Protocol Title: Phase 1 Dose Escalation Study of the Agonist Redirected Checkpoint, SL-172154 (SIRPα-Fc-CD40L), Administered Intratumorally in Subjects with Cutaneous Squamous Cell Carcinoma or Squamous Cell Carcinoma of the Head and Neck

Short Title: Phase 1 Study of SL-172154 (SIRPα-Fc-CD40L) Administered Intratumorally in Subjects with Cutaneous Squamous Cell Carcinoma or Squamous Cell Carcinoma of the Head and Neck

Protocol Identifying Number: SL03-OHD-102

Version Number: v1.0

Compound Number: SL-172154

Study Phase: Phase 1

Investigational New Drug (IND) Sponsor: Shattuck Labs

Legal Registered Address:
Shattuck Labs, Inc.
21 Parmer Way, Suite, 200
Durham, North Carolina 27709

Regulatory Agency Identifier Number(s)

IND: 149427

NCT:

Approval Date: 10 July 2020

Shattuck Labs Document Number	Date	Version
SL03-OHD-102_00	28 May 2020	Original
SL03-OHD-102_01	10 July 2020	Amendment No. 1

Rationale for Amendment Changes

The protocol is amended to address comments by the United States FDA during review of the IND (149427) for SL-172154.

Summary of Changes / See Appendix 16.6 for the complete delineation of changes made to the protocol for Amendment 01.

1. Revised section 5.1.4 Monitoring Dose Administration to specify that subjects must be monitored for injection-related reactions and cytokine-release syndrome for a minimum of 6 hours following intratumoral injection of SL-172154.
2. The protocol is modified to include ECG monitoring at Tmax after the first dose. In addition, a predose ECG assessment on cycle 2 day 1 has been added for safety purposes after repeated dosing as no accumulation of SL-172154 is expected.
3. The maximum number of target lesions assessed per RECIST v1.1 will be 10 lesions instead of 5 lesions.

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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
AK	Actinic keratosis
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
AUC0-last	Area under the serum concentration time curve, time 0 to the last quantifiable concentration
AUC0-inf	Area under the serum concentration time curve from time 0 extrapolated to infinity
AUC0-t	Area under the serum concentration time curve, time 0 to time = t
%AUCext	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
°C	Degrees Celsius
CBC	Complete blood count
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
CO2	Bicarbonate
CR	Complete response
CrCl	Creatinine clearance
CRF	Case report form
CRS	Cytokine release syndrome
CSCC	Cutaneous squamous cell carcinoma

CT	Computed tomography
CTCAE	Common terminology criteria for adverse event
CTLA-4	Cytotoxic T cell lymphocyte-associated antigen 4
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
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal growth factor receptor
EOI	End of injection(s)
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
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
Hgb	Hemoglobin
HNSCC	Head and neck squamous cell carcinoma
hr (time)	Hour(s)
HR	Heart rate
HSR(s)	Hypersensitivity reaction(s)
Hu5F9-G4	Human 5F9 (i.e., anti-CD47 monoclonal antibody)
IB	Investigator brochure
ICF	Informed consent
ICH	International Conference of Harmonisation
IEC	Institutional Ethics Committee
IFNγ	Interferon gamma
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukin
IND	Investigational new drug
INR	International normalized ratio
i.p.	Intraperitoneal

IP	Investigational product
irAE	Immune-related adverse event
IRB	Institutional Review Board
irSAE	Immune-related serious adverse event
ISR	Injection site reactions
ITI	Intratumoral injection
IV	Intravenous or intravenously
KA	Keratoacanthoma
Kd	Receptor off-rate constant
Kg	Kilogram
LDH	Lactate dehydrogenase
m2	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
Ng	Nanogram
NK	Natural killer
nM	Nanomolar
NOAEL	No observed adverse effect level
NSAID(s)	Non-steroidal anti-inflammatory drug(s)
ORR	Objective response rate
PBMC	Peripheral blood mononuclear cells
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
PT	Prothrombin time
QTcB	QT duration corrected for heart rate by Bazett’s formula

QTcF	QT duration corrected for heart rate by Fridericia's formula
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
SCC	Squamous cell carcinoma
SCCIS	Squamous cell carcinoma in situ
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
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
Tlast	Time of last observed quantifiable concentration
Tmax	Time of maximum observed concentration
TME	Tumor microenvironment
TNF-α	Tumor necrosis factor alpha
TSH	Thyroid stimulating hormone
TTR	Time to tumor response
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 Imaging Manual

Sponsor Signatory:

[redacted]

Chief Medical Officer, Shattuck Labs

10 July 2020

Date

STUDY SCHEMA

Study Design: Phase 1 Study of SL-172154 (SIRPa-Fc-CD40L) Administered Intratumorally

Primary objectives: Safety and tolerability of SL-172154 given intratumorally

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

Tumor type: Subjects with locally advanced or metastatic CSCC or HNSCC not amenable for standard therapy

Dose Escalation Study (N ~ 18 Subjects)

Dose Escalation Rules: mTPI-2

DLT Assessment Period: 21 days

Subjects per Cohort: ≥ 3

(n ~ 12 subjects)

Dose Level	SL-172154 ITI Dose (mg)
Start: 1	0.003
2	0.01
3	0.03
4	0.1

PD Cohort

Further assessment of SL-172154 at ITI dose that has been cleared for safety

(n ~ 6 subjects)

RP2D Decision

Based on totality of data

Safety, PK, PD and anti-tumor activity

SL-172154 Dosing Schedule

Cycle 1: Once weekly intratumoral administration for 3 weeks (D1, D8, D15) in first 21 days

Beyond: Starting C2D1 (day 22) dosing will occur on D1 of each 21-day cycle

Abbreviations: CSCC = cutaneous squamous cell carcinoma; ITI = intratumoral injection; PD = pharmacodynamic; PK = pharmacokinetics; mTPI = modified Toxicity Probability Interval; RP2D = recommended Phase 2 dose; HNSCC = head and neck squamous cell carcinoma

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 Intratumorally in Subjects with Cutaneous Squamous Cell Carcinoma or Squamous Cell Carcinoma of the Head and Neck
Protocol Number	SL03-OHD-102
Clinical Phase	Phase 1
Planned Sample Size	Approximately 18 subjects
Planned Number of Sites & Countries	Approximately 4-6 clinical sites in the United States
Recruitment Duration:	Approximately 12 months (1 year)
Study Duration	Estimate is 20 months from when the study opens to enrollment until completion of data analyses

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 (KD 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-2 secreting PBMCs, and the secretion of multiple cytokines were observed.

Treatment of mice with mSIRPα-Fc-CD40L intravenously (IV) led to a significant early and sustained activation of murine dendritic cells (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]. The in vivo anti-tumor activity of mSIRPα-Fc-CD40L monotherapy was studied in established syngeneic CT26 colorectal murine tumor models. The performance of intraperitoneal (i.p.) 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 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. Additionally, a robust increase in AH1 tetramer +/CD8+ cells in the spleen and the tumor was seen in mice treated with mSIRPα-Fc-CD40L or the anti-CD40/anti-CD47 combination in comparison to vehicle controls.

The anti-tumor activity of mSIRPα-Fc-CD40L, given by intratumoral injection (ITI), as monotherapy and in combination with murine anti PD-1 antibody was assessed in groups of female BALB/c mice inoculated with a CT26 colorectal carcinoma tumor in each rear flank. The mice were dosed on Days 0 (start of treatment), 2 and 5, and the treatment groups were: vehicle control (i.p. or ITI); mSIRPα-Fc-CD40L (300 µg; i.p), mSIRPα-Fc-CD40L (10 or 100 µg; ITI); and the combination of anti-PD-1 (100 µg; i.p) and mSIRPα-Fc-CD40L (10 or 100 µg; ITI).

Although only one of the two tumors was injected with mSIRPα-Fc-CD40L, a delay in tumor growth was observed in both. The 10 µg ITI dose of mSIRPα-Fc-CD40L was the most efficacious with 14% of mice completely rejecting both tumors. The rejection rate of both tumors was increased to ~42% when 10 µg ITI mSIRPα-Fc-CD40L was combined with i.p. anti-PD-1 treatment. Thus, intratumoral administration of mSIRPα-Fc-CD40L showed potent anti-tumor efficacy in both the treated (injected with mSIRPα-Fc-CD40L) and untreated tumor, suggesting that intratumoral mSIRPα-Fc-CD40L stimulated sufficient immune activation to promote an anenestic or bystander anti-tumor response. Moreover, no signs of injection site reactions, such as ulceration and inflammation, were observed with intratumoral mSIRPα-Fc-CD40L. Systemic depletion of peripheral B cells and an increase in peripheral dendritic cells observed 24 hours following intraperitoneal mSIRPα-Fc-CD40L were not observed after intratumoral mSIRPα-Fc-CD40L, supporting that much lower systemic exposure occurred following ITI. These findings support the hypothesis that direct injection of SL-172154 into a tumor can achieve a high local concentration of SL-172154 using relatively lower doses of drug than would be required with IV administration.

Two repeat IV dose toxicity studies in cynomolgus monkeys had similar trends in toxicokinetic parameters and demonstrated on-target pharmacological activity of SL-172154. The onset of antidrug antibodies (ADA), elevations in serum cytokines, activation of complement, and postdose changes in lymphocyte counts were similar between the dose range finding and Good Laboratory Practice (GLP) studies. The dose-dependent, infusion-related reactions observed with repeat dosing in the GLP study were attributed to exacerbated pharmacology of SL-172154 in the presence of ADA. Given the low ITI doses to be studied in clinical study SL03-OHD-102, low systemic exposure is anticipated in comparison to IV infusion, and thus the IV no observed adverse effect level of 1 mg/kg in monkeys provides systemic exposure and safety coverage. Consequently, the nonclinical safety assessment program supports the intratumoral administration of SL-172154 in the clinical study SL03-OHD-102. This trial is designed to evaluate the safety, pharmacokinetics, anti-tumor activity and pharmacodynamic effects of SL-172154 administered by ITI on days 1, 8, 15 of a 21-day in cycle 1 and then on day 1 of each subsequent 21-day cycle (cycles ≥ 2). Subjects that are eligible for enrollment have locally advanced or metastatic squamous cell carcinomas of the head and neck or skin that are not amenable to further treatment with surgery, radiation or standard systemic therapies that are known to provide clinical benefit for their condition.

Cutaneous squamous cell carcinoma (CSCC) and squamous cell carcinoma of the head and neck (HNSCC) were selected for investigation in this phase 1 study of ITI SL-172154 due to the fact that both of these tumor types have 1) a high percentage of tumors with increased CD47 expression, 2) mechanisms of tumor immune evasion that target both adaptive and innate immunity within the tumor microenvironment [Ferris, 2015] and 3) patients with select tumor lesions that are accessible and safe for ITI.

Study Objectives	
Primary Objective(s)	**Outcome Measures**
To evaluate the safety and tolerability of ITI administration of SL-172154 and to identify the maximum tolerated dose (MTD) or maximum administered dose (MAD) of SL-172154	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 when administered by intratumoral injection (ITI)	Based on review of all data collected during dose escalation and the pharmacodynamic cohort including safety, tolerability, PK, anti-tumor activity, and pharmacodynamic effects
To assess preliminary evidence of anti-tumor activity of SL-172154 when administered by ITI	Response 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]) • 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 • Change from baseline lesion diameter for injected lesion • Change from baseline lesion diameter for non-injected lesion
To evaluate anti-drug antibodies (ADA) to SL-172154 when administered by ITI during and after treatment.	• Number/proportion of subjects with positive ADA titer • ADA duration • Transient vs. persistent ADA
To characterize the pharmacokinetics (PK) of SL-172154 when administered by ITI	• 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 pharmacodynamic biomarkers in blood prior to, on-treatment and following SL-172154 when administered by ITI	Pharmacodynamic biomarkers in blood may include: • Changes from baseline in cell counts and percentages of circulating immune cells such as: T cells, B cells, natural killer (NK) cells, and myeloid cells • Circulating chemokine and cytokine levels
To assess pharmacodynamic biomarkers in tumor tissue prior to, on-treatment and following SL-172154 when administered by ITI	Pharmacodynamic biomarkers in tumor tissue may include: • Presence of SL-172154 in tumor tissue • Changes in T cells subsets, B cells and macrophages and assessment of SL-172154 in the tumor tissue • CD47 and CD40 expression • Programmed cell death ligand 1 (PD-L1) expression
To estimate progression-free survival (PFS)	• PFS: time from first dose to progression by RECIST v1.1 or death, whichever comes first

Study Design

This clinical trial is an open label, multi-center, dose escalation, Phase 1 study of SL-172154 administered by ITI injection. This trial is designed to evaluate the safety, PK, anti-tumor activity and pharmacodynamic effects of SL-172154 administered by ITI on days 1, 8, 15 of a 21-day in cycle 1 and then on day 1 of each subsequent 21-day cycle (cycles ≥ 2). Subjects that are eligible for enrollment have locally advanced or metastatic squamous cell carcinomas of the head and neck or skin that are not amenable to further treatment with surgery, radiation or standard systemic therapies that are known to provide clinical benefit for their condition.

