be used with corticosteroids when a more rapid increase in platelet count is required. This dosage may be repeated if necessary. • If treatment with corticosteroids and/or IVIG has been unsuccessful, subsequent treatment may include rituximab, thrombopoietin receptor agonists, or more potent immunosuppression

3.6.3 Management of Other AEs Not Specified

Severity (Symptoms)	Dose Modification	Toxicity Management
Any Grade	**Note:** Dose modifications are not required for AEs not deemed to be related to SL-172154 (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	• Treat accordingly, as per institutional standard
Grade 1	No dose modifications	• Treat accordingly, as per institutional standard
Grade 2	Consider holding SL-172154 until resolution to ≤Grade 1 or baseline.	• Treat accordingly, as per institutional standard
Grade 3	Hold SL-172154 until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume SL-172154. Otherwise, discontinue SL-172154. (**Note**: For Grade 3 labs, decision to hold should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor).	• Treat accordingly, as per institutional standard
Grade 4	Discontinue SL-172154. (**Note**: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor).	• Treat accordingly, as per institutional standard

(Reference: American Society of Clinical Oncology Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD.)

3.7 Discontinuation of Study Therapy

SL-172154 should be discontinued by the investigator when a subject meets one of the conditions requiring discontinuation outlined in Section 3.6. The investigator may, however, elect to discontinue SL-172154 for an AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents substantial clinical risk to the subject with continued dosing. If study therapy is permanently discontinued for reasons other than progressive disease or withdrawal of consent, the subject will remain in the study to be evaluated for disease progression. See the SOA in Section 6 for data to be collected at the time of discontinuation of SL-172154.

3.8 Antibody Detection and Compatibility Testing for Transfusion

SL-172154 binds to red cells and may obscure the assessment of ABO red blood cell phenotyping. There is also a possibility that treatment with SL-172154 may interfere with compatibility tests, including the antibody screen and crossmatch that are part of a routine pre-transfusion work up [Report_SL2020IB001].

At screening, before exposure to SL-172154, all subjects must have:

- ABO and D group (ABO/Rh) type and antibody screen and antibody identification if required
- Direct antiglobulin test (DAT)
- Phenotype/genotype for, at a minimum, the minor antigens Rh C/c E/e, K, Jk, Fy and MNSs.
- Inform the blood bank that the subject is to commence SL-172154.

Determining this extended RBC phenotype prior to exposure to SL-172154 will facilitate and allow the option of selecting extended antigen-matched RBCs should a blood transfusion be warranted, and compatibility not be able to be demonstrated due to drug interference.

After exposure to SL-172154:

In subjects who may/do require RBC transfusion after SL-172154 therapy has commenced, it is recommended that an ABO/D type, antibody screen, and auto control and/or DAT be performed as per routine testing methods.

Following guidance of the local Transfusion Service Medical Director (or equivalent person) and the Transfusion Service standard operating procedures the following considerations may apply if interference with testing is seen:

- If the ABO group cannot be concluded from the forward and reverse typing, a decision may be made to transfuse based on the RBC ABO forward type only, provided it is concordant with the ABO record pre-therapy, or alternatively group O red cells may be used for transfusion.
- Differential adsorption may allow valid reverse type and antibody screening.
- Performing an eluate on a DAT+ sample should follow local standard operation procedure.
- For emergency transfusions, the transfusion laboratory may consider using Group O or ABO type specific units if time permits, without consideration of extended phenotype if units are not available.

- For elective red cell transfusions when the crossmatch is incompatible, leukocyte-reduced units matched for the extended phenotype of the patient (as described above) will be used, i.e. the patient will receive units negative for the antigens that he/she lacks.
- Where matching for all specified blood groups is not possible (e.g., for MNS), local sites will decide on the best matched donor units to be used.

Plasma therapy will be blood-type specific. Platelets will be blood type compatible whenever possible, and if not, will have been tested and found not to have high titer anti-A or anti-B.

3.9 Criteria to Resume Treatment

A participant may resume SL-172154 as outlined in Section 3.6. If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time point per protocol.

3.10 Participant Withdrawal of Consent

- A participant may withdraw from the study at any time at his/her own request; or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of withdrawal of consent, an early discontinuation visit should be conducted, as shown in the SOA in Section 6. See SOA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the IP and from the study at that time. Every effort must be made to continue follow-up of participants for protocol-specified safety follow-up procedures to capture AEs, SAEs, and unanticipated problems (UPs).
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

3.11 Lost to Follow-up

- A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.
- The following actions must be taken if a participant fails to return to the clinic for a required study visit:
    - The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
    - Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter sent to the participant's last known mailing

address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered as lost to follow up and withdrawn from the study.

3.12 Premature Termination or Suspension of Study

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason. Written notification, documenting the reason for study suspension or termination, will be provided by the Sponsor to investigators, the Food and Drug Administration (FDA) and the European Medicines Agency and other regulatory authorities. If the study is prematurely terminated or suspended, the investigator will promptly inform the Institutional Review Board/Institutional Ethics Committee (IRB/IEC) and will provide the reason(s) for the termination or suspension. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected or destroyed and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further development of the IP
- Determination of unexpected, significant, or unacceptable risk to participants

3.13 Duration of Treatment

The planned treatment duration with IP is for a maximum of two years. In the absence of treatment delays due to AE(s), treatment may continue until two years or until one of the following criteria applies:

- Disease progression per RECIST v1.1 **NOTE**: See Section 8.2 for criteria allowing for continuing treatment past initial progression.
- Death
- Intercurrent illness that prevents further administration of treatment
- Unacceptable AE(s)
- Participant decides to withdraw from the study
- General or specific changes in the participant's condition that render the participant unacceptable for further treatment in the judgment of the investigator
- Participant non-compliance
- Pregnancy
- Termination of the study by Sponsor

All women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation. The investigator should immediately notify PrimeVigilance upon knowledge of pregnancy (Section 7.5).

Subjects with confirmed CR may elect to discontinue treatment after a minimum of 48 weeks of treatment and continue with all relevant study assessments including disease assessments until disease progression or start of another anticancer therapy.

Subjects may be eligible for treatment past progression if they meet criteria as outlined in Section 8.2.

Impact of formation of ADA on clinical efficacy (non-response or loss of response to the IP) and safety (product specific immunogenicity risk) will be evaluated on an on-going basis. If a subject develops ADA, the Sponsor and investigator may take into consideration these factors in assessing the duration of the therapy.

3.14 Duration of Follow-Up

Subjects who are withdrawn from study for unacceptable AE(s) will be followed until resolution or stabilization of the AE. Participants who permanently discontinue IP for reasons other than progression will continue with disease assessments until progression or start of another anti-cancer therapy. Participants who discontinue IP for any reason other than withdrawal of consent will be followed for survival for approximately 18 months post treatment discontinuation or until death or the end of the study, whichever occurs first. During survival follow-up, the date of the first anticancer therapy will also be collected.

3.15 End of Study Definition

End of Study is defined as approximately 2 years after the last subject is dosed on cycle 1, day 1 (C1D1) or the date the study is closed by the sponsor, whichever occurs first.

4. STUDY POPULATION

Participants may be considered for enrollment in the study if they meet all the eligibility criteria stated in Sections 4.1 and 4.2. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

4.1 Participant Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply.

1. Subject has voluntarily agreed to participate by giving written informed consent in accordance with ICH/GCP guidelines and applicable local regulations.
2. Subject must have a histologically confirmed diagnosis of an unresectable, locally advanced or metastatic ovarian cancer, or primary peritoneal cancer or fallopian tube cancer.
3. Subjects must be refractory or intolerant to existing therapy(ies) known to provide clinical benefit for their condition. Subject must have received platinum-based therapies, and should not be eligible for further platinum therapy, or should be intolerant to such therapy. Subjects with known HRD positive disease may participate if they have received prior

polyadenosine diphosphate ribose polymerase (PARP) inhibitor therapy given alone or with bevacizumab. NOTE: HRD testing is not required per protocol.

4. Subjects should not be primary platinum refractory as defined by progressing during or within 1 month of upfront platinum therapy.
5. Has measurable disease by RECIST v1.1 using radiologic assessment.
6. Subject age is 18 years and older.
7. Has an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
8. Has life expectancy of greater than 12 weeks.
9. Laboratory values must meet the following criteria.

Laboratory parameter	Threshold value
Absolute neutrophil count (ANC)	$\geq 1.5 \times 10^9$/L without growth factor support
Platelet count	$\geq 75 \times 10^9$/L
Hemoglobin (Hgb)	> 9.0 g/dL with no blood transfusions for at least 5 days prior to D1 of IP.
Creatinine clearance (CrCl)	≥ 30 milliliter (mL)/min (using modified Cockcroft-Gault formula; Appendix Section 16.4)
ALT/AST	≤ 3 x ULN
Total bilirubin	≤ 1.5 x ULN; subjects with isolated indirect hyperbilirubinemia are permitted if direct bilirubin ratio is <35% and total bilirubin is ≤ 3.0 x ULN
Left ventricular ejection fraction (LVEF) by echocardiogram (ECHO)	≥ Lower limit of normal (LLN) per institutional threshold If LLN is not defined for a given institution, then ejection fraction must be ≥50 %

10. Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test within 72 hours of D1 of IP. **NOTE**: FCBP - A female subject who is not sterile due to surgery (i.e., from bilateral tubal ligation/occlusion, bilateral oophorectomy, bilateral salpingectomy or complete hysterectomy) or who does not have a congenital or acquired condition that prevents childbearing or who is not naturally post-menopausal for at least 12 consecutive months (see Appendix Section 16.3 for additional details). Documentation of postmenopausal status must be provided. FCBP should use an acceptable method of contraception (see Appendix Section 16.3) to avoid pregnancy during treatment and for 30 days (which is expected to exceed 5 half-lives) after the last dose of IP. FCBP must start using acceptable contraception at least 14 days prior to D1 of IP.
11. Recovery from prior anti-cancer treatments including surgery, radiotherapy, chemotherapy or any other anti-cancer therapy to baseline or ≤ Grade 1. (**NOTE**: Low-grade or controlled toxicities such as alopecia, ≤ Grade 2 hypomagnesemia, ≤ Grade 2 neuropathy, ≤ Grade 2 hypothyroidism on supplementation may be allowed upon agreement by the Sponsor Medical Monitor).

12. Willing to consent to mandatory pre-treatment and on-treatment tumor biopsy(ies), unless there is excessive risk as determined by the investigator.

4.2 Participant Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Prior treatment with an anti-CD47 or anti-SIRPα targeting agent or a CD40 agonist.
2. Any anti-cancer therapy within the time intervals noted below prior to first dose (D1) of SL-172154.

Therapy	Washout period
Chemotherapy	3 weeks
Hormonal therapy	3 weeks
PD-1/L1 inhibitor and other immunotherapies not otherwise specified	3 weeks
Tumor vaccine	4 weeks
Cell-based therapy	8 weeks
Other mAbs or biologic therapies	3 weeks
Other investigational agents not covered above	4 weeks or 5 half-lives whichever is shorter
Major surgery	2 weeks
Radiation (except palliative intent which does not require washout)	2 weeks

3. Concurrent chemotherapy, immunotherapy, biologic or hormonal/hormonal suppression therapy for cancer treatment is prohibited. Concurrent use of hormones for non-cancer related conditions is acceptable.
4. Use of corticosteroids or other immunosuppressive medication, current or within 14 days of D1 of SL-172154 treatment with the following exceptions (i.e., the following are allowed with or within 14 days of D1 of IP):
    - Topical, intranasal, inhaled, ocular, intraarticular corticosteroids
    - Physiological doses of replacement steroid (e.g., for adrenal insufficiency) not to exceed 10 mg/day of prednisone or equivalent
    - Steroid premedication for reaction to IV contrast
5. Receipt of live attenuated vaccine within 28 days of D1 of IP.
6. Active or documented history of autoimmune disease. Exceptions include controlled Type I diabetes, vitiligo, alopecia areata or hypo/hyperthyroidism.
7. Hypersensitivity to the active drug substance or to any of the excipients for the agent to be administered or subjects with known hypersensitivity to Chinese hamster ovary cell products.
8. Active pneumonitis (i.e., drug-induced, idiopathic pulmonary fibrosis, radiation-induced, etc.).

9. Ongoing or active infection (e.g., no systemic antimicrobial therapy for treatment of infection within 5 days of D1 of IP).
10. Symptomatic peptic ulcer disease or gastritis, active diverticulitis, other serious gastrointestinal disease associated with diarrhea within 6 months of D1 of IP.
11. Clinically significant or uncontrolled cardiac/thromboembolic disease including any of the following:
    - Myocarditis
    - Unstable angina within 6 months from D1 of IP
    - Acute myocardial infarction within 6 months from D1 of IP
    - Uncontrolled hypertension
    - New York Heart Association Class II, III or IV congestive heart failure
    - Clinically significant (symptomatic) cardiac arrhythmias (e.g., sustained ventricular tachycardia, second- or third- degree atrioventricular block without a pacemaker, circulatory collapse requiring vasopressor or inotropic support, or arrhythmia that is not stabilized on therapy)
    - Clinically symptomatic thromboembolism on stable anticoagulation for less than three months
12. Untreated central nervous system or leptomeningeal metastases. Subjects with treated central nervous system metastases must have completed definitive treatment (radiotherapy and/or surgery) > 2 weeks prior to D1 of IP and no longer require steroids.
13. Women who are breast feeding.
14. Psychiatric illness/social circumstances that would limit compliance with study requirements and substantially increase the risk of AEs or compromised ability to provide written informed consent.
15. Another malignancy that requires active therapy and that in the opinion of the investigator and Sponsor would interfere with monitoring of radiologic assessments of response to IP.
16. Has undergone allogeneic stem cell transplantation or organ transplantation.
17. Known history or positive test for human immunodeficiency virus, or positive test for hepatitis B (positive for hepatitis B surface antigen [HBsAg]) or hepatitis C virus ([HCV]; if HCV antibody (Ab) test is positive check for HCV ribonucleic acid [RNA]).

    (**NOTE**: *Hepatitis B virus (HBV)*: Subjects who are hepatitis B core antibody positive, but HBsAg negative are eligible for enrollment. *HCV*: Subjects who are HCV Ab positive, but HCV ribonucleic acid (RNA) negative are eligible for enrollment).

4.3 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently treated in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities.

Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs.

4.4 Accrual Goal

The total sample size expected to complete this study is approximately 33 to 54 subjects (see Section 9.1). Approximately 6-10 clinical sites may participate in SL03-OHD-101. Overall, the study may complete accrual within approximately 25 months (~ 2 years).

5. PHARMACEUTICAL PRODUCT INFORMATION

5.1 Investigational Product (SL-172154)

5.1.1 Investigational Product Description

Investigational Product Name:	SL-172154
Formulation description:	Solution containing SL-172154 10 mg/mL. Refer to the Study Pharmacy Manual (SPM) for further description of the drug product.
Dosage form:	Supplied as frozen liquid solution in a glass vial.
Unit dose strength(s)/Dose Level(s):	SL-172154 10 mg/mL (Refer to Section 3.3 for dose levels)
Physical Description:	SL-172154 solution, 10 mg/mL in a glass vial closed with a FluroTec® rubber stopper and sealed with a flip-off aluminium seal. See the Study Pharmacy Manual (SPM) for additional detail.
Route/ Administration/ Duration:	Delivered as IV solution via a syringe pump or IV infusion pump. See the SPM for additional details. Duration of infusion depends on the dose. See Table 1: SL-172154 Dose Escalation Plan in Section 3.3 of the protocol.
Dosing instructions:	Determine the number of vials needed based on the assigned dose level (in mg/kg) and the subject's weight (in kg). See the SPM for instructions on IP preparation and information on compatible administration materials. Doses of SL-172154 are to be administered as an IV infusion via an infusion or syringe pump that can ensure precision to at least 0.1 mL/min.
Secondary Packaging/Quantity/Label type	This is an open label study. Each vial of SL-172154 will be supplied in a single vial carton. See SPM for details.
Manufacturer/ Source of Procurement:	Manufactured for Shattuck Labs by [redacted]

SL-172154 will be provided to sites by the Sponsor. The contents of the label will be in accordance with all applicable regulatory requirements.

5.1.2 Preparation/Handling/Administration/Storage of SL-172154/Investigational Product

5.1.2.1 Preparation

Standard aseptic technique including preparation of doses in a laminar flow hood is required.

SL-172154 solution, 10 mg/mL, is supplied as a frozen liquid. Before use, thaw each vial of SL-172154 solution, 10 mg/mL, overnight under refrigerated conditions, protected from light, or at room temperature, until completely thawed. Following thawing, gently swirl the vial to ensure uniformity. Only sterile normal saline (0.9%) should be used to dilute SL-172154. See the SPM for further details on the preparation of SL-172154.

5.1.2.2 Handling

Under normal conditions of handling and administration, IP is not expected to pose significant safety risks to site staff. A Safety Data Sheet (describing the occupational hazards and recommended handling precautions) will be provided to site staff if required by local laws or will otherwise be available from the Sponsor upon request.

In the case of unintentional occupational exposure notify the Sponsor and consult the SPM.

Refer to the SPM for detailed procedures for the disposal and/or return of unused IP.

5.1.2.3 Administration

Doses of SL-172154 are to be administered as an IV infusion via an infusion pump or syringe pump that can ensure precision within at least 0.1 mL/min. DO NOT USE an in-line filter for administration of SL-172154.

Premedication for IRR prophylaxis is required with each 10mg/kg or higher dose and is at the investigator's discretion for doses less than 10mg/kg. The following premedication is to be administered approximately 30 minutes prior to the start of each SL-172154 administration:

- acetaminophen (650 to 1000 mg PO)
- diphenhydramine (25-50 mg, or equivalent, PO or IV)
- ranitidine (50 mg IV or equivalent).

Infusion rate: The duration of infusion stipulated for each dose is outlined in Table 1: SL-172154 Dose Escalation Plan in Section 3.3.

***NOTE**: A physician must be present at the site or immediately available to respond to emergencies during all administrations of IP. A fully functional resuscitation facility must be available. IP must not be administered via IV push or bolus but as an IV infusion using an infusion or syringe pump.*

5.1.2.4 Storage

SL-172154 must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of SL-172154 drug product will be limited to the

investigator and authorized site staff. SL-172154 must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

SL-172154 drug product vials are to be stored frozen at a temperature ≤ minus (-) 60 °C (-60°C to -90°C). Maintenance of a temperature log is required. The drug product should be stored protected from light.

The expiry date will be on the single vial carton label, if required.

5.1.3 Investigational Product Accountability

In accordance with local regulatory requirements, the investigator or designated site staff must document the amount of IP dispensed and/or administered to study subjects, relevant dates, dilution amounts, SL-172154 lot or batch numbers as on the label, and the amount received from the Sponsor, when applicable. Product accountability records must be maintained throughout the course of the study. Refer to the SPM for further detailed instructions on product accountability.

5.1.4 Dosing and Change in Weight

The actual body weight in kg will be used for SL-172154 dose calculation in all subjects whose body weight** is ≤100 kg. For subjects with body weight >100 kg, the dose to be administered should be the same as that calculated for a subject weighing 100 kg. The subject should be dosed according to their C1D1 weight throughout the study (mg/kg) if there is no significant change in their weight from the weight recorded at the C1D1 visit. A change in weight (i.e., increase or decrease) of the subject by 10% OR greater will require re-calculation of dose (mg/kg).

**Subject weight should be per the institutional standard but no less precise than rounded to a whole number prior to calculating the dose to be administered (e.g., 72.5 kg should be rounded up to 73 kg, 72.4 kg should be rounded down to 72 kg).

5.1.5 Monitoring Dose Administration

SL-172154 must be administered in an outpatient oncology treatment center or inpatient unit to enable close monitoring of subjects and proactive management of AEs. The risks associated with administration of SL-172154 include infusion reactions and cytokine release syndrome as mentioned in Section 3.6. Therefore, appropriate drugs and medical equipment to treat acute HSRs and monitoring and management of CRS must be immediately available, and study personnel must be trained to recognize and treat these toxicities. Subjects will be monitored prior to, during, and after infusion of SL-172154. Vital signs will be measured as outlined in the SOA in Section 6 and as needed.