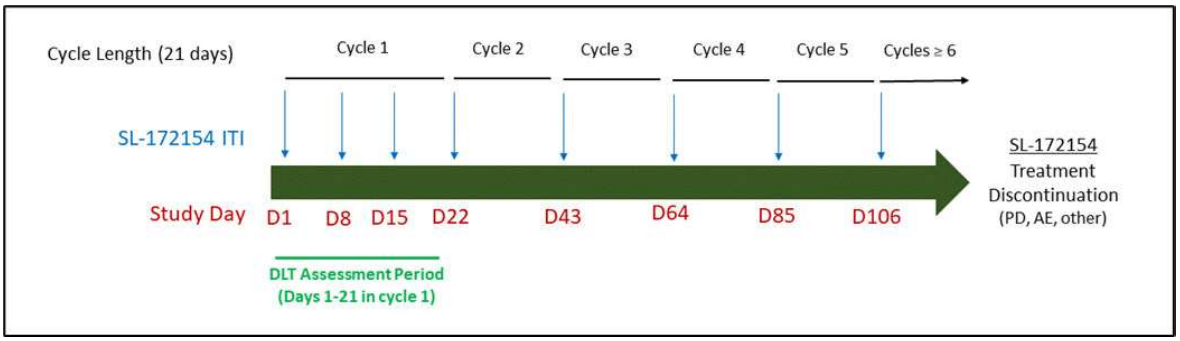
Dose escalation will utilize the modified Toxicity Probability Interval (mTPI-2) design [Guo, 2017] with target DLT rate of 30% for the MTD. The dose escalation decision rules are outlined in Table 5 in Section 9.1 of the protocol. Subjects will be enrolled in cohorts of approximately 3 subjects into sequential dose levels of SL-172154 and evaluated for DLT during the 21-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.

The Sponsor, in consultation with the SMC, may elect to open a pharmacodynamic cohort to obtain additional pharmacodynamic data from approximately 6 additional subjects at one or more dose levels that have completed evaluation for safety without exceeding the MTD. Subjects in the pharmacodynamic cohort must have tumor accessible and safe for biopsy from both an injected lesion and a non-injected lesion and must consent to providing paired biopsies for translational research.

Selection of the recommended phase 2 dose(RP2D) and schedule for SL-172154 monotherapy will be based upon the totality of the data in subjects treated in the dose escalation and the pharmacodynamic cohorts. The totality of the data refers to safety, tolerability, PK, clinical activity, and pharmacodynamic markers consistent with the mechanism of action. Approximately 6 subjects (inclusive of the subjects enrolled in the Dose Escalation and Pharmacodynamic cohort) may be treated at the RP2D. The planned total sample size for this study is approximately 18 subjects.

Treatment Schedule

Schedule of administration for ITI of SL-172154: Doses administered on days 1, 8, 15 of a 21-day cycle in cycle 1 and on day 1 of each subsequent 21-day cycle, starting on cycle 2, day 1 (day 22).



Dose Escalation Scheme

Dose Level	ITI Dose (mg) of SL-172154[a]	ITI Volume of Dose
Level 1 - starting dose	0.003	1.5 mL
Level 2	0.01	1.5 mL
Level 3	0.03	1.5 mL
Level 4	0.1	1.5 mL

a) Intermediate or higher dose levels may be tested based on emerging safety and/or pharmacodynamic data. Dose escalation will not exceed half-log increments.

Definition of Dose Limiting Toxicity

DLTs are as defined in the bulleted points below. Toxicities will be graded as per NCI CTCAE v5. The determinate period for DLT is the first 21 days of ITI SL-172154 dosing. **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 with the following exceptions:
  - Grade 3 fatigue lasting ≤ 7 days

Definition of Dose Limiting Toxicity (continued)

- Grade 3 anemia if not associated with clinical sequelae or not requiring transfusion of red blood cells (RBCs) within 48 hours.
- 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 injection-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours of onset with appropriate clinical management.
- Grade 3 rigors or chills lasting < 6 hours that respond to optimum medical therapy.
- Grade 3 fever lasting < 24 hours with or without medical therapy.
- 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
- Grade 3 skin toxicity (excluding injection-site reactions) that downgrades to Grade 2 or less within 7 days with optimal supportive care
- 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 (21 days) 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 two of the three scheduled dose of SL-172154 during the DLT assessment period may be taken into consideration when assessing the totality of the data in determining evaluability for 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. Subjects must have a histologically confirmed diagnosis of an unresectable or recurrent, locally advanced or metastatic cutaneous squamous cell carcinoma or squamous cell carcinoma of the head and neck that is not amenable to curative surgery or radiotherapy.
   - Cutaneous squamous cell carcinoma: Subjects with predominantly mixed histologies (eg, sarcomatoid, adenosquamous) are not eligible. Subjects with a minimal component of mixed histology in which the predominant histology is invasive squamous cell carcinoma are eligible

Inclusion Criteria (continued)

- Squamous cell carcinoma of the head and neck: Subjects must have primary tumor locations in the oropharynx, oral cavity, hypopharynx, larynx or unknown primary. Primary tumor sites of nasopharynx, maxillary sinus, and paranasal are excluded.

3. Subject must have received, been intolerant to, or ineligible for standard therapies that are known to provide clinical benefit for their condition as defined by:
   - HNSCC subjects must have received, been intolerant to, or ineligible for platinum-based chemotherapy and PD-1/L1 inhibitors in combination or sequentially.
   - CSCC subjects must have received, been intolerant to, or ineligible for PD-1/L1 inhibitors.
4. Has measurable disease by RECIST v1.1 using radiologic assessment and/or clinical examination. **NOTE:** If there are multiple lesions that are measurable per RECIST v1.1, at least one of these lesions must be considered injectable per inclusion criteria #5.
5. Subject has at least 1 tumor lesion that is cutaneous and/or subcutaneous and/or nodal and is deemed to be clinically accessible and safe for injection of SL-172154 by the investigator.
   - Must be able to be inject the lesion by direct visualization, palpation or by ultrasound guidance. Injections of deep or visceral lesions or injections which require magnetic resonance imaging (MRI) or computed tomography (CT) guidance are not permitted.
   - At baseline, non-nodal lesions must measure ≥ 1 cm in the longest diameter and nodal lesions must measure ≥ 1.5 cm in the longest diameter to be considered injectable.
   - Tumor lesion(s) selected for injection cannot exceed 6 cm in the longest diameter.
   - Lesions must be located in an anatomic location where SL-172154 can be safely administered and not in close proximity to critical structures (e.g., major blood vessels, nerve bundle, trachea or a major airway tract) as determined by the investigator.
   - Pharmacodynamic Cohort ONLY: Must have a second lesion that is non-injected and is amenable to tumor biopsy collection. (Note: This non-injected lesion is not required to be measurable per RECIST v1.1.)
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 lymphocyte count (ALC)	≥ 0.8 x 10^9/liter (L)
Absolute neutrophil count (ANC)	≥ 1.5 x 10^9/L without growth factor support
Platelet count	≥ 100 x 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
International normalized ratio (INR) and activated partial thromboplastin time (aPTT)	≤ 1.5 × ULN
QTcF interval	≤ 480 milliseconds

Inclusion criteria (continued)

10. Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test within 72 hours of D1 of IP. NOTE: FCBP unless they are surgically sterile (i.e., have undergone a complete hysterectomy, bilateral tubal ligation/occlusion, bilateral oophorectomy or bilateral salpingectomy), have a congenital or acquired condition that prevents childbearing or are naturally postmenopausal 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 exceeds 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. Male subjects with female partners must have azoospermia from a prior vasectomy or underlying medical condition or agree to use an acceptable method of contraception during treatment and for 30 days (which exceeds 5 half-lives) after last dose of SL-172154 (see Appendix 16.3). Male subjects of reproductive potential must start using acceptable contraception at least 14 days prior to D1 of treatment with SL-172154 as per Appendix Section 16.3.
12. Recovery from prior anti-cancer treatments including surgery, radiotherapy, chemotherapy, immunotherapy or any other anti-cancer therapy to baseline or ≤ Grade 1. (NOTE: Low-grade toxicities such as alopecia, vitiligo, endocrinopathies adequately treated with hormone replacement, ≤ Grade 2 lymphopenia, ≤ Grade 2 hypomagnesemia, ≤ Grade 2 neuropathy may be allowed upon agreement by the Sponsor Medical Monitor).
13. Subjects enrolled in the dose escalation cohort must be willing to undergo a baseline tumor biopsy and on-treatment biopsies of the injected tumor lesion. Subjects enrolled in the pharmacodynamic cohort must be willing to undergo baseline tumor biopsies of an injected and non-injected lesion and on-treatment biopsies of the injected and non-injected tumor lesion.

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
PD-1/L1 inhibitor and other immunotherapies not otherwise specified	4 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 therapy for anti-cancer intent is prohibited. Concurrent use of hormones for non-cancer related conditions is acceptable.

Exclusion Criteria (continued)

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 HSRs (e.g., reaction to IV contrast)

5. Receipt of live attenuated vaccine within 28 days of D1 of IP.
6. Hypersensitivity to any of the excipients or to Chinese hamster ovary cell products.
7. History of coagulopathy resulting in uncontrolled bleeding, eg, hemophilia, von Willebrand's disease. History of other bleeding disorders or a Grade ≥ 3 bleeding event within 3 months prior to first dose of IP.
8. Requires continuous anticoagulation therapy or antiplatelet therapy (except for ≤ 100 mg acetylsalicylic acid).
9. Active or documented history of autoimmune disease that has required treatment with a disease modifying agent or immunosuppressive therapy in the past two years. Exceptions include Type I diabetes, vitiligo, alopecia areata or hypo/hyperthyroidism.
10. Active pneumonitis or history of symptomatic pneumonitis in the past 2 years that required treatment (i.e. drug-induced, idiopathic pulmonary fibrosis, radiation-induced, etc.).
11. Ongoing or active infection (e.g., no systemic antimicrobial therapy for treatment of infection within 5 days of D1 of IP).
12. Symptomatic peptic ulcer disease or gastritis, active diverticulitis, other serious GI disease associated with diarrhea within 6 months of D1 of IP.
13. Clinically significant or uncontrolled cardiac 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
    - NYHA Class III or IV congestive heart failure
    - Clinically significant (symptomatic) cardiac arrhythmias (e.g., sustained ventricular tachycardia, second- or third- degree atrioventricular (AV) block without a pacemaker, circulatory collapse requiring vasopressor or inotropic support, or arrhythmia requiring therapy)
14. Untreated central nervous system (CNS) or leptomeningeal metastases. Subjects with treated CNS metastases must have completed definitive treatment (radiotherapy and/or surgery) > 2 weeks prior to D1 of IP and no longer require steroids.
15. Women who are breast feeding.
16. 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.
17. 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.
18. Has undergone allogeneic stem cell transplantation or organ transplantation.
19. 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 [HBcAb] positive, but HBsAg negative are eligible for enrolment. HCV: Subjects who are HCV Ab positive, but HCV RNA negative are eligible for enrolment).

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) 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.

Statistics

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 and complete the safety follow-up through the 21-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. Change from baseline diameter for injected and non-injected lesions will be evaluated.

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 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; 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.