5.1.6 Treatment of Investigational Product Overdose

In the event of an overdose (defined as administration of a dose and/or schedule greater than the dose and/or schedule that had been studied to date) of SL-172154, the investigator should:

- Contact the Sponsor immediately
- Closely monitor the subject for AEs/SAEs and laboratory abnormalities for at least 2 weeks following the infusion. The appropriate AE management guideline should be followed (Section 3.6). Pharmacologic effect could persist even after the IP is no longer detectable

in the serum. Subject should have recovered from toxicities that occurred because of the excess dose before the next scheduled dose is administered.

- Obtain a serum sample for PK analysis within 24 hours of the event if requested by the Sponsor (determined on a case-by-case basis)
- Document the quantity of the excess dose as well as the duration of the overdosing in the electronic case report form (eCRF)
- If a SAE related to overdose of the IP occurs, it should be documented and reported accordingly (Section 7.4)

Decisions regarding dose interruptions for overdose of IP will be made by the investigator in consultation with the Sponsor Medical Monitor based on the clinical evaluation of the subject.

5.2 Drug Accountability and Treatment Compliance

The investigator or designee is responsible for keeping accurate records of all study drug supplies received from the Sponsor, the amount of SL-172154 dispensed for administration to the subjects and the amount of unused or partially used drug remaining at the conclusion of the trial. An accurate and current accounting of IP administered to each subject must be maintained on an ongoing basis by a member of the study site staff in the Drug Accountability Record. Treatment compliance will be monitored by drug accountability as well as the subject's medical record and eCRF.

Handling and Disposal: Local requirements for disposal of hazardous drugs should be followed at each participating clinical site. It is the Investigator's responsibility to arrange for disposal of all partially used or empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

Prior to the return or destruction of IP, the Sponsor Study Monitor must have performed a complete reconciliation of all drugs ensuring accountability records are complete and accurate and are retained in the Investigator Site file or pharmacy file. IP that is returned to the IP supplier or destroyed on site must be documented in the accountability documentation. Arrangements for the return of SL-172154 will be made by the responsible Study Monitor.

Refer to the SPM for SL-172154 for further instructions on requirements for the IP under study.

6. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SOA. Protocol waivers or exemptions are not allowed.
- Assessments throughout the study are calendar based starting from the first day of dosing (day 1) in the first treatment cycle. Dose interruptions should not alter the assessment schedule for any subsequent treatment period.
- Adherence to the study design requirements, including those specified in the SOA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the informed consent (ICF) may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SOA.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue SL-172154.

6.1 SOA Table: Schedule 1 Dose Escalation, Dose Expansion and Pharmacodynamic Cohorts

Dosing Schedule 1		**D1, D8, D15 in cycle 1 over 28 days, thereafter every 2 weeks (D1, D15) over 28 days**																
Cycle Length = 28 days		**Cycle 1**							**Cycle 2**				**Cycle 3**		**Cycle ≥C4**		**Post**	
Procedures/Assessments[b]	**Screen[a]**	**D1**	D2	D3	**D8**	**D15**	D16	D22	**D1**	D2	**D15**	D16	**D1**	**D15**	**D1**	**D15**	**TXT[t]**	**F/U[u]**
Study Days	**Days -21 to -1**	1	2	3	8	15	16	22	29	30	43	44	57	71	85	99	w/in 30 d	Off TXT
Informed consent	X																	
Eligibility criteria[c]	X	X[c]																
Demographics/medical history	X																	
Cancer treatment history	X																	
Physical examination	X	X			X	X			X				X		X		X	
Vital signs/pulse oximetry[d]	X	X[d1]	X[d2]	X[d2]	X[d1]	X[d1]	X[d2]	X	X[d1]	X[d2]	X[d1]		X[d3]	X[d3]	X[d3]	X[d3]	X	
Height (screening only)/ weight	X	X				X			X		X		X	X	X	X	X	
ECOG performance status	X	X			X	X			X				X		X		X	
Pregnancy test[e]	X												X[e]				X	
Hematology profile[f]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry profile[f]	X	X	X		X	X	X	X	X		X		X	X	X	X	X	
Haptoglobin[f]	X		X															
Ferritin /C reactive protein[f]	X																X	
Coagulation profile[g]	X		X		X	X											X	
Type and Screen (ABO/Rh), Blood phenotyping and direct antiglobulin test[h]	X[h1]		X[h2]															
Thyroid test[i]	X																X	
Antiviral testing(HBV/HCV)[j]	X																	
Cardiac:12-Lead ECG/ECHO[k]	X																	
Tumor imaging and CA-125[l]	X[l]												X[l]				X[l]	X
PK/ADA sample(s)[m]		X	X	X	X	X	X		X	X			X		X[m1]		X[m2]	X[m3]
Cytokine/RBC binding[m]		X	X	X		X	X		X	X	X[m4]	X[m4]	X[m4]					
Complement[n]		X				X												
Immunophenotyping[n]		X	X	X		X	X		X	X	X	X						
Receptor Occupancy[n]		X	X	X		X	X		X	X	X	X						
SL-172154 administration[o]		X			X	X			X		X		X	X	X	X		

Dosing Schedule 1		**D1, D8, D15 in cycle 1 over 28 days, thereafter every 2 weeks (D1, D15) over 28 days**															
Cycle Length = 28 days		**Cycle 1**							**Cycle 2**				**Cycle 3**		**Cycle ≥C4**		**Post**	
Procedures/Assessments[b] Study Days	**Screen[a]**	**D1**	D2	D3	**D8**	**D15**	D16	D22	**D1**	D2	**D15**	D16	**D1**	**D15**	**D1**	**D15**	**TXT[t]**	**F/U[u]**
	Days -21 to -1	1	2	3	8	15	16	22	29	30	43	44	57	71	85	99	w/in 30 d	Off TXT
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
AEs/SAEs[p]	X	X	*Continuous Monitoring: Collect Ad hoc sample of clinical safety labs if IRR or CRS event occurs as outlined in Section 6.4.6.1*														X	X
Archival tumor tissue[q]	X																	
Tumor biopsy[r]	X									X[r]							X[r]	
HRD status[s]	X																	
Survival																		X

Day -1 = last day of screening period i.e., the day before the first dose of SL-172154 therapy is initiated on day 1 of cycle 1

Table Heading Abbreviations: C = cycle; D = day; F/u = follow up; TXT = treatment

a. **Screening:** Screening Period extends from Day -21 to Day -1. The following screening assessments must be performed within 72 hours of the first dose of SL-172154: hematology profile, chemistry profile, coagulation profile, ECOG score, physical exam, and pregnancy test. Baseline CT or positron emission tomography (PET)/CT or Magnetic resonance imaging (MRI) tumor assessments are required for all subjects within 28 days prior to the first dose of SL-172154.

b. **Assessment Window:** With the exception of Screening assessments and unless otherwise specified, assessments performed at ≤ 3-week intervals will have a +/- 3-day window and assessments performed at > 3-week intervals will have a +/- 1-week window. Assessments throughout the study are calendar based starting from the first day of dosing (day 1) in the first treatment period. Dose interruptions should not alter the assessment schedule for any subsequent treatment period.

c. **Inclusion/Exclusion criteria:** Subjects must meet eligibility criteria prior to first dose of SL-172154 on C1D1.

d. **Vital Signs:** Blood pressure (BP), heart rate (HR), temperature (T) and respiratory rate (RR) must be measured after the subject has been sitting for at least five minutes (min). Pulse oximetry will be collected to coincide with vital sign time points noted below.

   1) **Collect vital signs/pulse oximetry during Cycle 1 on D1, D8, D15 and Cycle 2 on D1 and D15**: Predose (within 30 min of starting the infusion) and 15 min (± 5 min), 0.5 hour [hr] (± 5 min), 1 hr (±10 min), 1.5 hr (± 10 min) 2 hr (± 10 min), 4 hr (± 10 min) , and 6 hr (± 10 min) **after start of infusion (SOI).**

   2) **Vital signs/pulse oximetry should be taken once prior to scheduled PK samples on C1D2, C1D3, C1D16 and C2D2**

   3) **Collect vital signs/pulse oximetry on dosing days ≥ C3D1:** Predose (within 30 min of starting the infusion) and at the end of infusion [EOI] (± 2 min)

e. **Pregnancy Test:** A serum pregnancy test (beta-human chorionic gonadotropin [β-hCG]) or urine pregnancy test must be performed at screening for all FCBP within 72 hrs of starting SL-172154. Repeat this test every 8 weeks during SL-172154 treatment (i.e., C3D1, C5D1, C7D1, etc.). *Contraception should be continued for at least 30 days after the last dose of SL-172154.*

f. **Hematology/Clinical Chemistry/Haptoglobin/Ferritin/C reactive protein:** will be performed at local laboratories according to the laboratory's normal procedures. See Section 6.4.6 for list of laboratory test required.

g. **Coagulation Tests:** prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), fibrinogen, d-dimer will be performed at local laboratories according to the laboratory's normal procedures.

h. **Blood phenotyping (ABO/Rh), and DAT:** These tests should be performed at local laboratories according to the laboratory's normal procedures.

   1) **At screening**: The following testing should be performed 1) ABO and D group (ABO/Rh) type and antibody screen and antibody identification if required; 2) DAT; 3) Phenotype/genotype for, at a minimum, the minor antigens Rh C/c E/e, K, Jk, Fy and MNSs.
   2) **C1/D2:** only need to perform blood phenotyping (ABO/Rh) and DAT.

i. **Thyroid Function Test**: Thyroid stimulating hormone (TSH), and free thyroxine 4 (T4) tests will be performed at local laboratories according to the laboratory's normal procedures.

j. **Antiviral Testing:** Please see exclusion criterion 17 in Section 4.2. These tests will be performed at local laboratories according to the laboratory's normal procedures.

k. **Cardiac Assessments (obtain within 28 days of first dose): 1) Electrocardiagram (ECG):** 12-lead ECG reading must be performed at screening to serve as a baseline for comparison in the event of a cardiac AE/SAE. **2) ECHO:** An ECHO must be performed at screening to serve as a baseline for comparison in the event of a cardiac AE/SAE.

l. **Tumor Assessment and CA-125:** Tumor assessments are required for all subjects within 28 days prior to the first dose of SL-172154. CA-125 should also be obtained at screening within 21 days of first dose of SL-172154. Baseline and on-treatment tumor assessments for all tumor types by RECIST v1.1 and iRECIST should include CT with contrast of chest, abdomen, and pelvis and other known sites of disease at each time point. Bone scan, positron emission tomography (PET)/CT, and/or MRI should be performed only if clinically indicated. Please refer to Section 8 for requirements regarding disease assessment. Tumor assessments must be performed at screening and at the following intervals until disease progression: approximately every 8 weeks through week 24 (e.g., C3D1, C5D1, C7D1), every 12 weeks up to year 2 (prior to cycles 10, 13, 16, 19, 22, 25, 28 and 31), and then every 24 weeks (prior to cycles 37, cycle 43, etc.) up to conclusion of the study. Confirmatory scans should be performed at least 4 weeks (>28 days) after initial documentation of an objective response or progressive disease. Subjects who discontinue study treatment for reasons other than disease progression (e.g., AE or withdrawal of consent) will be monitored for radiologic response until start of another anti-cancer therapy, or disease progression, withdrawal of consent or death. **CA-125** should be measured to coincide with each scheduled tumor assessment as outlined above with the last required sample for CA-125 obtained at the post treatment visit which occurs within 30 days of the last dose of SL-172154.

m. **PK/immunogenicity (i.e., ADA), cytokines and SL-172154 binding to red blood cells (RBCs):** Blood sample collection timings for PK, ADA, cytokines and measurement of RBC binding are outlined in Section 6.1.1 in supplementary Tables 2, 3, 4 and 5. PK/ADA/cytokine/RBC binding sample collection times on C1D1 through 48 hours postdose are provided in **Table 2**. PK/ADA/cytokine/RBC binding sample collection times in C2D1, C2D2, C2D15 and C2D16 are detailed in **Table 4**. PK/ADA sample collection times in C1D8 and cycles 3 and beyond are outlined in **Table 3** and **Table 5**, respectively**. Blood volumes required are provided in the SLM. PK, ADA, cytokine and RBC binding samples should not be collected from infusion port for drug delivery i.e., recommend having a separate line in the opposite arm for sample collection**.

   1) If subject has positive ADA test on D1 of cycle 13 or ADA results are not known, then follow up predose samples for PK/ADA should be collected every 3 cycles on D1 of subsequent treatment cycles (i.e., cycles 16, 19, 21 and 24) until ADA resolves to baseline **OR** until the last PK/ADA sample is collected within 105-125 days after the last dose of SL-172154.
   2) A PK/ADA sample is collected within 7 to 30 days after the subject discontinues SL-172154 therapy.

3) If subject has positive ADA tests during treatment or ADA results are not known a final PK/ADA sample is collected within 105-125 days after the last dose of SL-172154.
4) Cytokines will be collected in cycle 2 on days 15 and 16 as depicted in **Table 4** and on day 1 of cycle 3 as depicted in **Table 5**.

n. **Correlative laboratory studies**: Refer to supplementary **Table 6 for details in Section 6.1.2 plus see the SLM for amount of blood needed and sample shipment details.**
   - *Complement, Immunophenotyping and Receptor Occupancy*

o. **SL-172154 administration**: Subjects with confirmed CR who have had a minimum of 48 weeks of treatment may elect to discontinue SL-172154 and continue with all relevant study assessments including disease assessments. SL-172154 should be administered on D1, D8, and D15 according to the prescribed dosing schedule without deviation in cycle 1 to align with the safety DLT assessment and sample (PK, ADA, etc.) collection schedules. Beginning on cycle 2, day 1, a window of +/- 1 day is allowed for scheduled dosing days for drug administration.

p. **AE Monitoring**: Subjects will be followed continuously for AEs during the study and for 90 days after the last dose of SL-172154. After a subject is discontinued from SL-172154 or study therapy due to progressive disease or for other reasons, any ongoing AE should be followed until resolution (or return to baseline) and documented in the eCRF. If another anti-cancer agent is started within 90 days after the last dose of SL-172154, only SAEs and AEs that occur prior to the start of the new anticancer therapy should be recorded. In the event of a continuing SAE or a non-serious irAE, the subject will be asked to return for follow-up until the SAE or AE has resolved or is deemed to be continuing indefinitely. AEs will be characterized per NCI-CTCAE criteria v5.0 and events recorded in the eCRF.

   - Ad hoc blood samples for clinical safety labs should be collected for SAE related to IRR or CRS events as noted in Section 6.4.6.1 and the SLM.

q. **Archival tumor tissue (from a recent biopsy):** Archival tissue, if available, will be collected from **all subjects**. If an inadequate amount of archived tissue is available, the subject may still participate in the study if they meet eligibility criteria for the study. Moreover, archival tissue may be accepted in lieu of the pre-treatment tumor biopsy if the subject has not undergone treatment since time of specimen collection and if the sample was collected via core needle biopsy. Please notify the sponsor if archival tissue will be used in lieu of a pre-treatment fresh biopsy Provide formalin-fixed-paraffin-embedded (FFPE) tissue on slides (recommended minimum of 10 slides) or a block of FFPE tissue (the latter is preferred). **Refer to Section 6.7.2.2 and the SLM for details**.

r. **Tumor Biopsy**: Paired biopsies are required (pre- and on-treatment) obtained in subjects who have tumor accessible to core-needle biopsy and there is an acceptable level of risk as per investigator assessment. Biopsies will be obtained at baseline (to evaluate the immune status of the tumor before SL-172154 treatment) and following the first dose in cycle 2 on or between D2-D6 of cycle 2. In the event that a biopsy cannot be performed at cycle 2, please contact the medical monitor to discuss obtaining an on-treatment biopsy following the first dose on or between D2-D6 of a subsequent cycle. Biopsy at the time of progressive disease will be optional. **Please refer to Section 6.7.2.1 and SLM for details regarding biopsy**.

s. **Homologous recombinant deficiency (HRD) status**: Collection of HRD status (including BRCA status) is requested for all subjects during the screening period. Results from standard of care testing should be used. An HRD status that is unknown, not done, or unavailable at baseline will not preclude the subject from study participation.

t. **Post-Treatment**: A Post-Treatment visit will be conducted within 30 days (±3 days) after the last dose of SL-172154, or prior to the start of a new therapy, or at the end of study, or if the subject's participation is terminated early. See AE monitoring footnote above.

u. **Follow-Up**: All subjects will be contacted after discontinuing study therapy to collect survival status. Subjects should be contacted every 3 months (+/- 14 days) until approximately 18 months of follow up, death, withdrawal of consent, lost to follow-up or end of study. Contact may include clinic visit, telephone contact, email or mail to document survival status.

6.1.1 Supplementary Tables for SL-172154 Phase 1 Cohorts

Table 2: Phase 1 Serial PK, ADA, Cytokines and RBC Binding (C1/D1 - 48 hrs postdose)

Sample	Predose -30 min (± 25 min)	EOI (+5 min)	Collect blood for PK time at each time point unless otherwise specified[3]									
			Time points relate to post EOI									
			0.5 hr (±5 min)	1 hr (±5 min)	1.5 hr (±5 min)	2 hr (±10 min)	3 hr (±10 min)	4 hr (±15 min)	6 hr (±30 min)	8 hr (±30 min)	24 hr (±2 hr)	48 hr (±2 hr)
PK	X[1]	X[2]	X	X	X	X	X	X	X	X	X	X
RBC binding	X[1]	X[2]				X					X	
Cytokines	X[1]					X					X	X
ADA	X[1]											
Date and clock time for start/stop of infusion as well as sample collection (pre/post dose) will be recorded for all samples												

1. Collect predose samples for ADA, PK, cytokines and RBC binding.
2. EOI sample should be collected within 5 minutes after stopping the infusion. Duration of infusion is subject to change based on emerging data.
3. Sample collection out to 48 hrs post EOI but emerging data during dose finding may dictate changes in this schedule. **See SLM for the most accurate estimates of blood needed and for additional details on sample handling instructions**.

NOTE: The PK, ADA, cytokine and RBC binding samples **should not** be collected from infusion port for drug delivery i.e., recommend having a separate line in the opposite arm for PK, ADA, cytokine and RBC binding sample collection.

Table 3: Predose PK, ADA Sample (C1/D8)

Sample	C1/D8
	Predose **-30 min** (± 25 min)
PK	X
ADA	X

Table 4: Phase 1 Serial PK, ADA, Cytokines and RBC Binding (C1D15/D16, C2D1/D2, and C2D15/D16)

Sample	Collect blood for PK and other samples at each time point as specified[3]							
	C1/D15 and C2/D1		C1/D15 and C2/D1					C1/D16 and C2/D2
			Time points relate to post EOI[4]					
	Predose **-30 min** (± 25 min)	**EOI** (+ 5 min)	**0.5 hr** (± 5 min)	**1 hr** (±10 min)	**2 hr** (±10 min)	**4 hr** (±15 min)	**8hr** (±30 min)	**24 hr** (± 2 hr)
PK	X[1]	X[2]	X	X	X	X	X	X
RBC binding	X[1]	X[2]			X			X
Cytokines	X[1]				X			X
ADA	X[1]							

Sample	C2/D15		C2/D15		C2/D16	
	Predose **-30 min** (± 25 min)		**Time point relates to post EOI[4]**		**Time point relates to post EOI[4]**	
			2 hr (±10 min)		**24 hr** (± 2 hr)	
Cytokines[5]	X		X		X	

Date and clock time for start/stop of infusion as well as sample collection (pre/post dose) will be recorded for all samples

1. Collect predose samples for ADA, PK cytokines and RBC binding.
2. EOI sample should be collected within 5 minutes after stopping the infusion. Duration of infusion may change based on emerging data.
3. **SLM for the most accurate estimates of blood needed and for additional details on sample handling instructions**. The PK, ADA, cytokine and RBC binding samples **should not** be collected from infusion port for drug delivery i.e., recommend having a separate line in the opposite arm for PK, ADA cytokine, and RBC binding sample collection.
4. Sample collection out to 24 hrs post EOI but emerging data during dose finding may dictate changes in this schedule.
5. Cytokines will be collected at predose and 2 hrs post EOI on C2D15 and at 24 hrs post EOI on C2D16.

Table 5: Phase 1 Serial PK, ADA, Cytokines (C3/D1 and Beyond)

Sample	Collect blood for PK,PK/ADA or Cytokines at each time point as specified[3]				
	C3/D1	C3/D1	C3/D1	D1 of C4, C7, C10, C13[4], and C24	• **Collect sample for PK/ADA within 7 - 30 days post last dose of SL-172154 in all subjects** • **For subjects with positive ADA during treatment or ADA results are not known**: A final PK/ADA sample is collected within 105-125 days post last dose of SL-172154
	Predose -**30 min** (± 25min)	**EOI** (+ 5 min)	**2 hr Post EOI** (±10 min)	**Predose** - **30 min** (± 25 min)	
PK	X[1]	X[2]	X	X[1]	
Cytokines	X[1]		X		
ADA	X[1]			X[1]	
Date and clock time for start/stop of infusion as well as sample collection (pre/post dose) will be recorded for all samples					

1. Predose sample collected will include analysis of PK, ADA and cytokines on C3D1. Predose samples collected on D1 in cycles ≥ 4 will include analysis of PK and ADA.
2. Collect EOI sample within 5 min after stopping the infusion. Duration of infusion may change based on emerging data.
3. The PK/ADA sample **should not** be collected from infusion port for drug delivery i.e., recommend having a separate line in the opposite arm for PK sample collection. **See SLM for the most accurate estimates of blood needed and for additional details on sample handling instructions.**
4. If subject has positive ADA test on D1 of cycle 13 or if ADA results are unknown, then follow up predose PK/ ADA samples should be collected every 3 cycles on D1 of subsequent treatment cycles until ADA resolves to baseline or until the last PK/ADA sample is collected within 105-125 days after the last dose of SL-172154 therapy.

6.1.2 Correlative Sample Time points for SL-172154

Table 6: Complement, Immunophenotyping, Receptor Occupancy Time Points

Samples	C1/D1 and C2/D1		C1/D2 and C2/D2	C1/D3	C1/D15 and C2/D15		C1/D16 and C2/D16
	Predose (-90 to -5 min)	**1hr post EOI** (±10 min)	**24 hr post EOI** (± 2hr)	**48 hr post EOI** (± 2hr)	**Predose** (-90 to -5 min)	**1hr post EOI** (±10 min)	**24 hr post EOI** (± 2hr)
Complement (SC5b-9)[1,2]	X[2] (C1/D1 only)	X[2] (C1/D1 only)			X[2] (C1/D15 only)	X[2] (C1/D15 only)	
Immunophenotyping[1]	X	X	X	X	X	X	X
Receptor Occupancy[1]	X	X	X	X	X	X	X
Date and clock time for sample collection (pre/post dose) will be recorded for all samples							

1. Refer to SLM for details.
2. Complement is collected at predose and 1 hr post EOI time points on days 1 and 15 in cycle 1 only.

6.2 SOA Table: Schedule 2 Dose Escalation, Dose Expansion and Pharmacodynamic Cohorts

Dosing Schedule 2		**D1, D8, D15, D22 over 28 days in each cycle**																		
Cycle Length = 28 days		**Cycle 1**							**Cycle 2**						**Cycle ≥ 3**				**Post**	
	Screen[a]	**D1**	D2	D3	**D8**	**D15**	D16	**D22**	**D1**	D2	**D8**	**D15**	D16	**D22**	**D1**	**D8**	**D15**	**D22**	**TXT[t]**	**F/U[u]**
Procedures/ Assessments[b] Study Days	**Days -21 to -1**	**1**	2	3	**8**	**15**	16	**22**	**29**	*30*	**36**	**43**	*44*	**50**	**57 etc.**	**64 etc.**	**71 etc.**	**78 etc.**	**w/in 30 d**	**Off TXT**
Informed consent	X																			
Inclusion/exclusion criteria[c]	X	X[c]																		
Demographics & medical history	X																			
Cancer treatment history	X																			
Physical examination	X	X			X	X		X	X						X				X	
Vital signs/ pulse oximetry[d]	X	X[d1]	X[d2]	X[d2]	X[d1]	X[d1]	X[d2]	X[d1]	X[d1]	X[d2]	X[d1]	X[d1]		X[d3]	X[d3]	X[d3]	X[d3]	X[d3]	X	
Height (Screen only)/Weight	X	X				X			X			X			X		X			
ECOG performance status	X	X			X	X		X	X						X				X	
Pregnancy test[e]	X														X[e]				X	
Hematology profile[f]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry profile[f]	X	X	X		X	X	X	X	X		X	X		X	X		X		X	
Haptoglobin[f]	X		X																	
Ferritin/C reactive protein[f]	X																		X	
Coagulation profile[g]	X		X		X	X		X											X	
Type and Screen (ABO/Rh), Blood phenotyping and direct antiglobulin test[h]	X[h1]		X[h2]																	
Thyroid test[i]	X																		X	
Antiviral testing (HBV/HCV)[j]	X																			
Cardiac:12-Lead ECG/ECHO[k]	X																			
Tumor imaging and CA-125[l]	X														X[l]				X	X
PK/ADA/sample(s)[m]		X	X	X	X	X	X		X	X					X[m1]				X[m2]	X[m3]
Cytokine/RBC binding[m]		X	X	X		X	X		X	X		X[m4]	X[m4]		X[m4]					
Complement[n]		X				X														
Immunophenotyping[n]		X	X	X		X	X		X	X		X	X							
Receptor Occupancy[n]		X	X	X		X	X		X	X		X	X							
SL-172154 administration[o]		X			X	X		X	X		X	X		X	X	X	X	X		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
AEs/SAEs[p]	X	X	*Continuous Monitoring: Collect Ad hoc sample of clinical safety labs if IRR or CRS event occurs as outlined in Section 6.4.6.1*																X	X
Archival tumor tissue[q]	X																			
Tumor biopsy[r]	X									X[r]									X[r]	

Dosing Schedule 2		**D1, D8, D15, D22 over 28 days in each cycle**																	
Cycle Length = 28 days		**Cycle 1**							**Cycle 2**						**Cycle ≥ 3**				**Post**	
	Screen[a]	**D1**	D2	D3	**D8**	**D15**	D16	**D22**	**D1**	D2	**D8**	**D15**	D16	**D22**	**D1**	**D8**	**D15**	**D22**	**TXT[t]**	**F/U[u]**
Procedures/ Assessments[b] Study Days	**Days -21 to -1**	**1**	2	3	**8**	**15**	16	**22**	**29**	*30*	**36**	**43**	*44*	**50**	**57 etc.**	**64 etc.**	**71 etc.**	**78 etc.**	**w/in 30 d**	**Off TXT**
HRD Status[s]	X																			
Survival																			X	X

Day -1 = last day of screening period i.e., the day before the first dose of SL-172154 therapy is initiated on day 1 of cycle 1

Table Heading Abbreviations: C = cycle; D = day; F/u = follow up; TXT = treatment

a. **Screening:** Screening Period extends from Day -21 to Day -1. The following screening assessments must be performed within 72 hours of the first dose of SL-172154: hematology profile, chemistry profile, coagulation profile, ECOG score, physical exam, and pregnancy test. Baseline CT or positron emission tomography (PET)/CT or Magnetic resonance imaging (MRI) tumor assessments are required for all subjects within 28 days prior to the first dose of SL-172154.

b. **Assessment Window:** With the exception of Screening assessments and unless otherwise specified, assessments performed at ≤ 3-week intervals will have a +/- 3-day window and assessments performed at > 3-week intervals will have a +/- 1-week window. Assessments throughout the study are calendar based starting from the first day of dosing (day 1) in the first treatment period. Dose interruptions should not alter the assessment schedule for any subsequent treatment period.

c. **Inclusion/Exclusion criteria:** Subjects must meet eligibility criteria prior to first dose of SL-172154 on C1D1.

d. **Vital Signs:** Blood pressure (BP), heart rate (HR), temperature (T) and respiratory rate (RR) must be measured after the subject has been sitting for at least five minutes (min). Pulse oximetry will be collected to coincide with vital sign time points noted below.

   1) **Collect vital signs/pulse oximetry during Cycle 1 on D1, D8, D15, D22 and Cycle 2 on D1, D8 and D15**: Predose (within 30 min of starting the infusion) and 15 min (± 5 min), 0.5 hour [hr] (± 5 min), 1 hr (±10 min), 1.5 hr (± 10 min) 2 hr (± 10 min), 4 hr (± 10 min) , and 6 hr (± 10 min) **after start of infusion (SOI).**

   2) **Vital signs/pulse oximetry should be taken once prior to scheduled PK samples on C1D2, C1D3, C1D16 and C2D2**

   3) **Collect vital signs/pulse oximetry on C2D22 and dosing days ≥ C3D1:** Predose (within 30 min of starting the infusion) and at the end of infusion [EOI] (± 2 min)

e. **Pregnancy Test:** A serum pregnancy test (beta-human chorionic gonadotropin [β-hCG]) or urine pregnancy test must be performed at screening for all FCBP within 72 hrs of starting SL-172154. Repeat this test every 8 weeks during SL-172154 treatment (i.e., C3D1, C5D1, C7D1, etc.). *Contraception should be continued for at least 30 days after the last dose of SL-172154.*

f. **Hematology/Clinical Chemistry/Haptoglobin/Ferritin/C reactive protein:** will be performed at local laboratories according to the laboratory's normal procedures. See Section 6.4.6 for list of laboratory test required.

g. **Coagulation Tests:** prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), fibrinogen, d-dimer will be performed at local laboratories according to the laboratory's normal procedures.

h. **Blood phenotyping (ABO/Rh), and DAT:** These tests should be performed at local laboratories according to the laboratory's normal procedures.

1) **At screening**: The following testing should be performed 1) ABO and D group (ABO/Rh) type and antibody screen and antibody identification if required; 2) DAT; 3) Phenotype/genotype for, at a minimum, the minor antigens Rh C/c E/e, K, Jk, Fy and MNSs.
2) **C1/D2:** only need to perform blood phenotyping (ABO/Rh) and DAT.

i. **Thyroid Function Test**: Thyroid stimulating hormone (TSH), and free thyroxine 4 (T4) tests will be performed at local laboratories according to the laboratory's normal procedures.

j. **Antiviral Testing:** Please see exclusion criterion 17 in Section 4.2. These tests will be performed at local laboratories according to the laboratory's normal procedures.

k. **Cardiac Assessments (obtain within 28 days of first dose): 1) Electrocardiagram (ECG):** 12-lead ECG reading must be performed at screening to serve as a baseline for comparison in the event of a cardiac AE/SAE. **2) ECHO:** An ECHO must be performed at screening to serve as a baseline for comparison in the event of a cardiac AE/SAE.

l. **Tumor Assessment and CA-125:** Tumor assessments are required for all subjects within 28 days prior to the first dose of SL-172154. CA-125 should also be obtained at screening within 21 days of first dose of SL-172154. Baseline and on-treatment tumor assessments for all tumor types by RECIST v1.1 and iRECIST should include CT with contrast of chest, abdomen, and pelvis and other known sites of disease at each time point. Bone scan, positron emission tomography (PET)/CT, and/or MRI should be performed only if clinically indicated. Please refer to Section 8 for requirements regarding disease assessment. Tumor assessments must be performed at screening and at the following intervals until disease progression: approximately every 8 weeks through week 24 (e.g., C3D1, C5D1, C7D1), every 12 weeks up to year 2 (prior to cycles 10, 13, 16, 19, 22, 25, 28 and 31), and then every 24 weeks (prior to cycles 37, cycle 43, etc.) up to conclusion of the study. Confirmatory scans should be performed at least 4 weeks (>28 days) after initial documentation of an objective response or progressive disease. Subjects who discontinue study treatment for reasons other than disease progression (e.g., AE or withdrawal of consent) will be monitored for radiologic response until start of another anti-cancer therapy, or disease progression, withdrawal of consent or death. **CA-125** should be measured to coincide with each scheduled tumor assessment as outlined above with the last required sample for CA-125 obtained at the post treatment visit which occurs within 30 days of the last dose of SL-172154.

m. **PK/immunogenicity (i.e., ADA), cytokines and SL-172154 binding to red blood cells (RBCs):** Blood sample collection timings for PK, ADA, cytokines and measurement of RBC binding are outlined in Section 6.1.1 in supplementary Tables 2, 3, 4 and 5. PK/ADA/cytokine/RBC binding sample collection times on C1D1 through 48 hours postdose are provided in **Table 2**. PK/ADA/cytokine/RBC binding sample collection times in C2D1, C2D2, C2D15 and C2D16 are detailed in **Table 4**. PK/ADA sample collection times in C1/D8 and cycles 3 and beyond are outlined in **Table 3** and **Table 5,** respectively**. Blood volumes required are provided in the SLM. PK, ADA, cytokine and RBC binding samples should not be collected from infusion port for drug delivery i.e., recommend having a separate line in the opposite arm for sample collection**.

1) If subject has positive ADA test on D1 of cycle 13 or ADA results are not known, then follow up predose samples for PK/ADA should be collected every 3 cycles on D1 of subsequent treatment cycles (i.e., cycles 16, 19, 21 and 24) until ADA resolves to baseline **OR** until the last PK/ADA sample is collected within 105-125 days after the last dose of SL-172154.
2) A PK/ADA sample is collected within 7 to 30 days after the subject discontinues SL-172154 therapy.
3) If subject has positive ADA tests during treatment or ADA results are not known a final PK/ADA sample is collected within 105-125 days after the last dose of SL-172154.
4) Cytokines will be collected in cycle 2 on days 15 and 16 as depicted in **Table 4** and on day 1 of cycle 3 as depicted in **Table 5**.

n. **Correlative laboratory studies**: Refer to supplementary **Table 6 for details in Section 6.1.2 plus see the SLM for amount of blood needed and sample shipment details.**

- *Complement, Immunophenotyping and Receptor Occupancy*

o. **SL-172154 administration**: Subjects with confirmed CR who have had a minimum of 48 weeks of treatment may elect to discontinue SL-172154 and continue with all relevant study assessments including disease assessments. SL-172154 should be administered on D1, D8, D15 and D22 according to the prescribed dosing schedule without deviation in cycle 1 to align with the safety DLT assessment and sample (PK, ADA, etc.) collection schedules. Beginning on cycle 2, day 1, a window of +/- 1 day is allowed for scheduled dosing days for drug administration.

p. **AE Monitoring**: Subjects will be followed continuously for AEs during the study and for 90 days after the last dose of SL-172154. After a subject is discontinued from SL-172154 or study therapy due to progressive disease or for other reasons, any ongoing AE should be followed until resolution (or return to baseline) and documented in the eCRF. If another anti-cancer agent is started within 90 days after the last dose of SL-172154, only SAEs and AEs that occur prior to the start of the new anticancer therapy should be recorded. In the event of a continuing SAE or a non-serious irAE, the subject will be asked to return for follow-up until the SAE or AE has resolved or is deemed to be continuing indefinitely. AEs will be characterized per NCI-CTCAE criteria v5.0 and events recorded in the eCRF.

- Ad hoc blood samples for clinical safety labs should be collected for SAE related to IRR or CRS events as noted in Section 6.4.6.1 and the SLM.

q. **Archival tumor tissue (from a recent biopsy):** Archival tissue, if available, will be collected from **all subjects**. If an inadequate amount of archived tissue is available, the subject may still participate in the study if they meet eligibility criteria for the study. Moreover, archival tissue may be accepted in lieu of the pre-treatment tumor biopsy if the subject has not undergone treatment since time of specimen collection and if the sample was collected via core needle biopsy. Please notify the sponsor if archival tissue will be used in lieu of a pre-treatment fresh biopsy Provide formalin-fixed-paraffin-embedded (FFPE) tissue on slides (recommended minimum of 10 slides) or a block of FFPE tissue (the latter is preferred). **Refer to Section 6.7.2.2 and the SLM for details**.

r. **Tumor Biopsy**: Paired biopsies are required (pre- and on-treatment) obtained in subjects who have tumor accessible to core-needle biopsy and there is an acceptable level of risk as per investigator assessment. Biopsies will be obtained at baseline (to evaluate the immune status of the tumor before SL-172154 treatment) and following the first dose in cycle 2 on or between D2-D6 of cycle 2. In the event that a biopsy cannot be performed at cycle 2, please contact the medical monitor to discuss obtaining an on-treatment biopsy following the first dose on or between D2-D6 of a subsequent cycle. Biopsy at the time of progressive disease will be optional. **Please refer to Section 6.7.2.1 and SLM for details regarding biopsy**.

s. **Homologous recombinant deficiency (HRD) status**: Collection of HRD status (including BRCA status) is requested for all subjects during the screening period. Results from standard of care testing should be used. An HRD status that is unknown, not done, or unavailable at baseline will not preclude the subject from study participation.

t. **Post-Treatment**: A Post-Treatment visit will be conducted within 30 days (±3 days) after the last dose of SL-172154, or prior to the start of a new therapy, or at the end of study, or if the subject's participation is terminated early. See AE monitoring footnote above.

u. **Follow-Up**: All subjects will be contacted after discontinuing study therapy to collect survival status. Subjects should be contacted every 3 months (+/- 14 days) until approximately 18 months of follow up, death, withdrawal of consent, lost to follow-up or end of study. Contact may include clinic visit, telephone contact, email or mail to document survival status.

6.3 Demographics, Medical History, Screening and Safety Assessments

6.3.1 Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any trial specific procedures are performed and prior to starting treatment with SL-172154. Refer to Section 13.3.

6.3.2 Eligibility Criteria

Subjects must meet all the eligibility criteria outlined in the protocol to be eligible for participation.

6.3.3 Subject Demographics

The age, year of birth, sex, race, and ethnicity of each subject will be recorded during Screening.

6.3.4 Medical History

A complete medical history will be taken during the Screening period. The history will include the background and progress of the participant's malignancy and a description of prior therapies received to treat the disease under study and the response to these therapies.

6.3.5 Concomitant Medications

Concomitant medications and procedures will be recorded during the Screening period and throughout the study as specified in the SOA.

6.4 Safety Evaluations

6.4.1 Physical Examination

A complete physical examination should be performed at screening and at the post-treatment visit by a qualified physician or their designee. The exam will include, at a minimum, assessments of the head and neck, eyes, ears, nose throat, skin, thyroid, cardiovascular, respiratory, gastrointestinal and neurological systems, lymph nodes and extremities. Height (at screening) and weight will also be measured and recorded. Investigators should pay special attention to clinical signs related to previous serious illnesses. Physical exams should be performed per standard of care during the on-treatment period.

6.4.2 ECOG Performance Status

Participant's performance status will be assessed using the ECOG performance status tool (see Appendix Section 16.2).

6.4.3 Pulse Oximetry

Oxygen saturation will be measured with a pulse oximeter at room air without supplementation. Refer to footnote "d" in the SOA tables for details on when to collect pulse oximetry.

6.4.4 Vital Signs

Vital signs will be assessed in a semi-supine position at rest and will include temperature (T), systolic and diastolic blood pressure (BP), heart rate (HR), and respiratory rate (RR). BP and RR measurements should be preceded by at least 5 min of rest for the participant in a quiet setting without distractions. Refer to footnote "d" in the SOA tables for details on when to collect vital signs.

6.4.5 Cardiac Assessments

6.4.5.1 Electrocardiograms

A single, screening 12-lead ECG will be obtained as outlined in the SOA using an onsite standard of care ECG machine that automatically calculates HR and measures PR, QRS, QT, and corrected QTc (QTc) intervals. ECGs should be performed as clinically indicated during the conduct of the study. Any treatment emergent abnormalities of clinical consequence should be reported as AEs.

6.4.5.2 Echocardiogram

A screening ECHO will be obtained as outlined in the SOA to assess left ventricular ejection fraction. ECHOs should be performed as clinically indicated during the conduct of the study. Any treatment emergent abnormalities of clinical consequence should be reported as AEs.

6.4.6 Laboratory Assessments

Refer to the SOA in Section 6 for the timing and frequency of tests performed.