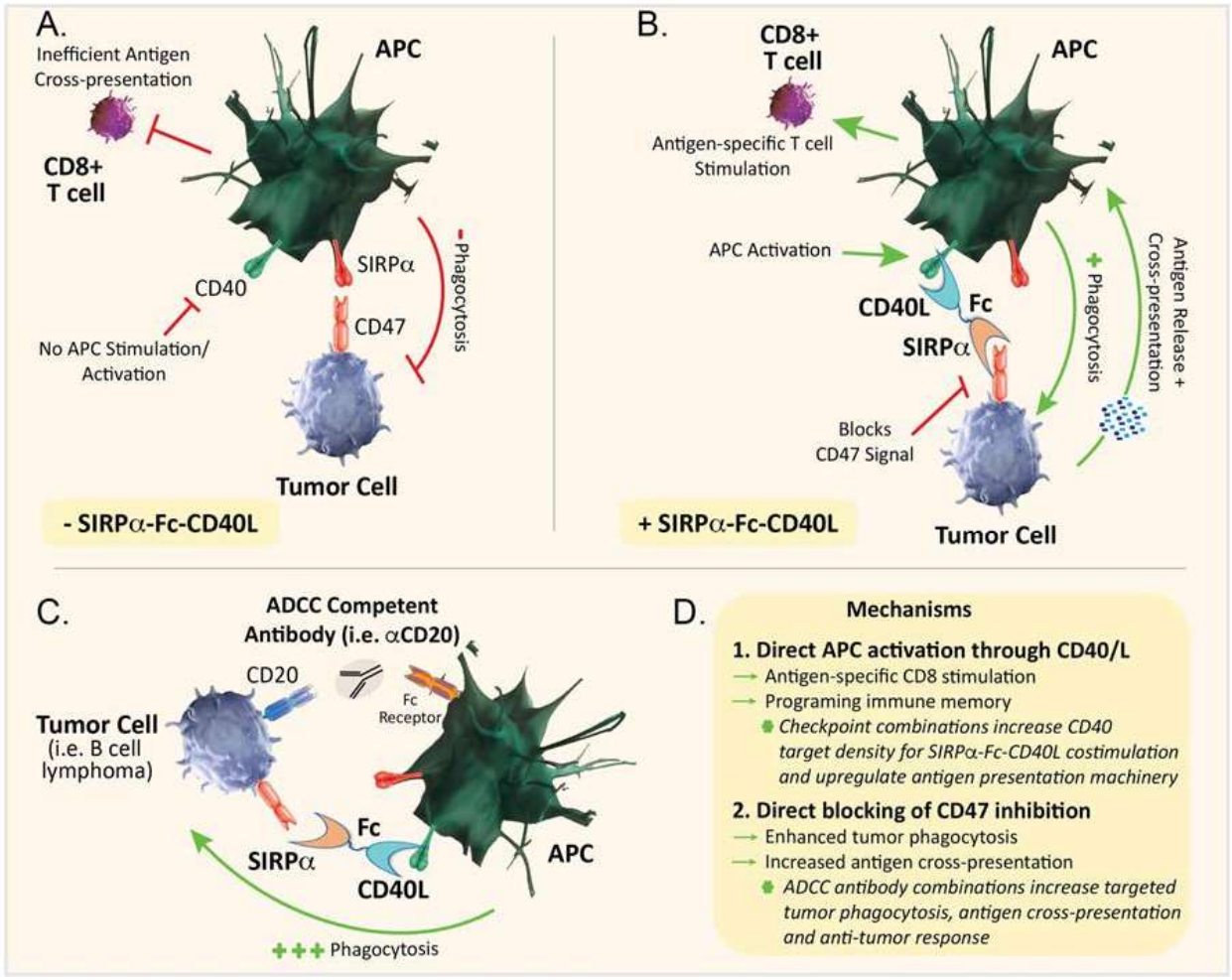
1.2 Investigational Product, SL-172154

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 1 A and B). 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). SL-172154 and rituximab (anti-CD20) were also shown to induce macrophage activation and the expression of type I interferon genes in macrophages, which was enhanced when the two agents were combined.

1.2.3 In Vivo Pharmacology

Treatment of mice with mSIRPα-Fc-CD40L intravenously (IV) led 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]. The in vivo anti-tumor activity of mSIRPα-Fc-CD40L monotherapy was studied in established syngeneic CT26 colorectal murine tumor models. The performance of intraperitoneal (i.p.) 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 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. Additionally, a robust increase in AH1 tetramer +/CD8+ cells in the spleen and the tumor was seen in mice treated with mSIRPα-Fc-CD40L or the anti-CD40/anti-CD47 combination in comparison to vehicle controls.

1.2.3.1 Antitumor Activity of mSIRPα-Fc-CD40L in Combination 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 by the intraperitoneal (i.p.) route of administration with the following two combinations: mSIRPα-Fc-CD40L + murine anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) antibody or murine 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. The synergy was noted when, in relation to mSIRPα-Fc-CD40L dosing, anti-CTLA-4 was administered first or concurrently, or anti-PD-1 was given concurrently. 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 was augmented when given in combination 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 (ADCP). 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 or mSIRPα-Fc-CD40L was 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 1 A and B). 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. SL-172154-mediated tumor phagocytosis can be enhanced through combination with a targeted ADCC competent antibody (Figure 1 C and D). 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.

1.2.3.2 Antitumor Activity of Intratumoral mSIRPα-Fc-CD40L Monotherapy and in Combination with Murine Anti-PD-1 Antibody

The antitumor activity of mSIRPα-Fc-CD40L, given by intratumoral injection (ITI), as monotherapy and in combination with murine anti-PD-1 antibody was assessed in groups of female BALB/c mice inoculated with a CT26 colorectal carcinoma tumor in each rear flank. The mice were dosed on Days 0 (start of treatment), 2 and 5, and the treatment groups were: vehicle control (i.p. or ITI); mSIRPα-Fc-CD40L (300 µg; i.p), mSIRPα-Fc-CD40L (10 or 100 µg; ITI); and the combination of anti-PD-1 (100 µg; i.p) and mSIRPα-Fc-CD40L (10 or 100 µg; ITI).

Although only one of the two tumors was injected with mSIRPα-Fc-CD40L, a delay in tumor growth was observed in both. The 10 µg ITI dose of mSIRPα-Fc-CD40L was the most efficacious with 14% of mice completely rejecting both tumors. No tumor rejections were observed in the i.p. anti-PD-1 group. The rejection rate of both tumors was increased to ~42% when 10 µg ITI mSIRPα-Fc-CD40L was combined with i.p. anti-PD-1 treatment. Thus, intratumoral administration of mSIRPα-Fc-CD40L showed potent anti-tumor efficacy in both the treated (injected with mSIRPα-Fc-CD40L) and untreated tumor, suggesting that intratumoral mSIRPα-Fc-CD40L stimulated sufficient immune activation to promote an *anenestic* or bystander anti-tumor response. Moreover, no signs of injection site reactions, such as ulceration and inflammation, were observed with intratumoral mSIRPα-Fc-CD40L. Systemic depletion of peripheral B cells and an increase in peripheral dendritic cells observed 24 hours following intraperitoneal mSIRPα-Fc-CD40L were not observed after intratumoral mSIRPα-Fc-CD40L, supporting that much lower systemic exposure occurred following ITI. These findings support the hypothesis that direct injection of SL-172154 into a tumor can achieve a high local concentration of SL-172154 using relatively lower doses of drug than would be required with IV administration.

1.2.4 Toxicology

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 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, and included assessments of serum SL-172154 concentrations and pharmacodynamic biomarkers. The GLP study was conducted with drug that is representative of the Good Manufacturing Process used for clinical drug supplies. 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 hemolytic potential using human whole blood, and the potential for interfering with pre-transfusion compatibility testing was assessed.

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. In the DRF study, 40 mg/kg was designated

as the highest non-severely toxic dose 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 contrast to the DRF study, there was evidence of toxicity in the GLP study that manifested as dose-dependent infusion-related reactions in the 10 and 40 mg/kg groups (Days 15 or 22). The acute clinical observations noted were paleness and decreased activity. The severity of signs and symptoms during dose administration resulted in 2 monkeys in the 40 mg/kg group being euthanized in extremis [a female on Day 15 (Dose 3) and a male on Day 22 (Dose 4)], and early termination of dosing in the 10 and 40 mg/kg groups. RBC hemolysis was investigated and ultimately ruled out as a potential causal or contributory factor to the infusion-related reactions since clinical hematology (erythrocyte count, hemoglobin, and hematocrit) and serum chemistry (lactate dehydrogenase and total bilirubin) evaluations at multiple timepoints in the study showed no evidence of hemolysis or anemia. Additionally, the in vitro incubation of SL-172154 with human whole blood did not result in any detectable hemolysis. 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. At the 1 mg/kg dose level, there were no clinical observations, abnormalities in clinical pathology parameters, or non-reversible pathology findings, thus 1 mg/kg was considered to be the no-observed-adverse-effect level (NOAEL) for IV infusion doses of SL-172154. The 1 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. Additionally, on Day 1, the mean terminal elimination half-life ($t_{½}$) was approximately 0.4 hours in the 1 mg/kg group and longer in the 10 mg/kg and 40 mg/kg groups with mean values of approximately 1.1 and 0.9 hours, respectively. Of note, transient low or non-quantifiable plasma SL-172154 concentrations on Day 29 precluded the determination of toxicokinetic parameters.

As expected, in the GLP study, SL-172154 was shown to occupy CD40 and CD47 receptors on circulating blood cells in a dose-dependent manner; on Day 1 (Dose 1) in the 10 and 40 mg/kg groups, >90% CD40 receptor occupancy on PBMCs and ~80% CD47 receptor occupancy on RBCs was observed. Similar on-target pharmacological effects were seen in both the DRF and GLP studies. A number of serum cytokines were transiently increased with the elevations being generally dose-dependent and tending to increase with repeated dosing. 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. 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. The emergence of ADA was not unexpected because SL-172154 is based on human amino acid sequences which have 82% identity to the cynomolgus. Transient and reversible complement activation, as evidenced by increased plasma complement split products, occurred and was coincident with the emergence of ADA.

In the GLP monkey study, IV infusion of SL-172154 was shown to be locally well tolerated as no visible lesions were observed at the injection site and microscopic findings were generally minimal

and deemed to be procedure-related. Additionally, in BALB/c mice with two implanted CT26 tumors, three intratumoral injections (Days 0, 2, and 5) of the murine analog, mSIRPα-Fc-CD40L, (10 or 100 μg) in one tumor were well tolerated, with no local injection site reactions observed.

Routine blood bank pre-transfusion compatibility tests with human RBCs and platelets and SL-172154 spiked AB human plasma (1 to 250 μg/mL) indicate that SL-172154 is expected to interfere with blood typing and compatibility testing.

In summary, the two repeat IV dose toxicity studies in cynomolgus monkeys had similar trends in toxicokinetic parameters and 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. The dose-dependent, infusion-related reactions observed with repeat dosing in the GLP study were attributed to exacerbated pharmacology of SL-172154 in the presence of ADA. Given the low ITI doses to be studied in clinical study SL03-OHD-102, low systemic exposure is anticipated in comparison to IV infusion, and thus the IV no observed adverse effect level (NOAEL) of 1 mg/kg in monkeys provides systemic exposure and safety coverage. Consequently, the nonclinical safety assessment program supports the intratumoral administration of SL-172154 in clinical study SL03-OHD-102.

1.3 Rationale for Investigation of SL-172154 by Intratumoral Administration

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 ITI mSIRPα-Fc-CD40L in the murine CT26 tumor model stimulated potent anti-tumor efficacy of both the treated and untreated tumors, and efficacy was further improved when combined with a sytemically administered PD-1 blocking antibody. Intratumoral mSIRPα-Fc-CD40L was well tolerated with no local injection site reactions observed and there was no evidence of the systemic B cell and dendritic cell fluctuation that was observed following i.p. dosing.

Injecting SL-172154 directly into the tumor aims to use the tumor as its own vaccine triggering strong priming of innate and adaptive immunity against tumor antigens locally. With direct injections into the tumor, a high intratumoral concentration of SL-172154 can be achieved in situ, using relatively lower doses of drug than would be required systemically. Local delivery can prevent significant systemic exposure and off-target toxicities. Additionally, it allows for combination therapies to be administered with less systemic toxicity than if the combination drugs were both given IV.

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 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.

1.3.1 Rationale for Selection of Tumor Types Under Investigation

Cutaneous squamous cell carcinoma (CSCC) and squamous cell carcinoma of the head and neck (HNSCC) were selected for investigation in this phase 1 study of ITI SL-172154 due to the fact that both of these tumor types have 1) a high percentage of tumors with increased CD47 expression, 2) mechanisms of tumor immune evasion that target both adaptive and innate immunity within the tumor microenvironment [Ferris, 2015] and 3) patients with select tumor lesions that are accessible and safe for ITI.