<table>
<tr><th colspan="3">Local Clinical Labs</th></tr>
<tr><th>Hematology</th><th colspan="2">Clinical Chemistry</th></tr>
<tr><td>Hemoglobin
Hematocrit
Platelet Count
Red Blood Cell Count
White Blood Cell Count
Automated WBC Differential
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td><td colspan="2">Blood urea nitrogen
Creatinine
Glucose
Sodium
Potassium
Calcium
Haptoglobin
C reactive protein
Magnesium
Phosphorus
Total Protein
Albumin
Lactate dehydrogenase
Bicarbonate
Ferritin
Liver Panel
Total and direct bilirubin
Alanine aminotransferase
Aspartate aminotransferase
Alkaline phosphatase</td></tr>
<tr><th>Blood Type and Screen</th><th colspan="2">Serum/Urine Pregnancy Test</th></tr>
<tr><td>ABO/Rh
D, C, E
Kell, Kidd
Direct antiglobulin test
Duffy, MNS
Antibody screen</td><td colspan="2">β-human chorionic gonadotropin</td></tr>
<tr><th>Coagulation</th><th>Thyroid</th><th>Antiviral Testing</th></tr>
<tr><td>Prothrombin time and International-normalized ratio
Activated partial thromboplastin time
Fibrinogen
D-Dimer</td><td>Thyroid stimulating hormone
Free thyroxine 4</td><td>Hepatitis B: HBsAg / HBV core Ab
Hepatitis C: HCV Ab / HCV RNA viral load</td></tr>
</table>

Refer to SOA and supplementary tables provided in Section 6 for the timing and frequency of central laboratory tests.

Central Laboratory Tests[a]
Cytokines and Chemokines
Complement (SC5b-9 test)
Binding of SL-172154 to RBCs
PK/Immunogenicity[a]
Pharmacokinetics (SL-172154 serum concentration)
Anti-drug antibodies
Flow Cytometry[a]
Receptor Occupancy Panels
Immunophenotyping Panels
Tumor IHC[a]
PD-L1 expression
CD47 and CD40 expression
Changes in T cell subsets, B cells, and macrophages

a) Samples in this table will be analyzed at a Central Lab. Refer to the SLM for details for sample collection procedures, handling, storage and shipment instructions.

6.4.6.1 Ad Hoc Labs for IRR or CRS AEs

Ad hoc labs should be collected as noted if IRR/CRS occurs. The samples to be collected are provided below.

Ad Hoc Labs[a,b]	
Required Local Clinical Labs	**Required Central Labs**
Complete blood count with differential Chemistry Panel D-Dimer Coagulation panel C reactive protein Ferritin	Pharmacokinetics (SL-172154 serum concentration) Anti-drug antibodies Complement (SC5b-9) Cytokines and Chemokines Immunophenotyping Panels

a) Refer to the SLM for sample collection procedures, handling, storage and shipment instructions. PK will be measured with each corresponding ADA sample.
b) Specific biomarker, PK, ADA, and local clinical samples will be collected as soon as possible if an AE related to CRS or IRR to SL-172154 occurs.

All protocol-required central laboratory assessments must be conducted in accordance with the SLM.

6.4.6.2 Pregnancy Testing

All FCBP subjects must have a negative pregnancy test (serum or urine) at Screening. A separate assessment is required if a negative Screening pregnancy test is obtained more than 72 hours before the first dose of SL-172154. Subjects with a positive pregnancy test must be excluded from the

study. Subjects with a negative pregnancy test result must agree to use an effective contraception method as described in Appendix Section 16.3.

In the rare event that β-hCG is elevated as a tumor marker, please see guidance in Appendix Section 16.3.1.

6.4.6.3 Blood Type and Screen (ABO/Rh) and DAT

SL-172154 does bind RBCs but has not been shown to cause hemolysis in NHPs. However, treatment with SL-172154 may make phenotyping difficult due to expected coating of the RBC membrane. Thus, blood phenotyping, type and screen (ABO/Rh), and DAT should be performed at screening before exposure to SL-172154. At screening the following testing should be performed: 1) ABO and D group (ABO/Rh) type and antibody screen and antibody identification if required; 2) DAT; 3) phenotype/genotype for, at a minimum, the minor antigens Rh C/c E/e, K, Jk, Fy and MNSs. At cycle 1/day 2, testing should only include ABO/Rh type and DAT testing as outlined in the SOA tables in Section 6.

6.5 Pharmacokinetics

6.5.1 Intensive PK Sampling

Intensive serial PK samples will be collected for all subjects enrolled in dose escalation cohorts. Actual dose administration and PK sampling times will be documented in the subject's medical record. In the first cycle starting on Day 1, samples will be collected as outlined in the SOA and supplementary tables provided. Beyond cycle 3 day 1, only predose samples will be collected for ADA and PK analyses. Refer to supplementary tables provided in Section 6.1.1 for details.

6.6 Anti-drug Antibody Assessments

Predose blood samples will be collected from all subjects enrolled in the study for determination of ADA starting on day 1 and periodically throughout the course of therapy (Refer to supplementary tables provided in Section 6.1.1 for details). If subject has a positive ADA test on D1 of cycle 13 or if ADA results are unknown, then predose samples for ADA should continue to be collected every 3 cycles on D1 of subsequent treatment cycles until ADA becomes negative or until a final ADA sample is collected within 105 – 125 days after permanently stopping treatment with SL-172154.

6.7 Pharmacodynamic/Biomarker Assessments

Blood samples and tumor tissue (where available) will be collected from all subjects in this study for pharmacodynamic/biomarker research as specified in the SOA and supplementary tables (Sections 6.1.1 and 6.1.2). Below is an overview of the Pharmacodynamic/Biomarker plan, the sample requirements, supporting analytics, and intended goal of performing the proposed assays.

A separate SLM detailing the preparation, storage, and shipping requirements for blood or fresh and archival tumor tissue collection during the study will be provided.

6.7.1 Pharmacodynamic Assessments in Blood

6.7.1.1 Cytokine and Chemokine Analysis

The levels of serum proteins such as cytokines and chemokines will be measured as noted in Section 6.4.6. Levels of serum cytokines/chemokines may provide context to AEs observed in subjects following infusion of SL-172154 and may act as pharmacodynamic markers of activity.

6.7.1.2 Receptor Occupancy

Receptor occupancy of SL-172154 on CD47 and CD40 will be measured by flow cytometry. This analysis will provide evidence that SL-172154 is engaging its expected targets and allows receptor occupancy (free and total) to be calculated and assessed across dose groups.

6.7.1.3 SL-172154 Binding to Red Blood Cells

Blood samples will be collected from all subjects enrolled in the study for determination of SL-172154 binding to RBCs starting on day 1 and periodically throughout the course of Cycles 1 and 2.

6.7.1.4 Immunophenotyping

Protein expression of phenotypic markers, proliferation markers, and activation markers will be assessed by flow cytometry. Changes in the composition of T cells, B cells and myeloid cells in the peripheral blood may provide insights into the mechanism of action of SL-172154 and serve as biomarkers for immune response.

6.7.2 Pharmacodynamic Assessment of Tumor Tissue

6.7.2.1 Fresh Tumor Biopsies

The efficacy of cancer immunotherapy is conditioned by the infiltration of tumors by activated tumor-specific T cells. The activity of these T cells will be affected by the immunosuppressive environment in the tumor (e.g., T-regulatory cells, and suppressive myeloid cells such as myeloid-derived suppressor cells and M2 macrophages). Therefore, the direct evaluation of the “immune landscape” inside the tumor is of great value for understanding the mechanism of action of SL-172154 and optimizing cancer immunotherapy. Immunohistochemistry (IHC) analyses will be performed on the fresh tumor samples. The immune infiltrate of the tumor will be assessed by visualizing and assessing the phenotype of cells in the tumor micro-environment by IHC. Additionally, the spatial distribution and redistribution upon treatment of immune cells within the TME has also been found to be linked to the response to immunotherapies and can be evaluated by these procedures. The immune profile of the tumor could be used to predict clinical response or validate the mechanism of the immune response to SL-172154. On-treatment biopsies of progressing lesions will be obtained for further characterization of the changes in the TME. For each time point, three core needle biopsies should be obtained for research studies (see SLM for details).

Baseline and on-treatment biopsies (to evaluate the immune status of the tumor before and on SL-172154 treatment) are required for all subjects for whom the biopsy has minimal risk. A Screening/Baseline biopsy and an on-treatment biopsy at Cycle 2 on or between day 2 through day

6 (the expected time of an immune response to SL-172154 therapy) must be obtained. Biopsy at the time of progressive disease will be optional. The time interval for the on-treatment biopsy may be changed by the Sponsor if pharmacodynamic data from the ongoing study indicates that a different time point would be more suitable.

It is strongly recommended that the biopsies are obtained from non-target and measurable lesions. If such a lesion is not present, a biopsy may be obtained from a target lesion that is 2 centimeters (cm) or more. The same lesion should be biopsied pre-and post- treatment, and measurement of the lesion that is biopsied should be documented. Where possible lymph node biopsies should be avoided in subjects with solid tumors as reliable measure of tumor infiltrating lymphocytes (or their activation) in a background of (non-tumor) lymphoid tissue is challenging. If feasible, biopsy material should be collected after disease progression has been confirmed and documented, ideally on lesions that have progressed.

Biopsy Collection Safety Considerations and Procedure
For a given subject, 3 core needle biopsies of the selected tumor lesion should be obtained at the time points noted in the SOA. Biopsies should be fixed in formalin and paraffin embedded. The entire block must be submitted. Please refer to the SLM for further instructions.
Only percutaneous biopsies will be performed on subjects with solid tumors. Mediastinal, open surgical or laparoscopic, gastrointestinal, peritoneal or bronchial endoscopic biopsies are permitted ONLY when obtained incidentally to a clinically necessary procedure and not for the sole purpose of the clinical trial. No laparoscopic, or endoscopic or open surgical procedure will be performed solely to obtain a biopsy for this protocol. However, excisional biopsy or endoscopic biopsy is allowed if medically indicated and can be used for analysis. Biopsies will be sent for analyses as defined in the protocol.

Contraindications to percutaneous biopsy:

- Significant coagulopathy or anticoagulation treatment that cannot be adequately corrected.
- Severely compromised cardiopulmonary function or hemodynamic instability.
- Lack of a safe pathway to the lesion.
- Inability of the subject to cooperate with, or to be positioned for, the procedure.

If a lesion is deemed appropriate for biopsy with minimal risk (no more than 2% risk of serious complication requiring hospitalization) to the participant by agreement between the investigators and Interventional Radiology, an attempt at biopsy should be made.

The use of imaging to facilitate biopsies will be decided by members of the Interventional Radiology team at the clinical site and may include ultrasound, CT scan, or MRI. Should CT scan be needed for biopsy, the number of scans for each procedure will be limited to the minimum number needed to safely obtain a biopsy. Tumor biopsies and local anesthesia will be performed only if they are of low risk (<2% major complication rate) to the participant as determined by the investigators and interventional radiologist.

6.7.2.2 Archival Tumor

Archival tissue, if available, will be collected from all subjects. Archival tumor tissue (1 block preferred or a minimum of 10 unstained slides of FFPE tissue; see SLM for details) that is representative of current disease status (e.g., metastatic disease) is requested. If an inadequate

amount of archived tissue is available, the subject may still participate in the study if they meet eligibility criteria for the study.

Archival tissue may be accepted in lieu of the screening/baseline fresh tumor biopsy if the subject has not undergone anti-cancer treatment since time of specimen collection and if the sample was collected via core needle biopsy. Please notify the sponsor if archival tissue will be used in lieu of the baseline fresh tumor biopsy.

6.8 Assessment of Anti-tumor Activity

The primary analysis of anti-tumor activity is according to RECIST v1.1 for solid tumors. Treatment beyond progression is permitted provided the subject meets protocol specified criteria (see Section 8.2). Disease assessment will be performed at baseline and at the following intervals until disease progression is confirmed: every 8 weeks through week 24, and every 12 weeks thereafter until year 2, and every 24 weeks until study conclusion. Refer to Section 8 for additional details. All subjects will be followed up for survival unless they withdraw consent.

6.9 Unscheduled Visit

In the event of an unscheduled visit, the subject should undergo safety screening to include a physical exam, vital signs (HR, BP, T, and RR) and pulse oximetry. Clinical hematology and chemistry labs may be collected if considered necessary for subject assessment. The reason for the unscheduled visit should be documented in the eCRF. All AEs or SAEs reported by the subject or observed by the investigator should be documented and reported; this includes relevant medical information gathered during the unscheduled visit related to clinical assessment of AEs or SAEs (Section 7.4).

7. SAFETY ASSESSMENTS

Subjects will be followed continuously for all AEs starting when a subject has signed the ICF, throughout the course of treatment and for 90 days after the last dose of IP. After a subject is discontinued from SL-172154 due to progressive disease or for other reasons, any ongoing AEs should be followed until resolution (or return to baseline) and documented in the eCRF. If another anti-cancer agent is started within 90 days after the last dose of SL-172154, only SAEs and AEs that occur prior to starting the new anticancer therapy should be recorded. All observed or volunteered AEs (serious or non-serious) and abnormal laboratory test findings, if applicable, whether suspected to have a causal relationship to SL-172154 or not will be recorded in the subject medical record and in the eCRF. AEs will be graded according to NCI-CTCAE v5.0. For all AEs, sufficient information will be pursued and/or obtained to permit an adequate determination of seriousness and outcome of the event (i.e., whether it should be classified as a SAE or not) and an assessment of the causal relationship between the AE and SL-172154. AEs will be followed until resolution (or return to baseline) or stabilization. Refer to Section 7.4 for documentation and reporting of AEs.

7.1 Definitions for Safety Parameters

Event	Definition
Adverse Event (AE)	The AE **observation period** starts at the time of signing informed consent and includes baseline or washout periods, even if no study treatment has been administered. An AE is **defined as** any untoward medical occurrence in a subject to whom the IP has been administered, regardless of whether the event is considered related to that product.

Event	Definition
	An AE is also **defined as** an undesirable medical condition due to a study-related procedure.
Adverse Reaction (AR)	AR is an untoward and unintended response in a subject to an IP. A causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	An AE or suspected AR that is considered "serious" if, in the view of either the investigator or Sponsor, it results in any of the following outcomes: • Death (**Note**: death is an outcome not an event) • A life-threatening AE (an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe) • Inpatient hospitalization or prolongation of existing hospitalization • A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions • A congenital anomaly/birth defect. • Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
Laboratory test(s) that meet definition of an AE or SAE:	• Any laboratory test result that meets the definition of an AE or SAE or requires holding or discontinuation of IP or requires corrective therapy, must be documented appropriately. • Ad hoc labs should be collected as noted in Section 6.4.6.1 above if IRR/CRS occurs. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the subject's medical record and recorded in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. All laboratory tests with clinically significant abnormal values during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator. If such values do not return to normal/baseline within a period judged reasonable by the investigator, the etiology should be identified, and the Sponsor notified. If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator (e.g., AE, SAE or dose interruption), then the results must be recorded in the eCRF.
Unexpected Adverse Reaction	An adverse reaction (causality related Adverse Event), the nature, severity or outcome of which is not consistent with the reference safety information section of the SL-172154 IB. Product reference safety information is contained in the current Guidance for Investigators in Section 6.0 of the Investigator's Brochure provided to the Investigator by the Sponsor.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	Suspected Adverse Reaction (causality related AE) that is serious and unexpected.

7.1.1 Events not Qualifying as AEs/SAEs

Because attribution of AEs is difficult in a FIH study, any toxicity experienced by subjects in this study should be recorded as AEs unless otherwise specified. The following are not considered to be AEs or SAEs:

- Medical or surgical procedures (e.g., endoscopy, appendectomy). The condition that leads to the procedure is considered the AE.
- Elective procedures, planned hospitalizations, and procedures for treatment of conditions noted in the subject's medical history (present prior to signing the ICF) that have not worsened are not considered AEs.
- Situations where an untoward medical occurrence did not occur (i.e., admission to hospital for social circumstances).
- Anticipated day-to-day fluctuations of pre-existing medical conditions that were present at start of study. These conditions are considered part of the subject's medical history and must be adequately documented on the appropriate page of the CRF.
- Clear progression of disease under study should not be reported as an AE or SAE (unless the investigator considers the progression of underlying neoplasia to be atypical in its nature, presentation or severity from the normal course of the disease in a particular subject). Signs and symptoms that are clearly consistent with the expected progression of the underlying cancer should not be reported as an adverse event, and hospitalizations due to the progression of cancer do not necessarily qualify for an SAE. If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.
- In the case where the medical condition is known when the participant enters the trial, only worsening (increased frequency or intensity of the episodes or attacks) will be documented as an AE. If the disease is detected during the trial, and if repeated episodes enable diagnosis of a chronic disease, the episodes will be grouped together in the CRF, and the diagnosis will be clearly described.
- Laboratory abnormalities: An isolated, out-of-range laboratory result in the absence of any associated, clinical finding may or may not be considered an AE, the Investigator's evaluation should be based on a consideration of the overall clinical context.

7.2 Classification of an Adverse Event

7.2.1 Assessment of Severity

The descriptions and grading scales found in the revised NCI-CTCAE version 5.0 will be utilized for AE reporting. A copy of these criteria can be downloaded from the website: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- **Grade 2:** Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL*

- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
- **Grade 4:** Life-threatening consequences; urgent intervention indicated
- **Grade 5:** Death related to AE

*Instrumental activities of daily living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

For AEs not included in the NCI-CTCAE v5.0 grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the subject's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events may be potentially life-threatening or incapacitating.

NOTE: A distinction should be drawn between serious and severe AEs. Severity is an estimate or measure of the intensity of an AE, while the criteria for serious AEs are indications of adverse subject outcomes for regulatory reporting purposes. A severe AE need not necessarily be considered serious and a serious AE need not be considered severe.

7.2.2 Assessment of Causality

The clinician's assessment of an AE's relationship to SL-172154 is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to SL-172154 assessed. In a clinical trial, the IP must always be suspect. To help assess causality, the following guidelines are used.

- **Related** – The AE is known to occur with the IP, there is a reasonable possibility that the IP caused the AE, or there is a temporal relationship between the IP and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the IP and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of IP caused the event, there is no temporal relationship between IP and event onset, or an alternate etiology has been established.

7.2.3 Expectedness

The Sponsor will be responsible for determining whether an AE is expected or unexpected.

- **Unexpected** - An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the safety information section 6.0 (Guidance for Investigators) of the IB [Report_SL2020IB001] for the IP. "Unexpected," as used in this

definition, also refers to AEs or ARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug not specifically mentioned as occurring with the IP under investigation.

- **Expected** - AEs that are common and known to occur for the IP being studied. Expectedness refers to the awareness of AEs previously observed, not on what might be anticipated from the properties of the IP.

7.3 Timing for Event Assessment and Follow-up

All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution. The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the pre-existing condition deteriorates at any time after the subject signs the main study ICF, it will be recorded as an AE. Unanticipated problems will be recorded in the data collection system throughout the study.

AEs characterized as intermittent require documentation of onset and duration of each episode.

7.4 Procedures for Recording and Reporting of Adverse Events

Event	Reporting Procedures
Adverse Event	Subjects will be followed continuously for AEs during the study and for 90 days after the last dose of IP. After a subject is discontinued from IP due to progressive disease or for other reasons, any ongoing AE should be followed until resolution (or return to baseline) and documented in the eCRF, regardless of whether the event(s) is attributed to trial medication. If another anti-cancer agent is started within 90 days of the last dose of SL-172154, only SAEs and irAEs that occur before the new anticancer therapy should be recorded. The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to trial medication, and action taken. Follow-up information should be provided as necessary. AEs will be followed either until resolution, or the event is considered stable. It will be left to the Investigator's clinical judgment to decide whether an AE is of sufficient severity to require the subject's removal from treatment. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the subject must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.
Serious Adverse Event	The study clinician will complete a SAE Form within the following timelines: • All deaths and immediately life-threatening events meeting the SAE criteria (as outlined in section 7.1), whether related or unrelated, will be recorded on the SAE Form and submitted to the study Sponsor or designee *within 24 hours of site awareness.* • Other SAEs regardless of relationship, will be submitted to the study Sponsor or designee *within 24 hours of site awareness*. All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the Sponsor and should be provided as soon as possible. The Sponsor will be responsible for notifying Regulatory Authorities of any unexpected fatal or life-threatening suspected adverse reaction (AR) as soon as possible *but in no case later than 7 calendar* days after the Sponsor's initial receipt of the information. The Sponsor will be responsible for

Event	Reporting Procedures
	notifying Regulatory Authorities of any other serious unexpected suspected adverse reaction as soon as possible *but in no case later than 15 calendar* days after the Sponsor's initial receipt of the information. **Sponsor Contact Information for SAE Reporting** **Email:** [redacted] **eFax number:** [redacted]

7.5 Reporting of Pregnancy

Although not an AE in and of itself, pregnancy as well as its outcome must be documented via the ***Pregnancy Report Form provided by the Sponsor***. Any pregnancy occurring in a participant or participant's partner from the time of consent to 30 days after the last dose of IP must be reported and then followed for outcome. Newborn infants born to the subject or subject's partner should be followed until 30 days old.

A FCBP must discontinue SL-172154 immediately if they become pregnant during the study. To ensure subject safety, each pregnancy must be reported to the Sponsor within two weeks of learning of its occurrence. The pregnancy must be followed to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as a SAE. Spontaneous abortions must be reported as a SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has discontinued SL-172154 must be promptly reported to the Sponsor.

7.6 Reporting of Overdose

The following events should also be reported to the Sponsor *within 24 hours* of knowledge of the event:

- An overdose of SL-172154
- Suspected transmission of an infectious agent due to contamination of drug product
- Other events related to misuse of IP

7.7 Study Halting Rules

Administration of IP will be halted if a fatal SAE is reported to the Sponsor related to SL-172154 monotherapy or combination therapy. The Sponsor will inform the investigators immediately if such an event is reported and screening and enrollment will stop accepting new study subjects. The Sponsor will convene an ad hoc meeting of the SMC to review the SAE and overall safety profile and provide recommendations. The study Sponsor will inform the regulatory authorities (i.e., FDA, European Medicines Agency, etc.) of the temporary halt and the disposition of the study.

7.8 Safety Oversight

An SMC will be implemented in this study and will consist of investigators and Sponsor representatives. SMC meetings will be conducted monthly (or more frequently if required) during dose escalation provided subjects have been enrolled and data are available to be reviewed. The SMC will operate in accordance with the SMC charter which will define roles and accountabilities and the process for safety review. Throughout the conduct of the study, safety data will be reviewed for each subject on an ongoing basis. Based on the AE profile, severity of the DLTs, indicators of potential anti-tumor activity, and other factors, a recommendation on whether to modify the dose and/or study design; or continue enrollment will be made by the Sponsor collaboratively with input from the SMC. Regulatory authorities and IRBs/IECs will be notified of any decisions to prematurely halt the study or subject enrollment. (See section 14.1 for details on safety meetings).

8. ANTI-TUMOR ACTIVITY ASSESSMENTS

Although the clinical benefit of SL-172154 has not yet been established, the intent of offering this IP is to provide a possible therapeutic benefit, and thus the participant will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. For the purposes of this study, participants should be evaluated for response as outlined in the SOA. Confirmatory scans should be performed at least 4 weeks (>28 days) after initial documentation of an objective response or progressive disease. All participants who underwent the first post baseline disease assessment at the 8-week time point or progress or die before to the first post baseline disease assessment will be considered evaluable for response.

Assessments must be performed on a calendar schedule and should not be affected by dose interruptions or delays. Refer to the SOA (Section 6) for the schedule of disease assessments. More frequent disease assessments may be performed at the discretion of the investigator. For subjects whose disease may be followed by well-characterized tumor markers (i.e., CA-125), disease assessments should include results of tumor marker assessments. If study treatment is withdrawn for reasons other than disease progression, radiographic disease assessments should continue as per the SOA until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent or death. See Sections 8.2 for criteria for continuing treatment past disease progression.

8.1 Disease Assessment

Imaging studies, preferable by contrasted computed tomography scan for disease assessment of chest, abdomen and pelvis and all other sites of known disease will be performed at baseline and at the following intervals until disease progression: every 8 weeks until week 24 and every 12 weeks thereafter until year 2 and every 6 months until study conclusion. PET-CT, MRI, and/or bone scan should be performed as clinically indicated. The same imaging modality used at baseline should be employed subsequently. Confirmatory scans should be performed at least 4 weeks (>28 days) after initial documentation of an objective response or progressive disease. Contrast enhanced imaging is required unless the subject is precluded from receiving contrast (e.g., hypersensitivity, renal impairment).

Treatment beyond progression will be permitted provided the subject meets protocol specified criteria in Section 8.2. If subjects discontinue investigational therapy prior to progressive disease,

they should continue to be followed with radiologic assessments until disease progression, start of a new anti-cancer therapy, withdrawal of consent or death.

8.1.1 Assessment of Response

Investigator-assessed response and progression will be evaluated in this study using RECIST v1.1 [Eisenhauer, 2009] and iRECIST [Seymour, 2017]. The RECIST v1.1 guideline and iRECIST guideline are included in this document (Section 16.5).

8.2 Criteria for Treatment Beyond Initial Progression

Subjects will be permitted to continue IP beyond initial progressive disease provided the subject does not have clinical symptoms of progression, is tolerating IP, has experienced no decline in their ECOG performance status and is gaining clinical benefit as assessed by the investigator. The subject must be made aware of the potential benefits and risks of continuing the IP in the setting of progressive disease by signing a separate written informed consent.

The subject may continue to be treated until one of the following criteria is met:

- Meets any of the criteria for discontinuation of IP (see Section 3.7)
- Develops clinical symptoms or signs such that the benefit-risk ratio of continuing therapy is no longer justified
- Experiences rapid progressive disease with risk to vital organs or critical anatomical sites requiring urgent medical intervention

9. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

9.1 Study Design and Sample Size Determinations

The dose escalation will utilize a mTPI-2 design [Guo, 2017] with target DLT rate of 30% for the MTD. The DLT evaluable population is defined in section 9.2.1.

The mTPI-2 design employs a simple Beta-Binomial Bayesian model with decision rules based on the unit probability mass from the posterior probability of DLT rate. With the target DLT rate of 30%, the posterior probability of DLT rate unit interval (0, 1) is divided into subintervals with equal length of 0.1 that correspond to different dose escalation decisions: subinterval of (0.25, 0.35) is to stay at the current dose, subintervals below 0.25 is to escalate to next higher dose, and subintervals above 0.35 is to de-escalate to the next lower dose. Subjects will be enrolled in cohorts of approximately 3 subjects during the dose escalation. After each cohort of approximately 3 subjects, the posterior unit probability for subintervals will be calculated based on a noninformative prior distribution for the DLT rate (Beta (1,1)) and the total number of subjects with DLTs and DLT evaluable subjects for the current dose. A dose escalation/stay/de-escalation decision that corresponds to the subinterval with the highest unit probability mass will be selected. A minimum of 3 DLT evaluable subjects will be enrolled to a dose level and evaluated for DLT before a dose escalation/stay/de-escalation decision can be made unless unacceptable toxicity is observed prior to the enrollment of 3 subjects e.g., two subjects experience DLT before the third subject enrolls. A dose level will be considered unsafe, with unacceptable toxicity and no additional subjects enrolled at that dose level and above, if it has an estimated 95% or more probability of exceeding the target DLT rate of 30%. The maximum number of subjects evaluated for DLT for each dose level will be 12 subjects (about 4 cohorts of 3 subjects) if the dose escalation

decision is to stay at the current dose from the first 3 cohorts. Based on the above design, the dose escalation decision rules are as the following for each dose level:

- When the number of DLT evaluable subject is <12 subjects:
  - Dose escalate if the observed DLT rate <25%;
  - Stay at the current dose if the observed DLT rate between 25%-33%;
  - Dose de-escalate if the observed DLT rate >33%;
- After reaching the maximum 12 subjects, the dose escalation decision will be either escalate or de-escalate as the following:
  - Dose escalate if the observed DLT rate ≤25%;
  - Dose de-escalate if the observed DLT rate ≥33%;

See Table 7 for dose escalation decision rules based on the total number of subjects evaluable for DLT and the number of DLTs observed.

Table 7. Dose Escalation Decision Rules for Each Dose Level based on mTPI-2

Number of subjects with DLTs	Number of Subjects									
	3	4	5	6	7	8	9	10	11	12
0	E	E	E	E	E	E	E	E	E	E
1	S	S	E	E	E	E	E	E	E	E
2	D	D	D	S	S	S	E	E	E	E
3	DU	DU	D	D	D	D	S	S	S	E
4	.	DU	DU	DU	D	D	D	D	D	D
5	.	.	DU	DU	DU	DU	DU	D	D	D
6	.	.	.	DU	DU	DU	DU	DU	DU	D
7	.	.	.	.	DU	DU	DU	DU	DU	DU
8	.	.	.	.	.	DU	DU	DU	DU	DU
E = escalate to the next higher dose level					S = stay at the current dose level					
D = de-escalate to the next lower dose level					DU = de-escalate to the next lower dose level and current dose level will never be used again due to unacceptable toxicity					

Note: For each dose level, a minimum of 3 subjects will be enrolled and evaluated before a dose escalation/stay/de-escalation decision can be made unless unacceptable toxicity is observed prior to the enrollment of 3 subjects e.g., 2 subjects experience DLT before the third subject enrolls.

Sample Size Determination:

The planned sample size is approximately 33-54 subjects. If only Schedule 1 is evaluated, the planned total sample size is 21 for dose escalation. If Schedule 1 and Schedule 2 are both fully evaluated in dose escalation, the maximum planned sample size for dose escalation is 42. This sample size assumes evaluation of five dose levels with approximately 21 subjects treated in the

dose escalation cohorts for each schedule 1 and schedule 2, assessment of approximately 6 subjects in an optional pharmacodynamic cohort and assessment of approximately 6 subjects in dose expansion. Overall, approximately 6-12 subjects are to be treated at the RP2D for SL-172154. In dose escalation cohorts, subject may be replaced if not DLT evaluable.

NOTE: The planned sample sizes may be revised if additional dose levels are evaluated or if more subjects (i.e., 4 subjects dosed in a cohort to ensure that at least 3 subjects are DLT evaluable) are enrolled. The Sponsor, in consultation with the SMC, may also elect to add subjects to the dose escalation if additional data are needed for RP2D determination.

9.2 Statistical Analyses

Complete details of the statistical analysis will be provided in the Statistical Analysis Plan (SAP). Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the SAP and final study report.

9.2.1 Analysis Populations

For the analysis, the following populations are defined:

Population	Description
Enrolled	All subjects who have signed the main study inform consent form (ICF).
Screen Failures	All subjects who have signed the main study ICF but have not received any study treatment.
All Treated	All subjects who have received at least one dose of IP. Safety data will be evaluated based on this population.
DLT Evaluable	All treated subjects 1) who have received ≥2 of the 3 scheduled doses of IP on schedule 1 or who have received ≥2 of the 4 scheduled doses of IP on schedule 2 during cycle 1 and complete the safety follow-up through the 28-day DLT evaluation period; or 2) who experience any DLT during the DLT evaluation period. DLT evaluable subjects will be used to guide dose escalation and to determine the MTD or MAD.
Response Evaluable	Subjects in the All Treated Population who have a baseline disease assessment and have at least one post-baseline disease assessment or have progressed or died before the first post-baseline disease assessment.
Pharmacokinetic	Subjects in All Treated Population from whom at least one PK sample is obtained and analyzed. The PK population will be used for the PK analysis.
Pharmacodynamic	Subjects in the All Treated Population for whom at least one pharmacodynamic sample is obtained and analyzed. The pharmacodynamic population will be used for the pharmacodynamic data analysis.

9.2.2 Interim Analyses

During the dose escalation, the number of subjects with DLTs will be determined after each cohort of approximately 3 subjects has been evaluated for DLT. The summary of DLTs for each dose level will be based on the number of subjects with DLTs from all subjects dosed and evaluated at

the corresponding dose level who meet the definition of the DLT Evaluable Population. Selected AE summary tables and listings may be provided during dose escalation to support dose escalation decisions.

9.2.3 General Data Analysis Consideration

Tabular summaries will be presented by dose levels/schedule/cohorts and total number of subjects in the corresponding population. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics.

As it is anticipated that accrual will be spread thinly across centers and summaries of data by center would be unlikely to provide valuable information, data from all participating centers will be pooled prior to analysis.

All data up to the time of study completion/withdrawal from study will be included in the analysis for each subject, regardless of duration of treatment.

9.2.4 Safety Analyses

The safety evaluation will be based on the All Treated Population and the DLT evaluation will be based on the DLT evaluable population.
DLTs will be summarized by dose level. Frequency tables will be used to describe safety and tolerability parameters AEs, irAEs, SAEs, fatal SAEs and AEs leading to discontinuation of SL-172154. Graphs may also be presented where appropriate. AEs will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ classification. Laboratory abnormalities will be graded according to the NCI CTCTAE v5., if applicable. Concomitant medications will be coded using the World Health Organization Drug Dictionary.

MTD: The MTD will be estimated using isotonic regression (based on the DLTs observed in DLT evaluable subjects). Specifically, the MTD is the dose for which the isotonic estimate of the DLT rate is closest to the target DLT rate of 30%. If two or more doses tie for the smallest difference, perform the following rules:

- If the estimated DLT rate < 30% for all doses, then select the higher dose among the tied doses;
- If the estimated DLT rate for the tied doses are a combination of < 30% for and > 30%, then select the higher dose among the tied doses;
- If the estimated DLT rate > 30% for all dose, then select the lower dose among the tied doses

NOTE: For subjects who undergo intra-subject dose escalation, DLTs will only be assessed during the DLT period applicable on the subject's initial dose level.

A MAD will be reported if the observed DLT rate is <25% among all dose levels. Otherwise, an MTD will be reported.

9.2.5 Efficacy Analyses

Anti-tumor activity data will be summarized by dose level/schedule and overall in the All Treated population and Response Evaluable population.

The primary analysis of anti-tumor activity assessment is based on RECIST v1.1 and exploratory analysis of anti-tumor activity assessment is based on iRECIST.

The ORR and CBR will be estimated along with a 95% confidence interval using the exact probability method. Change from baseline sum of diameters for target lesions will be provided for each subject. DOR and TTP will be evaluated, using the Kaplan-Meier method, for the subgroup of subjects with a confirmed response. The Kaplan-Meier method will be used to estimate the PFS/OS curve and PFS/OS rate at time of point of interest.

9.2.6 Pharmacokinetic Analysis

The PK analysis will be based on the PK population. Serum concentrations for SL-172154 will be summarized using tabular and graphical format. SL-172154 PK parameters will be summarized and analyzed using appropriate statistical methods. The Pharmacokinetics of SL-172154 will be described using the PK parameters listed in Table 8, as data permit.

Table 8: Serum SL-172154 PK Parameters

C_{max}	Maximum observed concentration
T_{max}	Time of maximum observed concentration
$AUC_{0\text{-}last}$	The area under the serum concentration time curve, from time 0 to the last quantifiable concentration, calculated by a combination of linear and logarithmic trapezoidal methods (Linear up/log down method).
$AUC_{0\text{-}t}$	The area under the serum concentration time curve, from time 0 to time=t, calculated by a combination of linear and logarithmic trapezoidal methods (Linear up/log down method).
$AUC_{0\text{-}inf}$	Area under the serum concentration time curve from time 0 extrapolated to infinity, calculated as $AUC_{last} + C_{last}$/terminal elimination rate constant (λ_z). Reliability of $AUC_{0\text{-}inf}$ values is contingent on the percent of the total area obtained by extrapolation: $AUC_{0\text{-}inf}$ values with <20% of the total area coming from C_{last}/λ_z are considered acceptable. Any exceptions to the above procedures will be clearly documented/justified in the PK report.
AUC_{tau}	The area under the serum concentration time curve, over the dosing interval following doses > first dose, calculated by a combination of linear and logarithmic trapezoidal methods (Linear up/log down method).
$\%AUC_{ext}$	Percentage of $AUC_{0\text{-}inf}$ due to extrapolation from T_{last} to infinity
$t_{½}$	Terminal elimination half-life, estimated using the equation $[\ln(2)/\lambda_z]$
CL	Clearance; calculated as Dose/$AUC_{0\text{-}inf}$
V_z	Volume of distribution; calculated as Dose/(λ_z * $AUC_{0\text{-}inf}$)

9.2.6.1 Anti-Drug Antibody Analysis

Individual subject ADA titer and status (positive, negative, inconclusive) vs. nominal time will be reported and summarized by dose level. Onset, duration and persistence of ADA by subject will also be summarized by dose level. ADA isotype may be reported, if supported by the data.

9.2.7 Pharmacodynamics Analyses

The pharmacodynamic analysis will be based on the pharmacodynamic population. Pharmacodynamic biomarkers values will be summarized descriptively by dose level, schedule and visit.

10. CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial complies with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by Sponsor or its designees
- Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.
- Independent audits will be conducted by the Sponsor or designee of the Sponsor to ensure GCP and monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA AND DOCUMENTS

11.1 Source Data

Source documents are where data are first recorded, and from which subjects' eCRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the eCRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

11.2 Access to Data

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB/IEC or regulatory authorities may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records to permit trial-related monitoring, audits and inspections.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB/IEC and Institutional regulations.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored by the Sponsor. This will not include the subject's contact or identifying information. Rather, individual subject's and their research data will be identified by a

unique study identification number. The study data entry and study management systems used by clinical sites and by Sponsor research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived by the Sponsor.

11.3 Data Recording and Record Keeping

All trial data will be entered on electronic data entry systems that are validated and are maintained in accordance with Standard Operating Procedures. The subjects will be identified by a unique trial specific number and/or code in any database. The name and any other identifying detail will NOT be included in any trial data electronic file.

12. QUALITY ASSURANCE PROCEDURES

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. Regular monitoring will be performed according to GCP. Data will be evaluated for compliance with the protocol, GCP, and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the conduct of the clinical trial and data generated, are documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

13. ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 Code of Federal Regulations (CFR) Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the International Conference of Harmonisation (ICH) E6 and consistent with the consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002), or ethical policy statement specific to the country, whichever provides the most protection to human subjects.

13.2 Institutional Review Board/Institutional Ethics Committee

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB/IEC for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is screened and enrolled. Any amendment to the protocol will require review and approval by the IRB/IEC before the changes are implemented to the study. All changes to the consent form will be IRB/IEC approved; a determination will be made regarding whether previously consented subjects need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent/Assent and Other Informational Documents Provided to Subjects

The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study. Subjects will be required to sign and date a study consent form prior to any study-related procedures are performed if they meet eligibility requirements of the protocol and wish to participate in the trial. If applicable, it will be provided in a certified translation of the local language.

- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative [defined as an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research] will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.
- Subjects who are rescreened are required to sign a new ICF.

The ICF may contain a separate section or a separate ICF may be used for optional exploratory research. The investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be informed that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study period. Subjects who decline to participate in this optional research will not provide this separate signature.

13.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB/IEC approved and the participant and/or the legally authorized representative will be asked to read and review the document. The investigator and/or his/her authorized designee will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign and date the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.4 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the Sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, study documentation, data, and all other study-related information generated will be held

in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the Sponsor.
The study monitor, auditors, other authorized representatives of the Sponsor including the contract research organization (CRO), if applicable, representatives of the IRB/IEC or the Sponsor supplying study product, the Federal government or its designee and applicable regulatory authorities will be granted direct access to the study participants' original medical records (including but not limited to office, clinic, hospital, or pharmacy records), all documents required to be maintained by the investigator, for verification of clinical trial procedures and/or data, without violating the confidentiality of the participants, to the extent permitted by the law and regulations.

All documents will be stored safely in a secure location to protect confidentiality. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant identification number/code, not by name. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB/IEC and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored a Sponsor location. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by research staff at the clinical sites and by authorized representatives of the Sponsor will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at a Sponsor location.

13.4.1 Research Use of Stored Human Samples, Specimens, or Specimen Data

- Intended Use: Samples and data collected under this protocol may be used to study the effects of the investigational drug on how one's immune system reacts and how the body responds to this type of treatment in treating different types of cancers.
- Storage: Access to stored samples will be limited to specified study personnel/vendor personnel. Samples will be identified by unique subject identification codes. Samples and data will be stored using subject ID assigned by the Sponsor and investigators.