1.3.1.1 Cutaneous Squamous Cell Carcinoma of the Skin

CSCC is the second most common malignancy in the United States, with approximately one million individuals diagnosed with CSCC in 2012, the most recent year that new statistics were available [Rogers, 2015]. Risk factors for CSCC include ultraviolet (UV) exposure, advanced age, and immunosuppression [Alam, 2001; Madan, 2010]. Although the vast majority of individuals with a diagnosis of CSCC have a very favorable prognosis, CSCC has a greater propensity for aggressive recurrences than basal cell carcinomas (BCC) and there is increased mortality in comparison with BCC patients that are age-matched controls [Rees, 2015].

Surgical resection is the mainstay of therapy for CSCC with the goal of achieving complete resection and an acceptable cosmetic outcome [Madan, 2010]. For the small percentage of patients who develop unresectable locally recurrent or metastatic disease, treatment options are limited. Small retrospective series and case reports have been published using a variety of radiation or chemoradiation therapies and durable disease control can be achieved in a subset of patients [Samstein, 2014; Nottage, 2017]. However, once local therapies are exhausted, patients have limited treatment options.

Regarding systemic therapy, 5-fluorouracil and cisplatin therapy have been studied in small single arm studies of CSCC but have never been shown to have meaningful clinical benefit and there are safety and tolerability concerns in patients with advanced age [Khansur, 1991]. Targeting of the

epidermal growth factor receptor (EGFR) in CSCC has been explored by several groups. In a phase 2 study of cetuximab monotherapy for patients with unresectable squamous cell carcinoma of the skin, median age was 79 years. The observed response rate was 28% (10/36 patients) with a median progression-free survival (PFS) of 4.1 months, and median overall survival (OS) of 8.1 months [Maubec, 2011]. While these studies have limitations, EGFR inhibitors are considered a treatment option [NCCN, 2019]. Recently, the PD-1 inhibitor, cemiplimab, was granted an indication by the United States Food and Drug Administration (FDA) in patients with locally advanced or metastatic CSCC who are not candidates for curative surgery or radiation. The indication was based on the results of a phase 1 and 2 study in which the overall response rate (ORR) in the 108 patients across both studies was 47.2% (3.7% complete response [CR], 43.5% partial response [PR]). The median duration of response (DOR) was not reached but 61% of patients had a DOR of ≥ 24 weeks [Libtayo-USPI, 2018; Migden, 2018].

A high percentage of CSCCs have detectable CD47 expression. In a panel of 117 cases of in situ and invasive epithelial cutaneous lesions, archival tissue from actinic keratoses (AK), SCC in situ (SCCIS), SCC, and keratoacanthoma (KA) were examined for CD47 expression by immunohistochemical analysis [Akel, 2016]. Significantly higher CD47 expression (both in percentage positivity and intensity, and combined score of percentage positivity and intensity) was seen in SCC compared with AK, SCIS and KA. Most SCCs (78%) showed more than 75% positivity (4+ score) compared with AK (0%), SCCIS (15%), and KA (35%). Given that CD47 expression appears to increase gradually along the spectrum of AK to SCCIS to SCC, these data suggest that CD47 is important in the transformation of an in situ malignancy into one that is frankly invasive. Given the increased CD47 expression and high degree of responsiveness to PD-1 inhibitors, the unique immune contexture of CSCCs makes this histology particularly suitable for investigation of intratumoral administration of SL-172154.

1.3.1.2 Squamous Cell Carcinoma of the Head and Neck

HNSCC is the ninth leading cancer by incidence worldwide and constitutes 90% of all head and neck cancers [Jemal, 2007]. In the US, approximately 50,000 new cases of HNSCC are diagnosed yearly and more than 10,000 deaths occur per year [Fitzmaurice, 2017]. Head and neck cancers encompass a group of malignancies arising from several anatomical mucosal sites, including the nasal cavity, paranasal sinuses, nasopharynx, oropharynx, hypopharynx, larynx and lips, and oral cavity with the vast majority being of squamous cell histology [Kok, 2020]. HNSCC are genomically heterogenous and the major drivers of tumorigenesis divide the population into two broad categories 1) virally mediated or human papilloma virus (HPV)-positive HNSCC and 2) non-virally mediated or HPV-negative HNSCC that results from alcohol, tobacco or betel nut exposure.

Most patients present with locally advanced disease with a high risk of recurrence, and approximately 10% of HNSCC patients present with metastatic disease. Surgical resection of the primary tumor and draining lymph nodes followed by risk-adapted adjuvant radiation, with or without platinum-based chemotherapy, or primary definitive concurrent chemoradiation, remain the principal treatments employed for locally advanced HNSCC [Cohen, 2019].

Despite advances in surgery and radiotherapy, the five-year survival rates for patients with HNSCC range between 40 to 50% across all stages for tumors caused by traditional carcinogens (HPV-negative). The median overall survival (OS) for patients with recurrent/metastatic disease

is 10–13 months [Marur, 2008]. Once local therapies have been exhausted for locally recurrent or metastatic disease, the prior standard of care in the first-line setting has been platinum-based doublet chemotherapy with cetuximab. Compared to chemotherapy alone, the addition of cetuximab in the regimen described extended median progression free survival (PFS) from 3.3 months to 5.6 months (HR 0.54; $P < 0.001$), median OS from 7.4 months to 10.1 months (HR 0.80; $P = 0.04$), and response rates from 20 to 36% ($P < 0.001$) [Vermorken, 2008]. Furthermore, until recently, second-line treatment options included only cetuximab, methotrexate, and a taxane; each of which is associated with response rates of 10–13%, and median PFS of 2–3 months without clear demonstration of an improvement in OS [Cohen, 2019].

In 2016, the United States FDA and in 2017 the European Medical Agency granted the first approvals for the PD-1 inhibitors, nivolumab and pembrolizumab, in the treatment of patients with recurrent HNSCC that is refractory to platinum-based regimens. The current first-line regimen for relapsed/metastatic HNSCC then adopted a new paradigm in 2019, when the results of the randomized controlled trial, comparing pembrolizumab combined with platinum and infusional 5-fluorouracil to the past gold-standard regimen of cetuximab plus the same chemotherapy combination, confirmed an overall survival benefit (hazard ratio, HR, for death at 0.65, 95% confidence interval, CI, 0.53–0.80) favoring the pembrolizumab-based treatment arm. Based on these results the FDA granted approval for pembrolizumab in combination with platinum and fluorouracil for the first-line treatment of patients with HNSCC and pembrolizumab as a single agent for the first-line treatment of patients with HNSCC whose tumors express a PD-L1 combined positive score ≥ 1 [Cohen, 2019; Kok, 2020]. Although PD-1 inhibitors have improved outcomes in HNSCC, resistance to these agents develop over time and better treatment paradigms are needed.

CD47 overexpression is a hallmark of multiple cancer types including HNSCC and evidence supports CD47 as a potential therapeutic target. Immunohistochemical staining of specimens from 48 cases of oral mucosa, 43 cases of dysplasia and 165 cases of primary HNSCC showed quantitatively higher CD47 expression in human HNSCC tissue as compared with normal oral mucosa indicating that CD47 is a tumor associated antigen [Wu, 2018]. Interestingly, positive immunostaining of CD47 was mainly localized in cancer cells and very prominent in the invasive cell layer. Furthermore, detailed analysis of HNSCC tissues revealed that CD47 staining was significantly increased with advanced pathology grade (grade II+III vs. I) and with lymph node metastases (N1+N2 vs. N0). Most importantly, in 165 primary HNSCCs with follow-up data, Kaplan–Meier survival analysis indicated that CD47 high expression (using the median CD47 protein expression histoscore of 58.37 as a cut-off value) confers worse overall survival ($p = 0.0459$). Thus, similar to CSCC, CD47 expression is increased in HNSCCs and the efficacy of PD-1/L1 inhibitors is well established. Based on these observations, this histology is particularly suitable for investigation of intratumoral SL-172154.

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 IV 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 intratumoral administration of SL-172154 in humans will be assessed 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 administered by IV, subcutaneous and/or ITI.

Based on a thorough review 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 SL-172154-related effects is most likely due to a combination of both the pharmacologic activity of the molecule and to immunologic reactions triggered by SL-172154 administration. The following are potential contributory factors to the dose-dependent infusion-related reactions: (1) elevations in serum cytokines; (2) postdose changes in lymphocyte number; (3) development of ADA and downstream complement activation.

AEs that have been observed following systemic 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].

AEs that have been observed following localized (subcutaneous or ITI) administration of CD40 agonists include injections site reactions (ISRs), CRS, flu-like symptoms (fever, chills, rigors, hypotension), fatigue, malaise, nausea, vomiting, loss of appetite, constipation, cholecystitis, and abdominal pain [Bentebibel, 2019; Irenaeus, 2019; Tran, 2019]. Subcutaneous administration of the CD40 agonist, MEDI-5083, given in sequential or concurrent combination with IV durvalumab in patients with advanced solid tumors resulted in dose-limiting ISRs with 89.5% of patients having any grade ISRs and 15.8% of patients having $\geq$ grade 3 ISRs [Tran, 2019]. Intratumoral administration of the CD40 agonist, ADC-1013, resulted in CRS associated with deep lesion injections (100%; 12/12) but not with superficial injections (0%; 0/6). ADC-1013 was detected in blood following injection into deep liver lesions whereas injections into superficial tumors resulted in nondetectable serum levels suggesting that intratumoral administration into vascularized lesions such as hepatic lesions resulted in higher immediate systemic exposure compared to intratumoral administration into other anatomical sites [Irenaeus, 2019].

AEs that have been observed following systemic 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]. Intralesional administration of

the CD47 antagonist TTI-621 (SIRPα FC) in patients with relapsed/refractory mycosis fungoides and Sezary Syndrome was well-tolerated with no ≥ grade 3 treatment emergent AEs, DLTs or SAEs reported. The most common treatment-related AEs that occurred in ≥ 20% of patients were chills, injection site pain and fatigue [Querfeld, 2018].

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

1) The data indicate a potential risk for injection-related reactions and CRS in humans. The infusion-related reactions 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, administration in an outpatient oncology clinic or inpatient setting, management guidelines (e.g., rescue treatments, prophylaxis), and extended monitoring when indicated. Furthermore, to minimize systemic exposure, injection of deep lesions such as highly vascularized hepatic tumors is not permitted. Only superficial lesions that can be injected by direct visualization, palpation, or ultrasound guidance will be treated with ITI of SL-172154. The steps taken to minimize the risks are outlined in the Toxicity Management Guidelines section of the protocol (Section 3.7). 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: 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. 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 3.7.1).

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. Furthermore, since SL-172154 binds to CD47 on RBCs and platelet membrane, it may obscure the assessment of red blood cell phenotyping and thus interfere with compatibility tests, including the antibody screening and crossmatching that are part of a routine pre-transfusion work up [Report_SL2020IB001]. To investigate this risk, blood phenotyping, type and screen (ABO/Rh), and direct antiglobulin test (DAT) will be performed at screening before and following exposure to SL-172154. Furthermore, investigator guidance is provided on blood cross-matching and transfusion procedures in protocol Section 3.8.

4) Injection Site Reactions: In the NHP studies, SL-172154 was locally well tolerated with no visible lesions observed at the IV administration site. On microscopic examination, findings

were generally minimal and deemed to be procedure-related. Similarly, ITI of mSIRPα-Fc-CD40L in the murine CT26 tumor model was well tolerated with no local injection site reactions observed. Regardless, subjects will be monitored for injection site reactions and specific monitoring, dose interruption, and management guidelines are outlined in protocol Section 3.7.

5) 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 3.7 follow these consensus guidelines in this 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 ITI studies and this class of agents and the management of associated toxicities such as CRS; (2) the proposed starting dose of intratumoral SL-172154 is estimated based on minimum anticipated biological effect level (MABEL) and is 25,000 times lower than the NOAEL observed in the NHP studies (Section 3.3). Systemic exposure is expected to be negligible with ITI administration and 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 3.7); (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. 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. By injecting SL-172154 directly into the tumor aims to use the tumor as its own vaccine triggering strong priming of innate and adaptive immunity against tumor antigens locally. With direct injections into the tumor, a high intratumoral concentration of SL-172154 can be achieved in situ, using relatively lower doses of drug than would be required systemically. Local delivery can prevent significant systemic exposure and off-target toxicities. Additionally, it allows for combination therapies to be administered with less systemic toxicity than if the combination drugs were both given IV.

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 CR rate of 21% [Advani, 2018; Advani, 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.

Anti-tumor activity of intratumoral administration of an agent targeting the CD47/SIRPα pathway has only been examined in one clinical study to date. In a phase 1 study, the SIRPα-Fc fusion protein, TTI-621, was administered intralesionally in patients with relapsed/refractory mycosis fungoides or Sezary syndrome [Querfeld, 2018]. This study demonstrated encouraging preliminary activity with 91% (20/22) of heavily pretreated patients having a reduction in their Composite Assessment of Index Lesion Severity scores within the treated lesions and 41% (9/22) having a ≥50% decrease in the severity score. Similar responses were seen in adjacent, non-injected lesions. In serial biopsies, intralesional TTI-621 administration resulted in a rapid influx of macrophages and CD8+T cells indicative of an innate and adaptive immune response.

Several different CD40 agonistic antibodies administered IV 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 ongoing clinical trials combining CD40 agonists with vaccines, checkpoint inhibitors and/or chemotherapy [O'Hara, 2019].

Multiple CD40 agonists have been administered via subcutaneous or ITI [Bentebibel, 2019; Irenaeus, 2019; Tran, 2019]. The most promising preliminary activity has been noted with intratumoral administration of the CD40 agonist, APX005M, in combination with IV pembrolizumab. In 13 checkpoint inhibitor-naïve melanoma patients the best overall response was as follows: partial response in 7/13 (54%) patients, stable disease in 4/13 (31%) and progressive disease in 3/13 (23%) [Bentebibel, 2019]. However, given that these patients were all checkpoint inhibitor-naïve, the contribution of each of the components on response rate is difficult to ascertain in the combination arm.

2. STUDY OBJECTIVES AND OUTCOME MEASURES

Objective	Outcome Measure
Primary Objectives	
To evaluate the safety and tolerability of ITI administration of SL-172154 and to identify the maximum tolerated dose (MTD) or maximum administered dose (MAD) of SL-172154	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	
To select the recommended Phase 2 dose (RP2D) for SL-172154 when administered by intratumoral injection (ITI)	Based on review of all data collected during dose escalation and the pharmacodynamic cohort including safety, tolerability, PK, anti-tumor activity, and pharmacodynamic effects
To assess preliminary evidence of anti-tumor activity of SL-172154 when administered by ITI	Response 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]) ▪ 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 ▪ Change from baseline lesion diameter for injected lesion ▪ Change from baseline lesion diameter for non-injected lesion

Objective	Outcome Measure
Secondary Objectives	
To evaluate anti-drug antibodies (ADA) to SL-172154 when administered by ITI during and after treatment.	▪ Number/proportion of subjects with positive ADA titer ▪ ADA duration ▪ Transient vs. persistent ADA
To characterize the pharmacokinetics (PK) of SL-172154 when administered by ITI	▪ 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 ($t_{1/2}$), Clearance (CL) and Volume of Distribution (Vz)
Exploratory Objectives	
To assess pharmacodynamic biomarkers in blood prior to, on-treatment and following SL-172154 when administered by ITI	Pharmacodynamic biomarkers in blood may include: ▪ Changes from baseline in cell counts and percentages of circulating immune cells such as: T cells, B cells, natural killer (NK) cells, and myeloid cells ▪ Circulating chemokine and cytokine levels
To assess pharmacodynamic biomarkers in tumor tissue prior to, on-treatment and following SL-172154 when administered by ITI	Pharmacodynamic biomarkers in tumor tissue may include: ▪ Presence of SL-172154 in tumor tissue ▪ Changes in T cells subsets, B cells and macrophages and assessment of SL-172154 in the tumor tissue ▪ CD47 and CD40 expression ▪ Programmed cell death ligand 1 (PD-L1) expression
To estimate progression-free survival (PFS)	▪ PFS: time from first dose to progression by RECIST v1.1 or death, whichever comes first

3. STUDY DESIGN

3.1 Description of Study Design

This clinical trial is an open label, multi-center, dose escalation, Phase 1 study of SL-172154 administered by ITI injection (see SCHEMA). This trial is designed to evaluate the safety, PK, anti-tumor activity and pharmacodynamic effects of SL-172154 administered by ITI on days 1, 8, 15 of a 21-day in cycle 1 and then on day 1 of each subsequent 21-day cycle (cycles ≥ 2). Subjects that are eligible for enrollment have locally advanced or metastatic squamous cell carcinomas of the head and neck or skin that are not amenable to further treatment with surgery, radiation or standard systemic therapies that are known to provide clinical benefit for their condition (Section 4).

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 5 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 3.5 for Definition of DLT) during the 21-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 3.4.

For each dose level, 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 12 DLT evaluable subjects at a given dose level, 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 approximately 6 additional subjects at one or more dose levels that have completed evaluation for safety without exceeding the MTD. Subjects in the pharmacodynamic cohort must have tumor accessible and safe for biopsy from both an injected lesion and a non-injected lesion 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 and other data 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.

3.2 Selection of Recommended Phase 2 Dose

Selection of the RP2D and schedule for SL-172154 will be based upon the totality of the data in subjects treated in the dose escalation and the pharmacodynamic cohorts. The totality of the data refers to safety, tolerability, PK, clinical activity, and pharmacodynamic markers consistent with the mechanism of action. Approximately 6 subjects (inclusive of the subjects enrolled in the Dose Escalation and Pharmacodynamic cohort) may be treated at the RP2D.

3.2.1 Sample Size

The planned total sample size for this study is approximately 18 subjects. This sample size assumes evaluation of approximately 12 subjects across 4 dose levels in dose escalation and approximately 6 subjects in the optional pharmacodynamic cohort. The goal is to enroll approximately 6 subjects at the potential RP2D, including subjects in dose escalation and the pharmacodynamic cohort.

3.3 Justification for Starting Dose and Schedule of SL-172154

The intratumoral starting dose for 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 *Alstroemeria-Mosaic Virus* (AIMV) medium. The starting dose for the study is informed by key data from cynomolgus monkey toxicology studies, including identifying the NOAEL, and the PK results.

A starting dose of 0.003 mg (3 µg) was chosen for the administration of SL-172154 to humans via ITI. Given as a total 1.5 mL injection (2 µg/mL), this concentration, prior to distribution within tissue at the administration site, is comparable to the EC_{50} value (1.8 µg/mL) observed for human and cynomolgus monkey in the PBMC proliferation assay. Because SL-172154 is delivered locally to the tumor lesion, this dose/concentration is considered appropriate for this route of injection without further correction. Dose escalation will allow for identification of an optimal dose for subjects with advanced disease.

Intratumoral delivery has the potential advantage of reducing systemic toxicity by delivering drug directly to the tumor lesion. For immune-stimulating agents, intratumoral injection may also serve as an in situ vaccination approach. The proposal to use a flat dose (mg or µg) is consistent with the recommendation from Marabelle *et al.* [Marabelle, 2018] for ITI of drugs with primary toxicity that is likely systemic.

Since SL-172154 will be administered directly into the tumor and is expected to remain primarily within the tumor tissue, PK modeling was not considered necessary to inform the starting dose. Rather, the starting dose is selected to match intratumoral concentrations of SL-172154 to effect concentrations (e.g., EC_{20}, EC_{50}) derived from the AIMV assay.

As a benchmark for toxicity, the NOAEL for SL-172154 administered IV to cynomolgus monkeys in a GLP toxicology study was 1 mg/kg [Report SL2020IB001]. The proposed SL-172154 starting dose of 0.003 mg (3 µg) in a 70 kg human is 0.04 µg/kg, and is 25,000 times lower than the NOAEL of 1 mg/kg. In monkeys, the 1 mg/kg dose administered IV corresponded with mean

Cmax and $AUC_{0\text{-last}}$ values of 1230 ng/mL and 518 ng•h/mL on Day 1. Assuming complete bioavailability following an intratumoral dose, Cmax is expected to be 0.049 ng/mL (25,000 times lower) and thus, systemic exposure is expected to be negligible with intratumoral administration. It also should be noted that the planned starting dose for ITI (0.003 mg; 0.00004 mg/kg for a 70 kg subject) is ~2500-fold below the starting SL-172154 IV dose of 0.1 mg/kg in clinical study SL03-OHD-101, thus ensuring that systemic exposure following ITI will remain substantially below exposures observed following IV administration.

Targeting the EC_{50} from the AIMV assay for an intratumorally administered drug is intended to provide a safe starting dose while minimizing the number of dose escalations needed to achieve a therapeutically effective dose. A starting dose based on 50% pharmacologic activity was found to be safe in 16 of 17 bispecific CD3 constructs administered IV or i.p. [Saber, 2017]. Given the considerations outlined above, a starting dose (0.003 mg) based on EC_{50} is expected to have a low likelihood of systemic toxicity while achieving local tumor concentrations consistent with in vitro pharmacologic response.

Justification for Schedule

The dosing schedule for the clinical trial incorporates SL-172154 administered by ITI on days 1, 8, 15 of a 21-day in cycle 1 and then on day 1 of each subsequent 21-day cycle (cycles ≥ 2). The rationale for the selected dose schedule is based on a paradigm of immune priming and immune boosting [Marabelle, 2018]. The immune priming phase refers to SL-172154 administered by ITI on days 1, 8, 15 of a 21-day in cycle 1. Immune priming refers to stimulating a de novo immune response via the generation of a novel, antigen specific, adaptive immune response. Given that SL-172154 may have a short half-life and potentially a short duration of local bioactivity on the CD40 agonist end, it is hypothesized that an initial dose-intense induction phase of ITI is necessary for the local priming of an antitumor immune response. This schedule for immune priming is supported by the NHP data as no toxicity was observed at the day 8 dose, minimal pharmacodynamic effects were noted at this time point, 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 and via the ITI route of administration.

The immune boosting phase refers to SL-172154 administered by ITI at day 1 of each subsequent 21-day cycle at cycle 2 and beyond. Immune boosting involves the enhancement of a pre-existing immune response against the tumor and is hypothesized to elicit a recall effect to a recent immune priming event or disinhibit a pre-existing antitumor immune response [Marabelle, 2018]. Thus, the 3-week treatment free interval beyond day 22 is based upon 1) subject acceptability and 2) the durability of binding for SL-172154 to CD47. Furthermore, this interval 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.

3.4 Dose Escalation of SL-172154 Administered by Intratumoral Injection

Dose escalation will proceed using a flat dose and fixed volume format (see Section 6.8 for additional details). Dose escalation will begin at the starting dose of 0.003 mg as outlined in Table

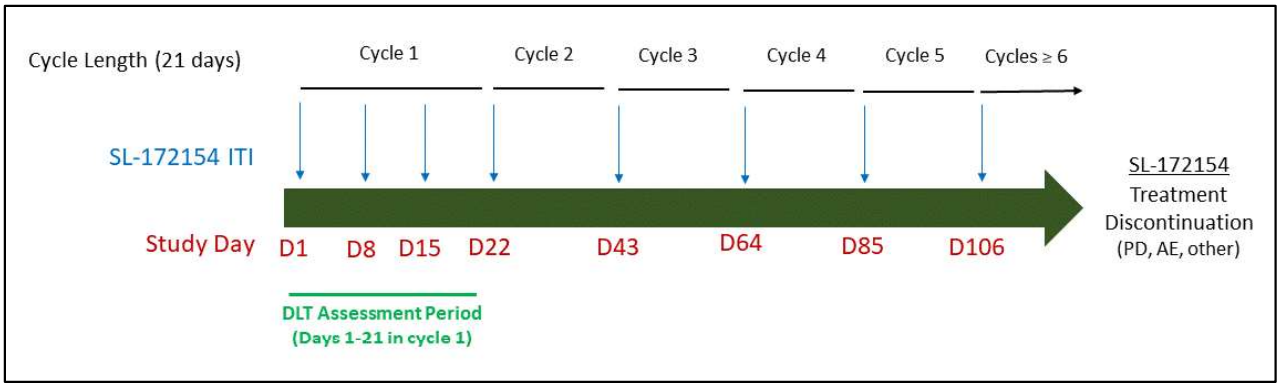
1 below; intermediate dose levels not shown may be explored based on emerging data (e.g., safety). Dose escalation of intratumoral SL-172154 will not exceed half-log increments. The DLT assessment period is 21 days in length and encompasses the first 21-day cycle of therapy. Dose escalation will follow mTPI-2 decision rules outlined in Table 5 in Section 9.1.