13.5 Future Use of Stored Specimens

Specimens collected for this study will be analysed and stored at the Sponsor Data Repository or Sponsor-approved vendor.

During the conduct of the study, an individual subject can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent related to bio-sample storage, will not be possible after the study is completed.

14. DATA HANDLING AND RECORD KEEPING

14.1 Communication and Data Dissemination Plan

During the study while subjects are receiving treatment with SL-172154, SMC meetings will be held to review relevant data with the investigators or delegates. These meetings will be held once a month (or more frequently if required) to share safety data and communicate results of ongoing

analyses. All available safety, PK, pharmacodynamic, and clinical outcome data for all subjects at the time of the scheduled SMC Meeting will be reviewed and summarized. Attendees of SMC meetings will include but not be limited to clinical investigators (or designees), the Sponsor Medical Monitor and Statistician. The SMC will operate in accordance with the SMC charter which will define roles and accountabilities and the process for safety review.

The Sponsor will remain in constant contact with the clinical sites during the enrollment period to ensure that cohort enrollment during the dose escalation of this study is completed as per protocol. All dose escalation or safety decisions made by the SMC will be documented in writing with copies maintained at each site and the Trial Master File at the Contract Research Organization.

14.2 Data Collection and Management Responsibilities

An eCRF will be used to record all subject data specified by this protocol. The eCRF must be completed by designated and trained study personnel. The eCRF will be electronically signed by the Principal Investigator or a Sub-investigator listed on the Form FDA 1572. Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Source documents may include but are not limited to, study progress notes, e-mail correspondence, computer printouts, laboratory data, and drug accountability records.

Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the subject's official electronic study record.

Clinical data (including but not limited to AEs, concomitant medications, and expected ARs data) and clinical laboratory data will be entered into the study database, a 21 CFR Part 11-compliant data capture system provided by the Sponsor. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered into an electronic data capture system directly from the source documents.

Study data will be entered into eCRFs at the study site. Prior to database lock, programmed computer edit checks and manual checks will be performed to check for discrepancies and reasonableness of the data. All issues resulting from the computer-generated checks are to be resolved as quickly as possible with clarification from study sites.

14.3 Study Records Retention

The Sponsor follows US regulations and ICH guidelines in its retention policy.

US IND regulations (21CFR 312.62c) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug(s) including eCRFs, consent forms, laboratory test results, and medication inventory records be kept on file by the Principal Investigator for 2 years following the date a marketing application is approved for the drug for the indication for which it is being studied. If no application is to be filed or if the application is not

approved for such indication, these records must be kept until 2 years after the investigation has been discontinued and regulatory authorities (i.e., FDA, European Medicines Agency, etc.) have been notified. ICH guidelines indicate that study documents should be retained until at least 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 IP. If there is a country or institutional policy that specific records and documents be retained for a longer period than described above, the applicable sites must comply with those policies in addition to US and ICH policies.

No study records should be destroyed without prior authorization from The Sponsor, the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the investigator when these documents no longer need to be retained.

14.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or GCP requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site to use continuous vigilance to identify and report deviations to the Sponsor Medical Monitor or designee as soon as protocol deviation is identified. All documentation regarding protocol deviations will be maintained in the regulatory file. All deviations must be addressed in study source documents and reported to Sponsor. Protocol deviations must be sent to the local IRB/IEC per their guidelines. The site Principal Investigator is responsible for ensuring all study staff understands the local IRB/IEC reporting guidelines and adhere to all related requirements and documentation.

14.5 Publications and Data Sharing Policy

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement. Authorship will be determined by mutual agreement and in line with the International Committee of Medical Journal Editors authorship requirements.

15. LITERATURE REFERENCES

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16. APPENDICES

16.1 mTPI-2 Dose Escalation Scenarios

See Table 7 in Section 9.1 for dose escalation decision rules based on the total number of subjects evaluable for DLT and the number of DLTs observed.

For each dose level, subjects will be enrolled in cohorts of approximately 3 to evaluate DLT and make a dose escalation/stay/de-escalation decision based on decision rules in table 6 in section 9.1 as the following steps:

- **Step 1**: The first cohort of at least 3 subjects will be enrolled and evaluated for DLT, and dose escalation/stay/de-escalation decision will be made among at least 3 DLT evaluable subjects. Assuming 3 subjects are DLT evaluable in cohort #1, the following decisions will be made based on the number of subjects with a DLT among the 3 DLT evaluable subjects:
    - If no subject with a DLT, dose escalate to the next higher dose level;
    - If 1/3 subject with a DLT, stay at the current dose level and move to step 2;
    - If 2/3 subjects with a DLT, dose de-escalate to next lower dose level;
    - If 3/3 subjects with a DLT, dose de-escalate to next lower dose level and the current dose level will never to be used;
    - If the first 2 subjects experience a DLT before the third subject enrolls, then de-escalate to the next lower dose level and the current dose level will never be used.
- **Step 2**: As there is 1 subject with DLT among 3 DLT evaluable subjects in cohort #1, approximately 3 subjects will be enrolled and evaluated for DLT at the current dose in cohort #2. Assuming 3 DLT evaluable subjects in cohort #2, the following decisions will be made based on the number of subjects with DLT among the 6 DLT evaluable subjects from cohort #1 and cohort #2:
    - If 1/6 subjects with a DLT (no subject with a DLT in cohort #2), then dose escalate to the next higher dose level;
    - If 2/6 subjects with a DLT (1 subject with a DLT in cohort #2), stay at the current dose level and move to step 3;
    - If 3/6 subjects with a DLT (2 subjects with a DLT in cohort #2), dose de-escalate to next lower dose level;
    - If 4/6 subjects with a DLT (3 subjects with a DLT in cohort #2), dose de-escalate to next lower dose level and the current dose level will never be used.
- **Step 3**: As there are 2 subjects with DLT among 6 DLT evaluable subjects in cohort #1 and #2, approximately 3 subjects will be enrolled and evaluated for DLT at the current dose in cohort #3. Assuming 3 DLT evaluable subjects in cohort #3, the following decisions will be made based on the number of subjects with DLT among the 9 DLT evaluable subjects from cohort #1, cohort #2 and cohort #3:
    - If 2/9 subjects with a DLT (no subject with a DLT in cohort #3), then dose escalate to the next higher dose level;

- If 3/9 subjects with a DLT (1 subject with a DLT in cohort #3), stay at the current dose level and move to step 4;
- If 4/9 subjects with a DLT (2 subjects with a DLT in cohort #3), dose de-escalate to next lower dose level;
- If 5/9 subjects with a DLT (3 subjects with a DLT in cohort #3), dose de-escalate to next lower dose level and the current dose level will never be used.

- **Step 4**: As there are 3 subjects with DLT among 9 DLT evaluable subjects in the first 3 cohorts, approximately 3 subjects will be enrolled and evaluated for DLT at the current dose in cohort #4. Assuming 3 DLT evaluable subjects in cohort #4, the following decisions will be made based on the number of subjects with DLT among the 12 DLT evaluable subjects from all 4 cohorts:
  - If 3/12 subjects with a DLT (no subject with a DLT in cohort #4) with 25% DLT rate, then dose escalate to the next higher dose level;
  - If 4-6 subjects with a DLT (1-3 subjects with a DLT in cohort #4) with 33% to 50% DLT rate, dose de-escalate to next lower dose level.

16.2 ECOG Performance Status Criteria

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)
2	In bed < 50% of the time. 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	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.	

16.3 Contraception Requirements

Females of reproductive potential must agree to avoid becoming pregnant. Female of reproductive potential are required to use adequate methods of birth control from the time of screening (i.e., at least 14 days prior to D1 of SL-172154) through at least 30 days after the last dose of SL-172154.

Definition of Female of Childbearing Potential:
A female subject who is not sterile due to surgery (i.e., from bilateral tubal ligation/occlusion, bilateral oophorectomy, bilateral salpingectomy or complete hysterectomy) or who does not have a congenital or acquired condition that prevents childbearing or who is not naturally post-menopausal for at least 12 consecutive months.

Definition of Female of Non-Reproductive Potential:
Female subjects will be considered of non-reproductive potential if they:

1. Are post-menopausal if defined as amenorrhoeic for 12 consecutive months without an alternative medical cause. In women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 consecutive months of amenorrhea, a single FSH measurement is insufficient;

   OR
2. Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

   OR
3. Have a congenital or acquired condition that prevents childbearing.

Definition of Male of Non-Reproductive Potential:
Male partners will be considered of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Highly Effective Methods of Contraception (<1% failure rate):
For contraception, subjects should comply with one of the following:

1. Practice abstinence† from heterosexual activity;

   OR
2. Use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:

- Single method (one of the following is acceptable):
  - intrauterine device
  - vasectomy of a female subject's male partner
  - contraceptive rod implanted into the skin
- Combination Methods
  - Female Subjects: The following hormonal contraceptives may be used by female subjects and requires use of a male condom for the male partner:
    - oral contraceptive pill (estrogen/progestin pill or progestin-only pill)
    - contraceptive skin patch
    - vaginal contraceptive ring
    - subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and IRBs/Independent IECs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. To participate in the study, subjects of childbearing potential must adhere to the contraception requirement (described above) from the time of screening and at least 14 days prior to D1 of SL-172154 through at least 30 days after the last dose of SL-172154.

16.3.1 Pregnancy Status

In the rare event that β-hCG is elevated as a tumor marker, pregnancy should be excluded. At minimum, this requires obstetrics evaluation, serial β-hCG measurements and ultrasound to exclude pregnancy.

16.4 Cockcroft-Gault Formula for Creatinine Clearance

$$\text{Creatinine clearance (mL/min)}^{1} = \frac{Q \times (140 - \text{age [yr]}) \times \text{ideal body weight [kg]}^{2}}{72 \times \text{serum creatinine [mg/dL]}}$$

Q = 0.85 for females
Q = 1.0 for males

OR

$$\text{Creatinine clearance (mL/min)}^{2} = \frac{K \times (140 - \text{age [yr]}) \times \text{ideal body weight [kg]}^{1}}{\text{serum creatinine [µmol/L]}}$$

K = 1.0 for females
K = 1.23 for males

1. Creatinine clearance has a maximum value of 125 mL/min.
2. Use ideal body weight (IBW) if body weight > 30% of IBW. Otherwise, use bodyweight

Calculation of IBW using the Devine Formula [Devine, 1974]:

Males = 50.0 kg + (2.3 x each inch over 5 ft) or 50.0 kg + (0.906 kg x each cm over 152.4 cm)
Females = 45.5 kg + (2.3 x each inch over 5 ft) or 45.5 kg + (0.906 kg x each cm over 152.4 cm)

Example:
Male, actual body weight = 90.0 kg; height = 68 inches; IBW = 50 + (2.3) (68 – 60) = 68.4 kg
This subject's actual body weight is >30% over IBW. Therefore, in this case, the subject's IBW of 68.4 kg should be used in calculating the estimated creatinine clearance

References:

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16.5 RECIST v1.1 and iRECIST Criteria

16.5.1 RECIST v1.1 Criteria

Measurable disease: Measurable tumor lesions (nodal, subcutaneous, lung parenchyma, solid organ metastases) are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 millimeter (mm) with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥10 mm by CT scan). Malignant lymph nodes must be ≥15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in mm (or decimal fractions of cm). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

Malignant lymph nodes: pathological nodes must meet the criterion of a short axis of ≥15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis, inflammatory breast disease, lymphangitic involvement of lung or skin, and abdominal masses followed by clinical exam are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Target lesions: When more than one measurable tumor lesion is present at baseline all lesions up to a maximum of 5 lesions in total (and a maximum of 2 lesions per organ), representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the eCRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

16.5.2 Evaluation of Response

Complete Response (CR): Disappearance of target and non-target lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures <10 mm (Note: continue to record the measurement even if <10 mm and considered CR). Residual lesions (other than nodes <10 mm) thought to be non-malignant should be further investigated (by cytology, specialized imaging or other techniques as appropriate for individual cases) before CR can be accepted. Response should be confirmed in a subsequent scan ≥4 weeks after the scan showing CR.

Partial Response (PR): At least a 30% decrease in the sum of the measures (longest diameters for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non-target lesions must be non-progressive disease. Response should be confirmed in a subsequent scan ≥4 weeks after the scan showing PR.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study. Documented at least once ≥4 weeks from baseline.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥5 mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment or where the tumor burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of progressive disease is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

16.5.3 iRECIST v1.1 Criteria

When using iRECIST, the definitions of measurable and non-measurable lesions still follow RECIST v1.1. The principles used to establish an objective tumor response when using iRECIST are largely unchanged from RECIST v1.1, however, responses assigned using iRECIST have a prefix of “i” (e.g., “immune” complete response [iCR]) to differentiate them from responses assigned using RECIST v1.1.

The major change is the concept of resetting the bar if RECIST v1.1 progression is followed at the next assessment by tumor shrinkage. This adaptation accounts for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression. Therefore, iRECIST requires confirmation of progression.

Confirming Progression: iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD. iCPD is confirmed if further increase in tumor burden, compared to the last assessment, is seen as evidenced by one or more of the following criteria:

- Continued increase in tumor burden (from iUPD) where RECIST v1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions.
    - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
    - Continued unequivocal progression in non-target disease with an increase in tumor burden
    - Increase in size of previously identified new lesion (s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions
- RECIST v1.1 criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.
- If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR or iCR if those criteria are met compared to baseline).

New Lesions: New lesions (NL) should be assessed and measured as they appear using RECIST v1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis (or 15 mm in short axis for nodal lesions) and recorded as New Lesions-Target (NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the eCRF.

Progressive disease is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions.

iRECIST Time Point Response Table

Target Lesions	Non-Target Lesions	New Lesions	Time Point Response	
			No prior iUPD	Prior iUPD
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR

Target Lesions	Non-Target Lesions	New Lesions	Time Point Response	
			No prior iUPD	Prior iUPD
iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	NLs confirms iCPD if NL were previously identified and increase in size (≥5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST v1.1 criteria for unequivocal PD)
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in SOM of at least 5 mm, otherwise remains iUPD
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in previously identified T lesion iUPD SOM ≥5 mm and/or NT lesion iUPD (prior assessment need not be unequivocal PD)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: • previously identified T lesion iUPD SOM ≥5 mm and/ • previously identified NT lesion iUPD (prior assessment need not be unequivocal PD) • size or number of new lesions previously identified
Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on: • increase in size or number of new lesions previously identified

Target Lesions	Non-Target Lesions	New Lesions	Time Point Response	
			No prior iUPD	Prior iUPD
* Using RECIST v1.1 principles. If no pseudo-progression of disease (PSPD) occurs, RECIST v1.1 and iRECIST categories for CR, PR and SD would be the same. ** in any lesion category. *** previously identified in assessment immediately prior to this TP. PD = progressive disease; SOM = sum of measurements Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.				

16.6 Summary of Changes for Protocol Amendment 02

Minor Editorial Changes:

- Title Page and all page headers have edits to denote version number/date of Amendment 02
- Updated TOC and List of Abbreviations
- Removed United Kingdom as a country for location of clinical sites from Synopsis section (Planned Number of Sites and Countries section)
- In Section 3.5.1 clarified that medications are prohibited during SL-172154 therapy (removed ~~study~~)
- Text deleted from footnote m to SOA table in 6.1: ~~CA-125 should be measured to coincide with each scheduled tumor assessment as outlined above with the last required sample obtained at the post-treatment visit which occurs within 30 days of last dose of SL-172154~~**~~Table~~** ~~4~~
- Section 6.1.1 Table 4 title heading added new text: *and RBC Binding*
- In Section 7.3 removed first sentence in last paragraph of this section: ~~Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity~~.

Changes Made to Address FDA Concerns:

1. Homologous recombinant deficiency (HRD) status will be collected for all subjects including BRCA status

   Section 6.1 SOA Table and footnotes
   - Revised to include collection of HRD information during screening and footnote S provided new text provided in italics as follows: ***Homologous recombinant deficiency (HRD) status***: *Collection of HRD status (including BRCA status) is required for all subjects during the screening period. Results from standard of care testing will be used.*
   - Footnotes T and U are now associated with Post Treatment and Follow up visits, respectively

2. Inclusion criteria revised to allow enrollment of subjects who fulfill the definitions below:
   a) all subjects with primary ovarian, peritoneal and fallopian cancers are required to have received platinum-based therapies.
   b) HRD positive subjects if they have failed prior PARP inhibitor therapy given with or without bevacizumab and,
   c) refractory or intolerant to existing therapy(ies) known to provide clinical benefit for their condition.

   Section 4.1 inclusion criterion #3 revised as follows:
   3. New Text provided in italics: ~~Subjects should not be eligible for further platinum therapy.~~ *Subjects must be refractory or intolerant to existing therapy(ies) known to provide clinical benefit for their condition. Subject must have received platinum-based therapies, and should not be eligible for further platinum therapy, or should be intolerant to such therapy. Subjects with HRD positive disease may participate if they have received prior polyadenosine diphosphate ribose polymerase (PARP) inhibitor therapy given alone or with bevacizumab.*

3. Treatment beyond progression per iRECIST requires that subjects have no decline in their ECOG performance status.

Section 8.2 provided new text in the 1st paragraph of this section as indicated (new text in italics):

- Subjects will be permitted to continue IP beyond initial progressive disease provided the subject does not have clinical symptoms of progression, is tolerating IP, *has experienced no decline in ECOG performance status* and is gaining clinical benefit as assessed by the investigator. The subject must be made aware of the potential benefits and risks of continuing the IP in the setting of progressive disease by signing a separate written informed consent.

4. The DLT assessment period for assessment of AEs that inform dose escalation decisions is 28 days (not 21 days as originally proposed).

Study Schema revised to note 28-day DLT assessment period

Synopsis Sections that include revisions indicating 28-day DLT assessment period:

- Study Design, Definition of DLT, and Statistical Analysis Sections

Protocol sections revised that include text revisions indicating 28-day DLT assessment period (replacing 21-day period)

- Section 3.1 Description of Study Design
- Section 3.3 Description of Dose Escalation Plan
- Section 3.4 Definition of Dose Limiting Toxicity
- Section 9.2.1 Analysis Populations (revised DLT evaluable population definition)

5. Provided further clarification of the intent to monitor subjects for 90 days after SL-172154 treatment is permanently discontinued.

Protocol sections with text revisions providing clarification of 90-day follow up post last dose of study therapy

- Section 6.1 SOA table footnote p revised as follows (new text in italics):

p. **AE Monitoring**: Subjects will be followed continuously for AEs during the study and for 90 days after the last dose of SL-172154. After a subject is discontinued from SL-172154 or study therapy due to progressive disease or for other reasons, any ongoing AE should be followed until resolution (or return to baseline) and documented in the eCRF. If another anti-cancer agent is started *within 90 days after the last dose of SL-172154*, *only SAEs and AEs that occur prior to the start of the new anticancer therapy* ~~within 30 days from last dose of SL-172154~~ should be recorded. In the event of a continuing SAE or a non-serious irAE, the subject will be asked to return for follow-up until the SAE or AE has resolved or is deemed to be continuing indefinitely. AEs will be characterized per NCI-CTCAE criteria v5.0 and events recorded in the eCRF.

- Section 7 text revision (new text in italics)

  Subjects will be followed continuously for *all*~~ny~~ AEs starting when a subject has signed the ICF, throughout the course of treatment and for 90 days after the last dose of IP. After a subject is discontinued from SL-172154 due to progressive disease or for other reasons, any ongoing AEs should be followed until resolution (or return to baseline) and documented in the eCRF. If another anti-cancer agent is started *within 90 days after the last dose of SL-172154*, only SAEs and irAEs that occur *prior to starting the new anticancer therapy* ~~within 30 days from last dose of SL-172154~~ should be recorded. All observed or volunteered AEs (serious or non-serious) and abnormal laboratory test findings, if applicable, whether suspected to have a causal relationship to SL-172154 or not will be recorded in the subject medical record and in the eCRF. AEs will be graded according to NCI-CTCAE v5.0. For all AEs, sufficient information will be pursued and/or obtained to permit an adequate determination of seriousness and outcome of the event (i.e., whether it should be classified as a SAE or not) and an assessment of the causal relationship between the AE and SL-172154. AEs will be followed until resolution (or return to baseline) or stabilization. Refer to Section 7.4 for documentation and reporting of AEs.