- Dose escalation in half-log increments (Table 1)
- Schedule of administration for ITI of SL-172154: Doses administered on days 1, 8, 15 of a 21-day cycle in cycle 1 and on day 1 of each subsequent 21-day cycle, starting on cycle 2, day 1 (day 22) (Figure 2).
- Cycle length: 21 days
- DLT assessment period: 21 days of cycle 1

Table 1: Intratumoral Dose Escalation Plan for SL-172154

Dose Level	ITI Dose (mg) of SL-172154[a]	ITI Volume of Dose
Level 1 - starting dose	0.003	1.5 mL
Level 2	0.01	1.5 mL
Level 3	0.03	1.5 mL
Level 4	0.1	1.5 mL
a) Intermediate or higher dose levels may be tested based on emerging safety and/or pharmacodynamic data. Dose escalation will not exceed half-log increments.		

Figure 2: ITI Schedule for SL-172154



3.5 Definition of Dose-Limiting Toxicity

DLTs are as defined in the bulleted points below. Toxicities will be graded as per NCI CTCAE v5. The determinate period for DLT is the first 21 days of ITI SL-172154 dosing. **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 with the following exceptions:
    - Grade 3 fatigue lasting ≤ 7 days
    - Grade 3 anemia if not associated with clinical sequelae or not requiring transfusion of red blood cells (RBCs) within 48 hours.
    - 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 injection-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours of onset with appropriate clinical management.
    - Grade 3 rigors or chills lasting < 6 hours that respond to optimum medical therapy.
    - Grade 3 fever lasting < 24 hours with or without medical therapy.
    - 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
    - Grade 3 skin toxicity (excluding injection-site reactions) that downgrades to Grade 2 or less within 7 days with optimal supportive care
    - 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 (21 days) 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 two of the three scheduled dose of SL-172154 during the DLT assessment period may be taken into consideration when assessing the totality of the data in determining evaluability for DLT and the RP2D.

3.6 Concomitant Medications, Treatments, and Procedures

Investigators may prescribe concomitant medications or treatments deemed necessary to provide supportive care except for prohibited medications (see Section 3.6.1) during treatment with SL-172154. 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.

Aspirin is permitted at doses ≤ 100 mg once daily. Chronic use of analgesic and/or anti-pyretic agents with no or low bleeding risk (for example, paracetamol/acetaminophen, metamizole, dipyrone, or propyphenazone) is recommended.

3.6.1 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 study treatment with SL-172154:

- 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 therapy, immunotherapy, or biologic therapy for cancer treatment
- Immunosuppressive medications for primary prophylaxis against injection-related reactions are not permitted. Subjects who require immunosuppressive medications (e.g., corticosteroids) for management of irAEs or injection-related reactions should be managed per Toxicity Management Guidelines in Section 3.7.
- Live attenuated vaccines during the study through 30 days after the last intratumoral dose of SL-172154
- Antiplatelet therapy (for example, clopidogrel, ticlopidine, dipyridamole, and anagrelide or > 100 mg acetylsalicylic acid).
- Full dose anticoagulation therapy (for example, warfarin, heparin, low molecular weight heparin, direct oral anticoagulants). Low dose anticoagulant therapy for thromboprophylaxis is permitted.

- Local anesthetic administered prior to ITI of SL-172154 is not permitted due to the low pH of local anesthetic and the potential impact on the function of the drug product. Local anesthetic use is permitted prior to biopsy of a non-injected lesion.

3.6.2 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 during ITI of SL-172154. 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).

Chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) with a high risk of bleeding (for example, indomethacin, ibuprofen, naproxen, or similar agents) is strongly discouraged unless at the discretion and responsibility of the investigator after careful assessment of the individual bleeding risk of the subject.

3.7 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 judgment 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 5.1.4 Monitoring Dose Administration for further information on ITI of SL-172154. In this protocol, the term “injection-related reactions” maps to the analogous term of “infusion-related reaction” in CTCAE v5.

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

Differentiating between injection-related reactions 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 injection-related reactions 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 judgment of the AE/SAE and the definition found in NCI-CTCAE v5.0 for injection-related reaction, allergic reaction, anaphylaxis, and CRS.

Primary prophylaxis against injection-related reactions is not permitted to avoid obscuring a potential safety signal and to enable an assessment of whether pre-medications should be required for all subjects. However, as noted in the guidance below, secondary prophylaxis (i.e., prevention of injection-related reactions following an initial episode) is appropriate and permitted at the discretion of the investigator.

NOTE: In the event of a Grade ≥ 2 injection-related reaction, subjects will be observed on-site or hospitalized for close observation until resolution of symptoms as per Section 3.7.1.

3.7.1 Toxicity Management Guidelines

<table>
<tr><th>Adverse Event</th><th colspan="2">General Guidance for Injection Site Reactions (ISR)</th></tr>
<tr><td rowspan="4">Injection Site Reactions</td><td colspan="2">Subjects will be monitored closely throughout the study for the following symptoms at the injection sites: pain, tenderness, pruritis, warmth, cellulitis, rash, erythema, swelling, induration, fluctuance, and nodules (granulomas or cysts). Digital photographs will be documented by the study team for evaluation on all subjects who have an injection site reaction that are serious, Grade 2 or above or if persistent beyond 2 weeks. Dermatology will be consulted on all subjects who have an injection site reaction considered serious, Grade 3 or above, or if persistent beyond 30 days and others if the Investigator or Medical Monitor feels it is medically necessary.</td></tr>
<tr><td>Severity (Symptoms)</td><td>Management</td></tr>
<tr><td>Grade 1</td><td>• Continue SL-172154 injection with close clinical follow-up.
• Symptomatic treatment and/or premedication of local injection site reactions with antihistamines (H1/H2 inhibitors), acetaminophen (or other low bleeding risk medications; Section 3.6) and opiates is acceptable. Antileukotrienes may also be considered as needed per discretion of the investigator. Due to their potential bleeding/immunosuppressive effects, the use of systemic NSAIDs and steroids within 24 hours of dosing SL-172154 should be avoided, if clinically feasible.</td></tr>
<tr><td>Grade 2</td><td>• Temporarily hold SL-172154 injection until AE has reverted to Grade 1 or baseline.
• Provide symptomatic treatment with acetaminophen as anti-pyretic, antihistamines, leukotriene inhibitors and/or opiates.
• Provide premedication prior to subsequent injections per investigator/institutional guidelines. Due to their potential bleeding/immunosuppressive effects, the use of systemic NSAIDs and steroids within 24 hours of injection with SL-172154 should be avoided if clinically feasible.
• If SL-172154 injection is delayed such that 2 consecutive scheduled injections are missed to allow for resolution of ISR despite optimal medical management, then the subject should permanently discontinue SL-172154 injections.</td></tr>
</table>

Injection site reaction (continued from previous page)	**Severity (Symptoms)**	**Management**
	Grade 3	• Hold SL-172154 injection until AE has reverted to Grade 1 or baseline. • Provide symptomatic treatment with acetaminophen as anti-pyretic, antihistamines, leukotriene inhibitors, steroids and/or opiates. • Obtain dermatology consultation. • If grade 3 AE persists for ≥ 7 days, permanently discontinue SL-172154 injections. • Provide pre-medications (acetaminophen as anti-pyretic, antihistamines, leukotriene inhibitors, steroids and/or opiates) for subsequent injections per investigator/institutional guidelines. • If grade 3 symptoms recur with pre-medications, then SL-172154 injections should be permanently discontinued.
	Grade 4	• Permanently discontinue SL-172154 injections. • Obtain dermatology consultation. • Treat urgently with non-operative and operative interventions as clinically indicated.

<table>
<tr><th>Adverse Event</th><th colspan="2">General Guidance for Injection-related Reactions [Rosello, 2017; Porter, 2018]</th></tr>
<tr><td rowspan="4">Injection-Related or Hypersensitivity Reactions</td><td colspan="2">In this protocol, the term “injection-related reactions” maps to the analogous term of “infusion-related reaction” in CTCAE v5. Acute reactions to the 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 common manifestations of 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 injection-related reactions with prompt institution of treatment. Subjects should be notified that symptoms may occur during the first injection and for up to several hours afterwards or with subsequent injections. Instruct subjects to contact their physician if symptoms or signs of an injection-related reaction occur.</td></tr>
<tr><td>Severity (Symptoms)</td><td>Management</td></tr>
<tr><td>Grade 1</td><td>• Injection(s) 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 injections per investigator/institutional guidelines</td></tr>
<tr><td>Grade 2</td><td>• Consider interrupting SL-172154 injection(s).
• 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.
• If symptoms resolve with treatment, SL-172154 injection(s) may be completed. If symptoms recur or do not resolve to baseline, then no further SL-172154 injection(s) will be administered at this visit.
• 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.
• The following prophylactic pre-medications are recommended for future injections: antipyretics, antihistamines with/without corticosteroids per institutional guidelines</td></tr>
</table>

	Severity (Symptoms)	Management
Injection-related or Hypersensitivity reactions (continued from previous page)	Grade 3	• Immediately discontinue injection(s) of SL-172154 • Begin IV infusion of normal saline and treat with epinephrine, bronchodilators, diphenhydramine, ranitidine, corticosteroids, oxygen, fluids, vasopressors, etc.as indicate 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. Strongly 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 injection at the next scheduled dose with pre-medication (e.g., corticosteroids, antihistamines, antipyretics). The next two subsequent injections of SL-172154 (after a grade 3 event of injection-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 injection. If symptoms recur, permanently discontinue SL-172154.
	Grade 4	• Permanently discontinue SL-172154 injection(s). • Admit to hospital for close observation until resolution of symptoms • Manage severe injection-related reactions per institutional standards (e.g., epinephrine, diphenhydramine, ranitidine, corticosteroids, bronchodilators, oxygen, fluids etc.). Epinephrine is the drug of choice in an anaphylactic reaction and its administration should not be delayed

<table>
<tr><th>Adverse Event</th><th colspan="2">General Guidance for Cytokine Release Syndrome (CRS) [Rosello, 2017; Porter, 2018]</th></tr>
<tr><td rowspan="4">Cytokine-release Syndrome</td><td colspan="2">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.</td></tr>
<tr><td>Severity (symptoms)</td><td>Management</td></tr>
<tr><td>Grade 1</td><td>• Injection(s) interruption is not indicated.
• 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 and provide symptomatic treatment with antipyretics, antiemetics, analgesics, histamine 1/histamine 2 (H1/H2) antagonists as needed; monitor fluid balance; assess for infection. Regularly evaluate for signs of further deterioration
• For subsequent injection(s), consider pre-medication (e.g., antipyretics, antihistamines) per institutional guidelines</td></tr>
<tr><td>Grade 2</td><td>• Interrupt SL-172154 injection(s).
• 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. 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 injections 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 injection.
• For subsequent injections, 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</td></tr>
</table>

Adverse Event	Severity (Symptoms)	Management
Cytokine-release Syndrome (continued from previous page)	Grade 3 or 4	• Interrupt SL-172154 injection(s). • 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 injection-related reactions and CRS per institutional standards (e.g., epinephrine, diphenhydramine, ranitidine, corticosteroids, bronchodilators, oxygen, fluids 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 injections of SL-172154 (after an event of grade 3 CRS) must be administered in an inpatient or outpatient setting with prolonged observation for a minimum of 12 hours after the completion of the injection. o After a Grade 3 CRS event, subjects must be premedicated with dexamethasone 20 mg, antipyretics and H1/H2 antihistamines prior to the next injection of SL-172154. o If there is no evidence of CRS with the subsequent injection, premedication with high dose steroids may be omitted for subsequent injections. 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.