- Section 7.4 AE Reporting procedures (new text in italics)

  Subjects will be followed continuously for AEs during the study and for 90 days after the last dose of IP. After a subject is discontinued from IP due to progressive disease or for other reasons, any ongoing AE should be followed until resolution (or return to baseline) and documented in the eCRF, regardless of whether the event(s) is attributed to trial medication. If another anti-cancer agent is started *within 90 days of the last dose of SL-172154*, only SAEs and irAEs that occur *before the new anticancer therapy* ~~within 30 days from last dose of SL-172154~~ should be recorded. The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to trial medication, and action taken. Follow-up information should be provided as necessary. AEs will be followed either until resolution, or the event is considered stable.

6. Revised the DLT criteria to include any deaths that are not clearly due to the underlying disease or extraneous causes.

   Section 3.4 Definition of Dose Limiting Toxicity and Corresponding Section in Synopsis
   - New Text: *Any death not clearly related to underlying disease or extraneous causes*

7. Clarified that subjects eligible for dose escalation must have tolerated SL-172154 therapy well and experienced AEs < or = Grade 1 in severity on the most recent cycle of study treatment.

   Section 3.3.1 Intrasubject Dose Escalation (and in Synopsis) revised to include new text in italics
   - Intrasubject dose escalation(s) may be considered on a case-by-case basis, provided that the subject has completed at least 2 cycles at the originally assigned dose, has tolerated treatment well, ~~and did not experience Grade 3 or higher toxicity~~, *and experienced ≤Grade 1 toxicity on the most recent cycle of SL-172154 therapy*.

8. Clarified that all AEs that occur in subjects enrolled in this study will be collected starting from the time subject consents to participate until they are discontinued from the study.

Section 7.1.1 Events not Qualifying as AEs/SAEs

- New text added**:** *Because attribution of AEs is difficult in a FIH study, any toxicity experienced by subjects in this study should be recorded as AEs unless otherwise specified.*

16.7 Summary of Changes for Protocol Amendment 03

Minor Editorial Changes:

- Title Page and all page headers have edits to denote version number/date of Amendment 03
- Reference to Investigator's Brochure (IB) for SL-172154 updated and IB now cited in section 1.4.1 point #3 Hemolysis and Anemia
- Updated TOC
- Updated document numbers denoted for Amendments 1 and 2 as shown below

Shattuck Labs Document Number	Date	Version
SL03-OHD-01_01~~00~~	03 March 2020	Amendment No. 1
SL03-OHD-01_02~~01~~	24 April 2020	Amendment No. 2

- Section 1.2.4 last sentence of 2nd paragraph text removed: Additionally, SL-172154 was evaluated in vitro for potential ~~binding to erythrocytes and~~ hemolysis
- Section 1.2.4 second sentence of 7th paragraph new text added (shown in italics) and text removed: In vitro incubation of SL-172154 with ~~erythrocytes from cynomolgus monkeys or~~ human~~s~~ *whole blood* did not result in any detectable hemolysis.
- Section 1.2.4 the last sentence of the last paragraph had text removed: Overall, the nonclinical safety assessment program supports the administration of SL-172154 as an intravenous infusion in the ~~proposed~~ first-in-human (FIH) clinical study SL03-OHD-101.
- New text added to footnote l to SOA table in section 6.1 as shown in italics. This new text is last sentence in the footnote: ***CA-125*** *should be measured to coincide with each scheduled tumor assessment as outlined above with the last required sample for CA-125 obtained at the post treatment visit which occurs within 30 days of the last dose of SL-172154.*

1. The protocol is amended to address the possibility that treatment with SL-172154 may interfere with compatibility tests including the antibody screen and crossmatch that are a part of a routine pre-transfusion work up should subjects on this study require a blood transfusion for supportive care.

   New Section 3.8 added entitled: Antibody Detection and Compatibility Testing for Transfusion

   - New Text in section provides guidance on antibody detection and compatibility testing of subjects on SL-172154 therapy who need a transfusion as supportive care.
   - Sections following the new section 3.8 and text are as follows:
     - Section 3.9 (previously 3.8) entitled Criteria to Resume Treatment
     - Section 3.10 (previously 3.9) entitled Participant Withdrawal of Consent
     - Section 3.11 (previously 3.10) entitled Lost to Follow-up
     - Section 3.12 (previously 3.11) entitled Premature Termination or Suspension of Study
     - Section 3.1.3 (previously 3.12) entitled Duration of Treatment
     - Section 3.14 (previously 3.13) entitled Duration of Follow-up
     - Section 3.15 (previously 3.14) entitled End of Study Definition

   Section 6.1 SOA Table footnote h1

   - Footnote h1 revised with new text added (shown in italics) and old text removed as follows:

1) **At screening**: *The following testing should be performed 1) ABO and D group (ABO/Rh) type and antibody screen and antibody identification if required; 2) DAT; 3) Phenotype/genotype for, at a minimum, the minor antigens Rh C/c E/e, K, Jk, Fy and MNSs*. ~~Full phenotyping should be performed to include ABO, Rh, D, C, E, Kell, Kidd, Duffy, MNS, and antibody screen~~
2) C1/D2: only need to perform blood phenotyping (ABO/Rh) and DAT.

Section 6.4.6.3 Blood Type and Screen (ABO/Rh) and DAT

- Paragraph revised with new text added (shown in italics) and old text removed as follows:

SL-172154 does bind RBCs but has not been shown to cause hemolysis in NHPs. However, treatment with SL-172154 may make phenotyping difficult due to expected coating of the RBC membrane. Thus, blood phenotyping, type and screen (ABO/Rh), and DAT should be performed at screening before exposure to SL-172154. At screening *the following testing should be performed: 1)* ~~full phenotyping should include~~ ABO *and D group (ABO*/Rh) *type and antibody screen and antibody identification if required; 2) DAT; 3) phenotype/genotype for, at a minimum, the minor antigens Rh C/c E/e, K, Jk, Fy and MNSs* ~~D, C, E, Kell, Kidd, Duffy, MNS, and antibody screen should be performed. Subsequent assessment~~ *At cycle 1/day 2, testing* should only include ~~(~~ABO/~~r~~Rh *type*~~)~~ and DAT testing as outlined in the SOA table in Section 6.1.

2. This amendment also addresses a comment provided by the FDA during review of the IND application for SL-172154 on allowable storage condition limits for diluted drug product at room temperature and under refrigerated conditions.

Section 5.1.2.1 Preparation

- Removed text and new text (in italics) added to this section as shown below. Microbial growth testing of drug product at room temperature and under refrigerated conditions is ongoing and this information will be provided in the Study Pharmacy Manual prior to enrollment of subjects.

Standard aseptic technique including preparation of doses in a laminar flow hood is required.

SL-172154 solution 10 mg, 1 mL is supplied as a frozen liquid. Before use, thaw each vial of SL-172154 solution, 10 mg/mL, 1 mL overnight under refrigerated conditions, protected from light, or thaw each vial at room temperature, until the entire solution is no longer frozen (e.g., within 1 hour). Following thawing, gently swirl the vial to ensure uniformity. Only sterile normal saline (0.9%) should be used to dilute SL-172154.

~~The dosing solution of SL-172154 can be held up to 24 hours under refrigerated conditions or 8 hours at room temperature (diluted drug product in bag or syringe) from a stability perspective; but should be used as soon as possible as the product does not contain an antimicrobial preservative. Preparation (e.g., dilution) and administration of study drug may occur at room temperature without protection from light.~~ See the SPM for *further* details *on the preparation of SL-172154*.

3. C reactive protein will be collected at the baseline screening and post treatment follow up visits.

Section 6.1 SOA Table

New text (shown in italics) added to Schedule of Assessments/Procedures column for screening visit

- In the row for ferritin new text added as shown in italics: Ferritin/*C reactive protein*

Section 6.4.6

- C reactive protein was added to the Local Clinical Labs Table under Clinical Chemistry

16.8 Summary of Changes for Protocol Amendment 04

Minor Editorial Changes

- **Title Page and all page headers** have edits to denote version number/date of Amendment 04
- **Title Page**: NCT number added
- **Updated TOC and List of Abbreviations** (Study Reference Manual (SRM) removed from list)
- Minor formatting changes were made throughout document
- **Key Trial Contacts Sponsor Signatory page**-deleted text: ~~Study Reference Manual~~ replaced with new text (italics) *Study Contact List*
- **Inclusion Criterion #3 in Synopsis and Section 4.1 added new text (italics): Subjects** must be refractory or intolerant to existing therapy(ies) known to provide clinical benefit for their condition. Subject must have received platinum-based therapies, and should not be eligible for further platinum therapy, or should be intolerant to such therapy. Subjects with *known* HRD positive disease may participate if they have received prior polyadenosine diphosphate ribose polymerase (PARP) inhibitor therapy given alone or with bevacizumab. *NOTE: HRD testing is not required per protocol*.
- **Synopsis Safety Oversight Section new text (italics added):** During the study while subjects are receiving treatment with SL-172154, SMC meetings will be held to review relevant data with the investigators or delegates. These meetings will be held once a month (or more frequently if required) *during dose escalation* to share safety data and communicate results of ongoing analyses.
- **Intrasubject Dose Escalation Section 3.3.1 (last two sentences of paragraph):** Approval for intrasubject dose escalation must be obtained from the Sponsor Medical Monitor *and must be* ~~.~~ ~~Dose escalation decisions will be~~ documented on an Intrasubject Dose Escalation Decision Form *provided by the Sponsor* ~~(see the Study Reference Manual; SRM).~~
- **Section 5.1.4** New text (italics) added to second paragraph: **Subject weight should be *per the institutional standard but no less precise than* rounded to a whole number prior to calculating the dose to be administered (e.g., 72.5 kg should be rounded up to 73 kg, 72.4 kg should be rounded down to 72 kg).
- **SOA Table 6.1**: New text (italics) added to Title: *Schedule 1* Dose Escalation, Dose Expansion and Pharmacodynamic Cohorts
    - Cross references to protocol sections updated and footnote letters updated
    - **Footnote a**: new text added (italics): Screening Period extends from Day -21 to Day -1. The following screening assessments must be performed within 72 hours of the first dose of SL-172154: hematology profile, chemistry profile, coagulation profile, *ECOG score, physical exam*, and pregnancy test.
- **Section 6.7.1.4 Text removed from Title:** ~~PBMCs for~~ Immunophenotyping
- **Section 7 Safety Assessments**: Subjects will be followed continuously for all AEs starting when a subject has signed the ICF, throughout the course of treatment and for 90 days after the last dose of IP. After a subject is discontinued from SL-172154 due to progressive disease or for other reasons, any ongoing AEs should be followed until resolution (or return to baseline) and documented in the eCRF. If another anti-cancer agent is started within 90 days after the last dose of SL-172154, only SAEs and ~~ir~~AEs that occur prior to starting the new anticancer therapy should be recorded.

- **Section 7.5 Pregnancy Reporting (first sentence, new text underlined):** Although not an AE in and of itself, pregnancy as well as its outcome must be documented via the ***Pregnancy Report Form provided by the Sponsor*** ~~***in the SRM***~~**.**
- **Section 14.1 Data Handling and Record Keeping:** Second paragraph revised as shown: It is the responsibility of the site to use continuous vigilance to identify and report deviations ~~by completing the Sponsor Protocol Deviation Form~~ to the Sponsor Medical Monitor or designee as soon as protocol deviation is identified. ~~A completed copy of the Sponsor Protocol Deviation Form~~ *All documentation regarding protocol deviations* will be maintained in the regulatory file. All deviations must be addressed in study source documents and~~,~~ reported to Sponsor. Protocol deviations must be sent to the local IRB/IEC per their guidelines. The site Principal Investigator is responsible for ensuring all study staff understands the local IRB/IEC reporting guidelines and adhere to all related requirements and documentation. ~~Further details about the handling of protocol deviations will be included in the study reference manual.~~

The protocol is amended to include exploration of a once weekly dosing schedule of SL-172154 in dose escalation to determine a recommended phase 2 dose for further study. (new text provided in italics)

- **Study Schema** revised to included schedule 2 in sample size estimate (33 to 54 subjects)
- **Synopsis sections** updated to accommodate addition of Schedule 2
  - **Planned Sample Size**: Approximately to 33 *to 54* subjects
  - **Recruitment Duration**: 25 ~~18~~ months (≤ ~ 2 years)
  - **Study Duration**: 39 ~~32~~ months (≤ ~3 years)
  - **Study Design**: This clinical trial is a FIH, open label, multi-center, dose escalation Phase 1 study of SL-172154 designed to evaluate the safety, PK, pharmacodynamic effects, and anti-tumor activity of SL-172154 monotherapy administered as an IV infusion. The planned total sample size is approximately 33 - *54* subjects. *If only Schedule 1 is evaluated, the planned total sample size for dose escalation is 21 subjects. If Schedule 1 and Schedule 2 are both fully evaluated across 5 dose levels in dose escalation, the maximum planned sample size for dose escalation is 42.* ~~assuming evaluation of approximately 21 subjects across 5 dose levels in dose escalation; a~~ *A*pproximately 6 subjects *may be enrolled* in an optional pharmacodynamic cohort; and approximately 6 subjects in the dose expansion cohort *at the dose and schedule selected for further evaluation*.
  - **Treatment Schedule**:
    - *Schedule 1:* SL-172154 will be administered IV on days 1, 8, 15 of a 28-day cycle in cycle 1 and then every 2 weeks thereafter (on days 1 and 15 in cycles ≥ 2).
    - *Schedule 2: SL-172154 will be administered IV once weekly on days 1, 8, 15, and 22 every 28 days in every cycle. The starting dose on schedule 2 would be instituted at the current dose level that has completed evaluation for safety on schedule 1 and then continue dose escalation as defined by the mTPI-2 design.*

    Alternative schedules may be explored if emerging data indicate less frequent dosing of SL-172154 should be evaluated. In this case, SL-172154 may be administered once every two weeks, once every three weeks or once every four weeks. *The starting dose on these alternate schedules would be instituted at the current dose level that has completed evaluation for safety and then continue dose escalation as defined by the mTPI-2 design, emerging safety data and as recommended by the Safety Monitoring Committee (SMC).*

~~The starting dose on this altered schedule would be instituted at the current dose level (for a less intensive dose schedule) or a lower dose level (e.g., for a weekly dose as noted for sSchedule 2) as defined by the mTPI-2 design, emerging safety data and as recommended by the Safety Monitoring Committee (SMC).~~

- **Statistical Analysis:** The safety evaluation will be based on the All Treated Population defined as all subjects who received at least one dose of study treatment. Frequency tables will be used to describe safety and tolerability parameters AEs, irAEs, SAEs, fatal SAEs and AEs leading to discontinuation of SL-172154. Changes in toxicity grade for clinical chemistry and hematology will also be summarized. AEs will be mapped to a Medical Dictionary for Regulatory Activities preferred term and system organ classification. Laboratory abnormalities will be graded according to the NCI CTCTAE v5., if applicable. The DLT evaluation will be based on the DLT evaluable population (defined as All Treated subjects enrolled in the dose escalation cohorts 1) who have received ≥2 of the 3 scheduled doses of IP during cycle 1 *on Schedule 1 (or at least 2 of the 4 scheduled doses of SL-172154 on Schedule 2)* and complete the safety follow-up through the 28-day DLT evaluation period; or 2) who experience any DLT during the DLT evaluation period). DLTs will be summarized by dose level. The MTD will be estimated using isotonic regression.

- **Protocol sections updated to accommodate addition of Schedule 2**
  - **Section 3.1** second paragraph: This Phase 1 trial is designed to evaluate the safety, PK, pharmacodynamic effects, and anti-tumor activity of SL-172154 monotherapy ~~administered IV on days 1, 8, 15 of a 28-day cycle in cycle 1 and then every 2 weeks thereafter (on days 1 and 15 in cycles ≥ 2).~~ Subjects with platinum-ineligible ovarian, fallopian tube, and primary peritoneal cancers (Section 4.1) are eligible for treatment.
  - **Dose Escalation Section 3.1**

    Dose escalation will utilize the modified Toxicity Probability Interval (mTPI-2) design [Guo, 2017] with target DLT rate of 30% for the MTD. The dose escalation decision rules are outlined in Table 7 in Section 9.1. Subjects will be enrolled in cohorts of approximately 3 subjects into sequential dose levels of SL-172154 and evaluated for DLT (see Section 3.4 for Definition of DLT) during the 28-day DLT evaluation period starting from the first dose of SL-172154. At each dose level, a minimum 3-day stagger between dosing the first and second subject is required. The planned dose escalation is in half-log increments as outlined in Table 1 and Section 3.3. *During dose escalation, two possible schedules (Schedule 1 and Schedule 2) for administration of SL-172154 may be explored as outlined in Section 3.3. Schedule 1 will be evaluated first. A transition to Schedule 2 may be implemented for reasons outlined in Section 3.2.1. If Schedule 2 is opened for enrollment, then enrollment on Schedule 1 will be halted. If Schedule 2 is opened, the Sponsor may also elect to stop enrollment in Schedule 2 early (e.g., based on safety) and resume enrollment in Schedule 1. The MTD or MAD may be determined for either Schedule 1 or Schedule 2. Alternatively, a less intensive dosing schedule may be instituted if safety, pharmacokinetic and/or pharmacodynamic data on Schedule 1 support less frequent dosing of SL-172154.*

    For each dose level *evaluated on Schedule 1 or Schedule 2*, the minimum number of subjects evaluable for DLT (see Section 9.2.1 for definition of DLT evaluable subject) will be 3 unless unacceptable toxicity is observed prior to enrollment of 3 subjects (e.g., the

first 2 subjects experience a DLT before the third subject enrolls). The maximum number of subjects evaluable for DLT at a dose level will be 12 (e.g., this may be reached by sequential enrollment of 4 cohorts of 3 subjects) assuming the dose decision is to stay at the current dose from the first 3 cohorts. ~~After enrollment of~~ *If* ~~reach~~ *the maximum of* 12 DLT evaluable subjects at a given dose level is reached, a dose escalation decision will be made if ≤3 subjects experience a DLT (DLT rate ≤25%); and a dose de-escalation decision will be made if ≥4 subjects experience a DLT (DLT rate >=33%).

- **Pharmacodynamic Cohorts Section 3.1 (first sentence)**
  The Sponsor, in consultation with the SMC, may elect to open a pharmacodynamic cohort to obtain additional pharmacodynamic data from a total of approximately 6 additional subjects at one or more dose levels that have completed evaluation for safety without exceeding the MTD *on the selected schedule*.
- **Dose Expansion Section 3.1 (first sentence)**
  Approximately 6 subjects may be enrolled in the dose expansion cohort *on a selected schedule*.
- **Sample Size Section 3.1.2**
  If only Schedule 1 is evaluated, T~~*t*~~he planned total sample size *is 21 for dose escalation. If Schedule 1 and Schedule 2 are both fully evaluated in dose escalation, the maximum planned sample size for dose escalation is* ~~36.~~ *42.* ~~for this study is approximately 33 subjects~~. This sample size assumes evaluation of approximately 21 subjects across 5 dose levels in dose escalation *on Schedule 1 and 21 subjects across 5 dose levels on Schedule 2. Approximately 6 subjects may be enrolled in an optional pharmacodynamic cohort. After a dose and schedule are selected*~~, and~~ approximately 6 subjects *will be* in*cluded in* the dose expansion cohort. The number of subjects in dose expansion will vary depending on the number of subjects enrolled in both the dose escalation and pharmacodynamic cohorts at a potential RP2D. The goal is to enroll approximately 12 subjects at the potential RP2D, including subjects in *the* dose escalation, pharmacodynamic ~~cohort,~~ and dose expansion *cohorts*. *Overall, the total sample size estimate for this study is 33 subjects, assuming only Schedule 1 is evaluated, and* ~~12 potential subjects are enrolled at the RP2D and~~ *54 subjects if both Schedule 1 and Schedule 2 are fully evaluated. See Section 9.1 for more details.*
- **New Section 3.2.1 Criteria for Decision to Transition from Schedule 1 to Schedule 2**
  New text provided in this section.
- **Section 3.3 Dose Escalation Plan**
  Dose escalation will begin *on Schedule 1* at the starting dose of 0.1 milligrams per kilogram (mg/kg) as outlined in Table 1 below. Intermediate or higher dose levels not shown may be explored based on emerging data (e.g., safety and pharmacodynamic data). Dose escalation of SL-172154 will not exceed half-log increments. The DLT assessment period is 28 days in length and ends 14 days after the last dose is administered in the first cycle *on Schedule 1 and 7 days after the last dose is administered on Schedule 2*. Dose escalation will follow the mTPI-2 decision rules outlined in Table 7 in Section 9.1.