<table>
<tr><th>Adverse Event</th><td colspan="2">General Guidance for Management of Immune-related Adverse Events (irAEs) [Haanen, 2017; Puzanov, 2017; Brahmer, 2018]</td></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 injection is continued, and treatment with corticosteroids is usually not indicated</td></tr>
<tr><td>Grade 2</td><td>• SL-172154 injection 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 injection.
• 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 injections and start IV methylprednisolone 1-2 mg/kg/day.
• If no improvement, consider adding alternative immunosuppressant.</td></tr>
</table>

<table>
<tr><th>Adverse Event</th><th colspan="2">General Guidance for Hepatotoxicity</th></tr>
<tr><td rowspan="4">Hepatotoxicity</td><td colspan="2">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 polymerase chain reacation, 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 PD/thrombosis. Guidelines are based on elevations in ALT, AST and bilirubin per CTCAEv5. Discontinue SL-172154 injections 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.</td></tr>
<tr><td>Severity (Symptoms)</td><td>Management</td></tr>
<tr><td>Grade 1</td><td>• Continue SL-172154 injection with close monitoring.
• Monitor liver function at least weekly; if liver function is stable, reduce frequency of blood tests.</td></tr>
<tr><td>Grade 2</td><td>• Hold SL-172154 injection
• 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 injection when toxicity ≤ G1 and corticosteroid taper to ≤ 10 mg/day prednisone or equivalent.</td></tr>
<tr><td>Grade 3</td><td>• Grade 3: hold SL-172154 injection.
• Permanently discontinue SL-172154 injections 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 injections 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.</td></tr>
</table>

Hepatotoxicity (continued from previous page)	**Severity (Symptoms)**	**Management**
	Grade 4	• Grade 4: permanently discontinue SL-172154 injection. • 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.

<table>
<tr><th>Adverse Event</th><th colspan="2">General Guidance for Hematologic Toxicity</th></tr>
<tr><td rowspan="5">Anemia</td><td colspan="2">Subjects with cancer can have multiple causes of cytopenias and thus blood counts must be monitored carefully. When administered systemically, 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. Please refer to Section 3.8 for guidance re blood cross-matching and transfusion procedures.</td></tr>
<tr><td>Severity (Symptoms)</td><td>Management</td></tr>
<tr><td>Grade 1</td><td>• Continue SL-172154 injection with close clinical follow-up and laboratory evaluation</td></tr>
<tr><td>Grade 2</td><td>• Consider holding SL-172154 injection 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.</td></tr>
<tr><td>Grade 3</td><td>• Hold SL-172154 injection 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.</td></tr>
<tr><td>Grade 4</td><td>• Permanently discontinue SL-172154 injections.
• 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.</td></tr>
</table>

	Severity (Symptoms)	Management
Thrombocytopenia	Grade 1	• Continue SL-172154 injection with close clinical follow-up and laboratory evaluation.
	Grade 2	• Consider holding SL-172154 injection until AE has reverted to Grade 1 or baseline. • Consider Hematology Consult
	Grade 3 or 4	• Hold SL-172154 injection 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

Adverse Event	General Guidance for Influenza-like Symptoms	
Influenza-like Symptoms	Influenza-like symptoms refers to a group of symptoms similar to those observed in subjects with the flu. It may include fever, chills, myalgias, arthralgias, malaise, loss of appetite and dry cough. All subjects should be closely monitored for development of injection-related reactions and cytokine release syndrome given the overlapping symptoms. Alternative infectious etiologies should be investigated and ruled out, if warranted. Treatment of systemic drug-related events should be consistent with the severity of the reaction as well as institutional standards. Per CTCAE v5, toxicity grading for influenza-like symptoms ranges from grade 1 through grade 3.	
	Severity (Symptoms)	**Management**
	Grade 1	• Continue SL-172154 injection with close clinical follow-up. • Consider pre-medication (acetaminophen as anti-pyretic, antihistamines such as H1/H2 blockers and/or opiates) for subsequent injections per investigator/institutional guidelines. Due to their potential bleeding/immunosuppressive effects, the use of non-steroidal anti-inflammatory drugs (NSAIDs), leukotriene inhibitors and steroids within 24 hours of injection with SL-172154 should be avoided if clinically feasible.
	Grade 2	• Consider holding SL-172154 injection until AE has reverted to Grade 1 or baseline. • For flu-like symptoms that persist for ≥ 7 days, the AE should resolve to baseline or grade ≤ 1 prior to administering the next scheduled injection. • Provide pre-medications (acetaminophen as anti-pyretic, antihistamines, leukotriene inhibitors and/or opiates) for subsequent injections per investigator/institutional guidelines. Due to their potential bleeding/immunosuppressive effects, the use of non-steroidal anti-inflammatory drugs (NSAIDs) and steroids within 24 hours of injection with SL-172154 should be avoided if clinically feasible. • If SL-172154 injection is delayed such that 2 consecutive scheduled injections are missed to allow for resolution of prolonged Grade 2 symptoms despite optimal medical management, then the subject should permanently discontinue SL-172154 injections.
	Grade 3	• Hold SL-172154 injection until AE has reverted to Grade 1 or baseline. • Provide pre-medications (acetaminophen as anti-pyretic, antihistamines, leukotriene inhibitors, steroids and/or opiates) for subsequent injections per investigator/institutional guidelines. If grade 3 flu-like symptoms recur with pre-medications, then SL-172154 injections should be permanently discontinued. • If SL-172154 injection is delayed such that 2 consecutive scheduled injections are missed to allow for resolution of prolong Grade 3 flu-like symptoms despite optimal management, then the subject should permanently discontinue SL-172154 injections

3.7.2 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 injection until resolution to ≤Grade 1 or baseline.	• Treat accordingly, as per institutional standard
Grade 3	Hold SL-172154 injection 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 injections. (**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 injections. (**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.)

3.8 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 subject (as described above) will be used, i.e. the subject 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 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 3.7. 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.

Treatment may continue 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 declines further therapy with ITI of SL-172154 in the absence of disease progression
- 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).

If study therapy is permanently discontinued for reasons other than PD or withdrawal of consent, the subject will remain in the study to be evaluated for disease progression. See the Schedule of Assessments (SOA) in Section 6 for data to be collected following discontinuation of SL-172154 at the post-treatment and follow-up visits.

3.10 Criteria to Resume Treatment

A participant may resume ITI of SL-172154 per the guidance outlined in Section 3.7. If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time point per protocol.

3.11 Participant Discontinuation/Withdrawals from Study

- 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 discontinuing from the study, 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.

3.12 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.

3.13 Duration of Treatment

The planned treatment duration with ITI SL-172154 should be until progressive disease. Subjects with complete resolution of all injectable lesions should discontinue treatment and continue with all relevant study assessments including disease assessments. The subject will be followed until disease progression as per protocol.

Impact 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 discontinue IP for any reason other than withdrawal of consent will be followed for AEs for 90 days after the last dose of IP. Subjects who are withdrawn from study for unacceptable

AE(s) will be followed until resolution or stabilization of the AE. Subjects who permanently discontinue IP for reasons other than progression will continue with disease assessments until progressive disease, start of another anti-cancer therapy, withdrawal of consent, death, or end of the study, whichever occurs first.

3.15 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 and the FDA. If the study is prematurely terminated or suspended, the investigator will promptly inform the Institutional Review Board (IRB) 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, 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

3.16 End of Study Definition

End of Study is defined as approximately 1 year 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. Subjects must have a histologically confirmed diagnosis of an unresectable or recurrent, locally advanced or metastatic cutaneous squamous cell carcinoma or squamous cell carcinoma of the head and neck that is not amenable to curative surgery or radiotherapy.

    - Cutaneous squamous cell carcinoma: Subjects with predominantly mixed histologies (eg, sarcomatoid, adenosquamous) are not eligible. Subjects with a minimal component of mixed histology in which the predominant histology is invasive squamous cell carcinoma are eligible.

    - Squamous cell carcinoma of the head and neck: Subjects must have primary tumor locations in the oropharynx, oral cavity, hypopharynx, larynx or unknown primary. Primary tumor sites of nasopharynx, maxillary sinus, and paranasal are excluded.

3. Subject must have received, been intolerant to, or ineligible for standard therapies that are known to provide clinical benefit for their condition as defined by:

    - HNSCC subjects must have received, been intolerant to, or ineligible for platinum-based chemotherapy and PD-1/L1 inhibitors in combination or sequentially.

    - CSCC subjects must have received, been intolerant to, or ineligible for PD-1/L1 inhibitors.

4. Has measurable disease by RECIST v1.1 using radiologic assessment and/or clinical examination. NOTE: If there are multiple lesions that are measurable per RECIST v1.1, at least one of these lesions must be considered injectable per inclusion criteria #5.

5. Subject has at least 1 tumor lesion that is cutaneous and/or subcutaneous and/or nodal and is deemed to be clinically accessible and safe for injection of SL-172154 by the investigator.

    - Must be able to be inject the lesion by direct visualization, palpation or by ultrasound guidance. Injections of deep or visceral lesions or injections which require magnetic resonance imaging (MRI) or computed tomography (CT) guidance are not permitted.
    - At baseline, non-nodal lesions must measure $\geq$ 1 cm in the longest diameter and nodal lesions must measure $\geq$ 1.5 cm in the longest diameter to be considered injectable.
    - Tumor lesion(s) selected for injection cannot exceed 6 cm in the longest diameter.
    - Lesions must be located in an anatomic location where SL-172154 can be safely administered and not in close proximity to critical structures (e.g., major blood vessels, nerve bundle, trachea or a major airway tract) as determined by the investigator.
    - Pharmacodynamic Cohort ONLY: Must have a second lesion that is non-injected and is amenable to tumor biopsy collection. (Note: This non-injected lesion is not required to be measurable per RECIST v1.1.)

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 lymphocyte count (ALC)	$\geq 0.8 \times 10^9$/liter (L)
Absolute neutrophil count (ANC)	$\geq 1.5 \times 10^9$/L without growth factor support
Platelet count	$\geq 100 \times 10^9$/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
International normalized ratio (INR) and activated partial thromboplastin time (aPTT)	≤ 1.5 × ULN
QTcF interval	≤ 480 milliseconds

10. Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test within 72 hours of D1 of IP. NOTE: FCBP unless they are surgically sterile (i.e., have undergone a complete hysterectomy, bilateral tubal ligation/occlusion, bilateral oophorectomy or bilateral salpingectomy), have a congenital or acquired condition that prevents childbearing or are naturally postmenopausal 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 exceeds 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. Male subjects with female partners must have azoospermia from a prior vasectomy or underlying medical condition or agree to use an acceptable method of contraception during treatment and for 30 days (which exceeds 5 half-lives) after last dose of SL-172154 (see Appendix 16.3). Male subjects of reproductive potential must start using acceptable contraception at least 14 days prior to D1 of treatment with SL-172154 as per Appendix Section 16.3.

12. Recovery from prior anti-cancer treatments including surgery, radiotherapy, chemotherapy, immunotherapy or any other anti-cancer therapy to baseline or ≤ Grade 1. (NOTE: Low-grade toxicities such as alopecia, vitiligo, endocrinopathies adequately treated with hormone replacement, ≤ Grade 2 lymphopenia, ≤ Grade 2 hypomagnesemia, ≤ Grade 2 neuropathy may be allowed upon agreement by the Sponsor Medical Monitor).

13. Subjects enrolled in the dose escalation cohort must be willing to undergo a baseline tumor biopsy and on-treatment biopsies of the injected tumor lesion. Subjects enrolled in the pharmacodynamic cohort must be willing to undergo baseline tumor biopsies of an injected and non-injected lesion and on-treatment biopsies of the injected and non-injected tumor lesion.

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
PD-1/L1 inhibitor and other immunotherapies not otherwise specified	4 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 therapy for anti-cancer intent 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 HSRs (e.g., reaction to IV contrast)

5. Receipt of live attenuated vaccine within 28 days of D1 of IP.

6. Hypersensitivity to any of the excipients or to Chinese hamster ovary cell products.

7. History of coagulopathy resulting in uncontrolled bleeding, eg, hemophilia, von Willebrand's disease. History of other bleeding disorders or a Grade ≥ 3 bleeding event within 3 months prior to first dose of IP.

8. Requires continuous anticoagulation therapy or antiplatelet therapy (except for ≤ 100 mg acetylsalicylic acid).

9. Active or documented history of autoimmune disease that has required treatment with a disease modifying agent or immunosuppressive therapy in the past two years. Exceptions include Type I diabetes, vitiligo, alopecia areata or hypo/hyperthyroidism.

10. Active pneumonitis or history of symptomatic pneumonitis in the past 2 years that required treatment (i.e. drug-induced, idiopathic pulmonary fibrosis, radiation-induced, etc.).

11. Ongoing or active infection (e.g., no systemic antimicrobial therapy for treatment of infection within 5 days of D1 of IP).

12. Symptomatic peptic ulcer disease or gastritis, active diverticulitis, other serious GI disease associated with diarrhea within 6 months of D1 of IP.