    - Schedule *1* ~~of~~ administration for SL-172154: Given on days 1, 8, and 15 in cycle 1 over 28 days and then every two weeks thereafter on days 1 and day 15 in cycles ≥ 2 every 28 days.

- *Schedule 2 administration for SL-172154: Given on days 1, 8, 15 and 22 of each 28-day cycle*
- Cycle length *for Schedules 1 and 2*: 28 days
- DLT assessment period *for Schedules 1 and 2*: 28 days

- **Dose Escalation Plan Table depicted in Synopsis and in Section 3.3 as Table 1:** Revisions made to as shown below: New text inserted as footnote b and previous text b, c, and d footnotes in table 1 are now c, d, and e respectively.
  - (+/-10 minutes) or (+/- 15 minutes) window added to duration of infusion times
  - Modified wording in the new footnote e

Dose Level	IV Dose of SL-172154 (mg/kg)[a,b,c,d,e]	Duration of Infusion[d]
Level 1 - starting dose	0.1	30 minutes *(+/- 10 minutes)*
Level 2	0.3	30 minutes *(+/- 10 minutes)*
Level 3	1.0	30 minutes *(+/- 10 minutes)*
Level 4	3.0	60 minutes*(+/- 15 minutes)*
Level 5	10.0	60 minutes *(+/- 15 minutes)*

a) *Dosing will begin on Schedule 1 with* SL-172154 administered in 28-day cycles on days 1, 8, and 15 in cycle 1 and then on days 1 and 15 in cycles ≥ 2.

b) *Dose escalation on Schedule 2 may be tested: If Schedule 2 is opened, SL-172154 may be administered once weekly on days 1, 8, 15, and 22 of each 28-day cycle.*

c) Intermediate or higher dose levels may be tested based on emerging safety and pharmacodynamic data.

d) The actual body in kilograms (kg) will be used for dose calculation in all subjects who body weight is ≤100 kg. For subjects with body weight >100 kg, the dose to be administered should be the same as that calculated for a subject weighing 100 kg (see Section 5.1.4).

e) Infusion time may change based on final drug volume needed for administration or observed safety *and tolerability of the infusion for the subject and/or observed* safety-findings-during the study. Please refer to the Study Pharmacy Manual (SPM) for details.

- **Evaluation of an Alternative Dosing Schedule in Section 3.3:** Safety*, pharmacokinetic and/or* and pharmacodynamic data from the dose escalation cohorts and pharmacodynamic cohorts, if available, may support exploration of a more or less intensive dosing schedule for SL-172154. *If* ~~safety and pharmacodynamic~~ these data *from Schedule 1 support exploration of more frequent dosing then cohort enrollment on Schedule 2 will be instituted in lieu of Schedule 1. The starting dose on Schedule 2 will be at at dose level that has completed evaluation for safety on Schedule 1 as defined by the mTPI-2 design. Dose escalation (or de-escalation) may then proceed on schedule 2 as shown in Table 1. During dosing on Schedule 2, SL-172154 will be administered once weekly (D1, D8, D15, and D22) every 28 days. If less frequent dosing is supported by safety, pharmacokinetic and/or pharmacodynamic data,* SL-172154 may be administered weekly, once every two weeks, once every three weeks or once every four weeks. The starting dose *on a less frequent* ~~this altered~~ schedule would be instituted at *a* ~~the current~~ dose level *that has completed evaluation for safety* ~~(for a less intensive dose schedule) or a lower dose level (for a weekly~~

~~dose schedule)~~ as defined by the mTPI-2 design, emerging safety data and as recommended by the SMC.

- **Definition of Dose-Limiting Toxicity Section 3.4 (second sentence 1st paragraph in this section):** The determinate period for DLT is the first 28 days of SL-172154 dosing *on Schedule 1 or Schedule 2*.
- **Definition of Dose-Limiting Toxicity Section 3.4 (last paragraph in this section):** A Grade ≥ 3 AE(s) that occurs beyond the DLT period or Grade 2 events that require continuous interruption of SL-172154 for more than 6 weeks or AEs that result in subjects not receiving at least 2 of the 3 scheduled doses of SL-172154 *on Schedule 1 (or at least 2 of the 4 scheduled doses of SL-172154 on Schedule 2)* during the DLT assessment period due to AE(s) may be taken into consideration when assessing the totality of the data in determining DLT and the RP2D.
- **Accrual Goal in Section 4.4:** The total sample size expected to complete this study is approximately 33 *to 54* subjects (see Section 9.1). Approximately 5 clinical sites may participate in SL03-OHD-101. Overall, the study may complete accrual within approximately 25~~18~~ months (≍ ~ 2 years).
- **New SOA Table in Section 6.2 and footnotes**
  - Subsequent Numbering in Section 6 reordered according to addition of new SOA Table in 6.2
  - e.g., Demographics and Medical History Screening and Safety Assessments is now Section 6.3 (instead of 6.2) etc. for subsequent sections and subsections that follow as noted below
    - Safety Evaluations now Section 6.4 not 6.3
    - Pharmacokinetics now Section 6.5 not 6.4
    - Anti-drug Antibodies now Section 6.6 not 6.5
    - Pharmacodynamic/Biomarker Assessments now 6.7 not 6.6
    - Assessment of Anti-Tumor Activity now 6.8 not 6.7
    - Unscheduled Visits now 6.9 not 6.8.

- **Sample Size Determination in Section 9.1:** The planned sample size is approximately 33-*54* subjects. *If only Schedule 1 is evaluated, the planned total sample size is 21 for dose escalation. If Schedule 1 and Schedule 2 are both fully evaluated in dose escalation, the maximum planned sample size for dose escalation is 42.* This sample size assumes evaluation of five dose levels with approximately 21 subjects treated in the dose escalation cohorts *for each schedule 1 and schedule 2*, assessment of approximately 6 subjects in an optional pharmacodynamic cohort and assessment of approximately 6 subjects in dose expansion. Overall, approximately 12 subjects are to be treated at the RP2D for SL-172154. In dose escalation cohorts, subject may be replaced if not DLT evaluable.
- **Definition of DLT Evaluable Population in Section 9.2.1:** All treated subjects 1) who have received ≥2 of the 3 scheduled doses of IP during ~~cycle 1~~ *on schedule 1 or who have received ≥2 of the 4 scheduled doses of IP on schedule 2 during cycle 1* and complete the safety follow-up through the 28-day DLT evaluation period; or 2) who experience any DLT during the DLT evaluation period. DLT evaluable subjects will be used to guide dose escalation and to determine the MTD or MAD.

- **Section 9.2.3 General Data Analysis Consideration (first sentence):** Tabular summaries will be presented by dose levels/*schedule*/cohorts and total number of subjects in the corresponding population.

16.9 Summary of Changes for Protocol Amendment 05

Minor Editorial Changes:

Document Headers

Updated to denote version 05 of protocol

Title page

Approval date changed to 12 July 2021; protocol version number changed to version 05

Rational for Global Amendment 05 added

Table of Contents

Updated to include new Appendix Section 16.9

Page numbers revised

List of Tables

Revised Table numbers due to addition of new Table to add C1D8 predose PK sample

1. The protocol is amended to include infusion pre-medication instructions (Section 5)

- Section 3.6 3rd paragraph revised as shown below (new text in italics):
  ~~Primary~~ *Discretionary use of primary* prophylaxis ~~against~~ for IRR~~s~~ *prevention* ~~is not permitted~~ *for subjects enrolled at 3.0 mg/kg or less is permitted* ~~to avoid obscuring a potential safety signal~~. However, as noted in *Section 3.6.1, secondary prophylaxis (i.e., prevention of IRRs following an initial episode) for these subjects is appropriate and permitted at the discretion of the investigator for all dose levels. Primary prophylaxis for IRR prevention is required with each SL-172154 administration* ~~and to enable an assessment of whether pre-medications should be required for all subjects~~ for subjects enrolled at 10mg/kg or higher dose levels. See Section 5.1.2.3 for details regarding the primary prophylaxis medications. ~~However, as noted in the guidance below, secondary prophylaxis (i.e., prevention of IRRs following an initial episode) is appropriate and permitted at the discretion of the investigator.~~
- Section 3.6.1 AE: Infusion or Hypersensitivity Reactions (new text in italics):
  - Grade 1 Management 3rd bullet: Consider pre-medication (antipyretics, histamine (H1 and H2 antihistamines~~)~~, leukotriene inhibitors, corticosteroids) for subsequent infusions per investigator/institutional guidelines *if pre-medications are not already required*.
  - Grade 2 Management 4th bullet: If the infusion is interrupted, then restart the infusion at no more than 50% of the rate at which the reaction symptoms occurred. *For subsequent infusions, consider starting infusion at 50% rate at which the symptoms occurred and titrate to tolerance.*
  - Grade 3 Management 2nd bullet: Begin IV infusion of normal saline and treat with epinephrine, bronchodilators, diphenhydramine, ranitidine, corticosteroids, oxygen, fluids, vasopressors, *etc. and ~~,~~ consider opioids (e.g., meperidine) for rigors~~, etc.~~* as indicate*d* and per institutional guidelines.
  - Grade 3 Management 4th bullet: Rechallenge should not be attempted in cases of true anaphylaxis. In other cases, once subject has completely recovered, carefully consider if it is safe for the subject to receive SL-172154 at the next scheduled dose with pre-medication (e.g., corticosteroids, antihistamines, antipyretics) and slow infusion (≤ 50% of the rate at which the reaction occurred). The next two subsequent infusions of SL-172154 (after an event of grade 3 event of infusion-related reaction) must be administered in an inpatient or outpatient setting with prolonged observation for a minimum of 12 hours after the completion of the infusion. *Start infusion at 50% rate at which the symptoms occurred.* If

no further symptoms, rate may be escalated at intervals and increments as clinically appropriate. If symptoms recur, permanently discontinue SL-172154.

- Grade 4 Management 3rd bullet: Manage severe IRRs per institutional standards (e.g., epinephrine, diphenhydramine, ranitidine, corticosteroids, bronchodilators, oxygen, fluids, *etc. and consider opioids (e.g., meperidine) for rigors*~~, etc.~~). Epinephrine is the drug of choice in an anaphylactic reaction and its administration should not be delayed

- Section 3.6.1 AE: Cytokine-release Syndrome (new text in italics):
  - Grade 1 Management 3rd bullet: Maintain IV access. Symptomatic treatment with antipyretics, antiemetics, analgesics, histamine 1/histamine 2 (H1/H2) antihistamines as needed; monitor fluid balance; assess for infection. *Consider opioids (e.g., meperidine) for rigors.* Regularly evaluate for signs of further deterioration
  - Grade 2 Management 2nd bullet: Start IV infusion with normal saline. Administer oxygen if needed. Treat with antipyretics, H1/H2 antagonists (diphenhydramine 50 mg IV plus ranitidine 50 mg IV), and/or methylprednisolone 1-2 mg/kg or equivalent dose of corticosteroid every 6 hours and manage per institutional guidelines. *Consider opioids (e.g., meperidine) for rigors.* Closely monitor cardiac and other organ functions.
  - Grade 3 or 4 Management 3rd bullet: Manage severe IRRs and CRS per institutional standards (e.g., epinephrine, diphenhydramine, ranitidine, corticosteroids, bronchodilators, oxygen, fluids, *meperidine for rigors,* etc.). Epinephrine is the drug of choice in an anaphylactic reaction and its administration should not be delayed
  - Grade 3 or 4 Management; for Grade 3 CRS, may consider rechallenge after consultation with medical monitor. If rechallenge is given: New sub-bullet #2 as follows *Start infusion at 50% rate at which the symptoms occurred. If no further symptoms, rate may be escalated at intervals and increments as clinically appropriate.*

- Section 5.1.2.3 **Administration** (new text in italics) as shown below:
  Doses of SL-172154 are to be administered as an IV infusion via an infusion pump or syringe pump that can ensure precision within at least 0.1 mL/min. DO NOT USE an in-line filter for administration of SL-172154.

  Premedication for IRR prophylaxis is required with each 10mg/kg or higher dose and is at the investigator's discretion for doses less than 10mg/kg. The following premedication is to be administered approximately 30 minutes prior to the start of each SL-172154 administration:
  - *acetaminophen (650 to 1000 mg PO)*
  - *diphenhydramine (25-50 mg, or equivalent, PO or IV)*
  - *ranitidine (50 mg IV or equivalent).*

2. The protocol is amended to include collection of a PK/ADA predose sample on C1/D8 and immunophenotyping, receptor occupancy and cytokine samples on C1D3.

- SOA Tables in Sections 6.1 and 6.2 added X to column on C1/D8 to identify assessment of PK/ADA sample collection on this study visit.
  - Footnote m in both SOA tables updated to denote collection of C1/D8 PK/ADA sample as shown below (new text in italics):

  PK/immunogenicity (i.e., ADA), cytokines and SL-172154 binding to red blood cells (RBCs): Blood sample collection timings for PK, ADA, cytokines and measurement of RBC binding are outlined in Section 6.1.1 in supplementary Tables 2, *3,* ~~and~~ 4 *and 5*. PK/ADA/cytokine/RBC binding sample collection times on C1D1 through 48 hours

postdose are provided in Table 2. PK/ADA/cytokine/RBC binding sample collection times in C2D1, C2D2, C2D15 and C2D16 are detailed in Table 4. PK/ADA sample collection times in *C1D8 and* cycles 3 and beyond are outlined in *Table 3* and Table 5~~4~~, *respectively*. **Blood volumes required are provided in the SLM. PK, ADA, cytokine and RBC binding samples should not be collected from infusion port for drug delivery i.e., recommend having a separate line in the opposite arm for sample collection**.

- In Section 6.1.1 new table and caption added at links provided i.e., Table 3: Predose PK, ADA Sample (C1/D8) for PK/ADA predose sample on C1D8
- SOA Tables in Sections 6.1 and 6.2 added X to column on C1/D3 to identify assessment of immunophenotyping, receptor occupancy and cytokine samples on this study visit
- In Section 6.1.1 an X was added to Table 2 for collection of a cytokine sample in cycle 1 at the 48 hr (± 2 hr) post EOI time point.
- In Section 6.1.2 a new column was added to Table 6 to collect an immunophenotyping and receptor occupancy samples on C1D3 i.e., at the 48 hr (± 2 hr) post EOI time point

3. Minor editorial changes and clarification edits to text

- 6-10 clinical sites may participate as denoted in Section 4.4 Accrual Goal (new text in italics).
  The total sample size expected to complete this study is approximately 33 to 54 subjects (see Section 9.1). Approximately *6-10* ~~5~~ clinical sites may participate in SL03-OHD-101. Overall, the study may complete accrual within approximately 25 months (~ 2 years).
  - Planned number of Sites and Countries in Synopsis changed from 5 to 6-10 sites
- Section 5.1.2 Title change (new text in italics): **Preparation/Handling/*Administration*/Storage of SL-172154/Investigational Product**
- Section 3.1.1 text change to 1st paragraph second sentence to reflect 6 to 12 subjects may be treated at RP2D instead of 12 (new text in italics): Approximately *6*-12 subjects (inclusive of the subjects enrolled at this dose in the Dose Escalation, Pharmacodynamic cohort, and Dose Expansion) may be treated at the RP2D.
- Section 3.1.2 text change to second to last sentence to reflect 6 to 12 subjects may be treated at RP2D instead of 12 (new text in italics): The goal is to enroll approximately *6*-12 subjects at the potential RP2D, including subjects in the dose escalation, pharmacodynamic, and dose expansion cohorts. Overall, the total sample size estimate for this study is 33 subjects assuming only Schedule 1 is evaluated, and 54 subjects if both Schedule 1 and Schedule 2 are fully evaluated. See Section 9.1 for more details.
- In Tables 2, 3, 4, and 5 in Section 6.1.1: For predose PK, ADA, Cytokine and RBC binding samples collected approximately 30 min before dosing, the window for sample collection was increased from ±5 min to ±25 min
- In Table 6 in Section 6.1.2: For predose complement, immunophenotyping or receptor occupancy samples collected before SL-172154 is given, the predose window for sample collection is now (- 90 to -*5*~~30~~ min)
- SOA tables in Sections 6.1 and 6.2 Footnote n text modified as shown (new text in italics): **Correlative laboratory studies**: Refer to supplementary Table ~~5~~*6* for details in Section 6.1.2 plus see the SLM for amount of blood needed and sample shipment details.
- Text changes (next text in italics) to title of Section 6.4.6.1 Ad Hoc Labs for *IRR or CRS* ~~S~~SAEs
- Text changes made in Section 6.4.6.1: Ad hoc labs should be collected as noted if IRR/CRS ~~or an immune related serious adverse event (irSAE)~~ occurs. The samples to be collected are provided below.

- Table in Section 7.1 Laboratory test(s) that meet definition of an AE or SAE text changed in definition of 2nd bullet as shown: Ad hoc labs should be collected as noted in Section 6.4.6.1 above if IRR/CRS ~~or an irSAE~~ occurs.
- Section 7.1.1 next text in italics added to bullet #5 as shown: Clear progression of disease under study should not be reported as an AE or SAE (unless the investigator considers the progression of underlying neoplasia to be atypical in its nature, presentation or severity from the normal course of the disease in a particular subject). Signs and symptoms that are clearly consistent with the expected progression of the underlying cancer should not be reported as an adverse event, and hospitalizations due to the progression of cancer do not necessarily qualify for an SAE. *If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.*
- In Section 7.6 the following text changes were made as shown (new text in italics):
  The following events should also be reported to the Sponsor within 24 hours of knowledge of the event: ~~The following events should also be reported to the Sponsor and PrimeVigilance *within 24 hours*:~~
  - ~~Overdose:~~ An overdose of SL-172154 ~~should be reported within 24 hours to the Sponsor~~
  - Suspected transmission of an infectious agent due to contamination of drug product
  - Other events related to misuse of IP

16.10 Summary of Changes for Protocol Amendment 06

Minor Editorial Changes:
Document Headers
Updated to denote version 06 of protocol
Title page
Approval date changed to 24 August 2021; protocol version number changed to version 06
Rationale for Global Amendment 06 added
Table of Contents
Updated to include new Appendix Section 16.10
Page numbers revised

1. **The protocol is amended to remove the Absolute Lymphocyte Count eligibility criteria**

- Protocol Synopsis: removed ALC eligibility criteria from laboratory parameters required for study enrollment

- Section 4.1: removed ALC eligibility criteria from laboratory parameters required for study enrollment

2. **The protocol is amended to update the investigational product information to reflect the current program-level description of SL-172154.**

- Formulation description in Section 5.1.1 has been updated:

Solution containing SL-172154 10 mg/ml ~~formulated in 40nM histidine, 150 mM NaCl, at pH 7.3~~. Refer to the Study Pharmacy Manual (SPM) for further description of the drug product.

- Physical description in Section 5.1.1 has been updated:

SL-172154 solution, 10 mg/ml in a ~~5ml~~ glass vial closed with a FluroTec® rubber stopper and sealed with a flip-off aluminum seal.

- Preparation of SL-172154 language has been updated in Section 5.1.2.1 (new text in italics):

Standard aseptic technique including preparation of doses in a laminar flow hood is required. SL-172154 solution, 10 mg/*mL*, ~~1 mL~~ is supplied as a frozen liquid. Before use, thaw each vial of SL-172154 solution *10 mg/mL*, ~~1 mL~~ overnight under refrigerated conditions, protected from light, or ~~thaw each vial~~ at room temperature, until *completely thawed* ~~the entire solution is no longer frozen (e.g., within 1 hour)~~.

3. **The protocol is amended to update the Schedule of Assessments for Schedule 1**

- Section 6.1: added weight assessment to C1D1 to correctly reflect language in Section 5.1.4