13. Clinically significant or uncontrolled cardiac 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
    - NYHA Class III or IV congestive heart failure
    - Clinically significant (symptomatic) cardiac arrhythmias (e.g., sustained ventricular tachycardia, second- or third- degree atrioventricular (AV) block without a pacemaker, circulatory collapse requiring vasopressor or inotropic support, or arrhythmia requiring therapy)

14. Untreated central nervous system (CNS) or leptomeningeal metastases. Subjects with treated CNS metastases must have completed definitive treatment (radiotherapy and/or surgery) > 2 weeks prior to D1 of IP and no longer require steroids.

15. Women who are breast feeding.

16. 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.

17. 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.

18. Has undergone allogeneic stem cell transplantation or organ transplantation.

19. 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 [HBcAb] positive, but HBsAg negative are eligible for enrolment. *HCV*: Subjects who are HCV Ab positive, but HCV RNA negative are eligible for enrolment).

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 18 subjects (see Section 9.1). Approximately 4-6 clinical sites may participate in SL03-OHD-102. Overall, the study may be complete recruitment within approximately 12 months (1 year). Study duration is estimated to be 20 months which includes the enrollment period and completion of all study-related data analyses.

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 formulated in 40 mM histidine, 150 mM NaCl, at pH 7.3.
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 Table 1 in Section 3.4 for dose levels)
Physical Description:	SL-172154 solution, 10 mg/mL 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 intratumoral solution via a sterile syringe and needle. See the SPM for additional details. See Table 1: Intratumoral Dose Escalation Plan in Section 3.4 of the protocol. See Section 6.8 of the protocol for instructions on SL-172164 administration by ITI.
Dosing instructions:	Determine the number of vials needed based on the assigned dose level (in mg). See the SPM for instructions on IP preparation and information on compatible administration materials. Doses of SL-172154 are to be administered as an intratumoral injection.
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 [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/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, 1 mL is supplied as a frozen liquid. Before use, thaw each vial of SL-172154 solution overnight under refrigerated conditions, protected from light, or thaw each vial at room temperature immediately prior to dose preparation 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.

See the SPM for details on storage and preparation conditions.

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 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 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 Monitoring Dose Administration

ITI of 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 by ITI include injection-related reactions and CRS as mentioned in Section 3.7. 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 ITI of SL-172154. All subjects must be observed for at least 6 hours at the center after each intratumoral injection of SL-172154. See Section 6.8 of the protocol for instructions on SL-172154 administration by ITI. Vital signs will be measured as outlined in the SOA in Section 6 and as needed.

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.

5.1.5 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 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 injection. The appropriate AE management guideline should be followed (Section 3.7). 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 IP received from the Sponsor, the amount of SL-172154 administered 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 SL-172154 administered by ITI 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 IP 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 ITI of SL-172154 for further instructions regarding 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 ITI of SL-172154.

6.1 SOA Table for ITI Dose Escalation of SL-172154

Dosing Schedule		**D1, D8, D15 in cycle 1 over 21 days, thereafter once (D1) every 21 days**									**Post TX[r]**	**Follow up[s]**
Cycle Length = 21 days		**C1**	**C1**	**C1**	**C1**	**C1**	**C2**	**C2**	**C3**	**≥C4**		
Procedures/Assessments[b]	**Screen[a]**	**D1**	D2	**D8**	**D15**	D16	**D1**	D2	**D1**	**D1**		
Study Days	Days -21 to -1	**1**	2	**8**	**15**	16	**22**	23	**43**	**64**	w/in 30d of last dose	f/u > 30d after last dose
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[d1]	X[d1]	X[d2]	X[d1]	X[d2]	X[d3]	X[d3]	X	
Height (screening only)/weight	X						X		X	X	X	
ECOG performance status	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	
Chemistry profile[f]	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											
Type and Screen (ABO/Rh), Blood phenotyping and direct antiglobulin test[h]	X[h1]		X[h2]									
Antiviral testing (HBV/HCV)[i]	X											
Tumor imaging[j]	X								X		X	X
PK/ADA[k]		X	X		X	X	X	X		X[k1]	X[k2]	X[k3]
Immunophenotyping/cytokines[l]		X	X		X	X			X			
SL-172154 administration by ITI[m]		X		X	X		X		X	X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	
AEs/SAEs[n]	X	*Continuous: Collect ad hoc sample if injection-related reaction or CRS event occurs[n]*									X[n]	X[n]
Archival tumor tissue[o]	X											
Tumor biopsy[p]	X						X[p]		X[p]		X[p]	
Cardiac Evaluation: ECG[q]	X	X[q]					X[q]					

Day -1 = last day of screening period i.e., the day before the first dose of SL-172154 ITI therapy is initiated on day 1 of cycle 1
Table Heading Abbreviations: C = cycle; D = day; f/u = follow up; TXT = treatment; w/in = within

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, and pregnancy test. Baseline computed tomography (CT) or positron emission tomography (PET)/CT or 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 cycle. Dose interruptions should not alter the assessment schedule for any subsequent treatment cycle.

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**: Predose (within 30 min of starting the injection) 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 end of injection (EOI)**.
   2) Vital signs/pulse oximetry should be taken once prior to scheduled PK samples on **C1D2, C1D16 and C2D2.**
   3) **Collect vital signs/pulse oximetry on dosing days ≥ C3D1:** Predose (within 30 min of start of the injection(s)) and at the 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 9 weeks during SL-172154 treatment (i.e., C4D1, C7D1, C10D1, 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 6.3.6 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 a) ABO and D group (ABO/Rh) type and antibody screen and antibody identification if required; b) DAT; c) 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. **Antiviral Testing:** Please see exclusion criterion 19 in Section 4.2. These tests will be performed at local laboratories according to the laboratory's normal procedures.

j. **Tumor Assessment:** Tumor assessments are required for all subjects within 28 days prior to the first dose of SL-172154. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline, on treatment and during follow-up. Baseline and on-treatment tumor assessments by RECIST v1.1 should include CT with contrast of chest, abdomen, and pelvis and clinical examination (if applicable) of all known sites of disease at each time point. Bone scan, positron emission tomography (PET)/CT, and/or MRI should be performed if clinically indicated. Tumor lesions will only be considered measurable by clinical examination when they are superficial, and dimensions are accurately assessed using calipers or rulers. For skin lesions assessed by clinical examination, documentation by color photography including a ruler to estimate the size of the lesion, is required at all time points. 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 6 weeks through week 54 (e.g., C3D1, C5D1, C7D1), every 12 weeks up to year 2 (prior to cycles 23, 27, 31, and 35), and then every 24 weeks (prior to cycles 43, cycle 51, 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 and preferably at the next scheduled tumor assessment visit that is about 6 weeks later. Subjects who discontinue study treatment for reasons other than disease progression (e.g., AE) will be monitored for response until start of another anti-cancer therapy, disease progression, withdrawal of consent, death, or end of the study, whichever occurs first.

k. **PK/immunogenicity (i.e., ADA):** Blood sample collection timings for PK, ADA are outlined in Section 6.1.1 in Supplementary Tables 2 and 3. PK/ADA sample collection times on C1D1, C1D15 and C2D1 through 24 hours postdose are provided in Table 2 PK/ADA sample collection times in cycles 3 and beyond are outlined in Table 3. **Blood volumes required are provided in the SLM. PK/ADA samples should be collected from a line that is distant or on the opposite side of the ITI site.**

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, 22 and 25) 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.

l. Correlative laboratory studies: Refer to supplementary Table 4 for details in Section 6.1.2 plus see the SLM for amount of blood needed and sample shipment details.

- Immunophenotyping and cytokines

m. **SL-172154 ITI administration**: 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. Following the dose on cycle 2, day 1, a window of +/-3 days is allowed for scheduled dosing days for drug administration in 21-day cycles. All subjects must be observed for at least 6 hours at the center after each intratumoral injection of SL-172154. Please refer to Section 6.8 for detailed instructions on SL-172154 administration by ITI.

n. **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, any ongoing AE should be followed until resolution (or return to baseline) and documented in the eCRF. If another anti-cancer agent is started, only SAEs and AEs that occur prior to starting the new anticancer therapy should be recorded. In the event of a continuing AE, the subject will be asked to return for follow-up until the 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 injection-related reaction or CRS events as noted in Section 6.3.6.3 and the SLM.

o. **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 punch biopsy or core needle biopsy and adequate sample is available for analysis. 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 6.6.2.2 and the SLM for details**.

p. **Tumor Biopsy**: Pre- and two on-treatment paired biopsies are required for all subjects. Biopsies will be obtained at baseline to evaluate the immune status of the tumor before SL-172154 treatment. The first on-treatment biopsy should be taken prior to the cycle 2/day 1 dose on study days 18-22. The second on-treatment biopsy should be taken prior to the cycle 3/day 1 dose on study days 39-43. For subjects assigned to the dose escalation cohort, a baseline and two on-treatment biopsies should be obtained from the same injected lesion. For subjects assigned to the pharmacodynamic cohort, a baseline and two on-treatment biopsies should be obtained from both an injected lesion and a non-injected lesion. The same tumor lesion should be biopsied at the baseline and on-treatment time points to allow for direct comparison. Biopsy at the time of PD will be optional. **Please refer to Section 6.6.2.1 and SLM for details regarding biopsy**.

q. **Electrocardiogram (ECG):** Local ECG machines available at the site should be used. A single ECG will be collected during screening to determine eligibility. ECGs will be obtained in triplicate for assessment of QT/QTc as outlined below (See Section 6.3.5 for additional details).

- Cycle 1, Day 1: Predose and 1 hour and 4 hours after ITI SL-172154
- Cycle 2, Day 1: Predose only

r. **Post-Treatment**: A Post-Treatment visit will be conducted within 30 days (±3 days) after the last dose of SL-172154 and prior to the start of a new therapy if applicable.

s. **Follow-Up (>30 days post last dose of SL-172154)**: All subjects who discontinue IP for any reason other than withdrawal of consent will be followed for AEs for 90 days after the last dose of IP.

6.1.1 Supplementary Tables for SL-172154 PK/ADA Sampling Times

Table 2: Serial PK/ADA (C1/D1-24 hours postdose, C1D15 – 24 hrs postdose, C2D1 – 24 hours postdose)

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

1. Collect pre-dose samples for ADA, PK.
2. End of injection (EOI) sample should be collected within 5 minutes after stopping the injection. Date and clock time for start/stop of injection as well as sample collection (pre/post dose) will be recorded.
3. Sample collection out to 24 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 samples **should be collected from a line that is distant or on the opposite side of the ITI site**.
4. Sample collection out to 24 hrs post EOI but emerging data during dose finding may dictate changes in this schedule.

Table 3: Serial PK/ADA (C4/D1 and Beyond)

Study Day	**D1 of C4, C7, C10, C13[3], through to25**	Collect a PK/ADA sample within 7 to 30 days after the subject discontinues SL-172154 therapy. Collect sample for PK/ADA within 105-125 days post last dose of SL-172154.
Sample	**Predose** **- 30 min** (± 5 min)	
PK	X[1,2]	
ADA	X[1,2]	
Date and clock time for sample collection (pre/post dose) will be recorded for all samples		

1. Predose sample collected will include analysis of ADA and PK.
2. The PK, ADA samples **should be collected from a line that is distant or on the opposite side of the ITI site**. **See SLM for the most accurate estimates of blood needed and for additional details on sample handling instructions.**
3. 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, 22 and 25) 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.

6.1.2 Correlative Sample Time Points for SL-172154

Table 4: Immunophenotyping and Cytokine Time Points

Samples	**C1D1/C1D15/C3D1**		**C1D2/C1D16**
	Predose (-90 to -30 min)	**1hr post EOI** (±10 min)	**24 hr post EOI** (± 2hr)
Immunophenotyping[1]	X	X	X
Cytokines[1]	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.

6.2 Demographics, Medical History, Screening and Safety Assessments

6.2.1 Informed Consent

The participant or his/her legally authorized representative must 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.

6.2.2 Eligibility Criteria

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

6.2.3 Subject Demographics

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

6.2.4 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. The receipt and response to prior PD-1/L1 inhibitor therapies will be recorded.

6.2.5 Concomitant Medications

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

6.3 Safety Evaluations

6.3.1 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, genitals 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.

6.3.2 ECOG Performance Status

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

6.3.3 Pulse Oximetry

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

6.3.4 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 table for details on when to collect vital signs.

6.3.5 Electrocardiogram Monitoring for QTc Evaluation

QTcF is the QT interval corrected for heart rate according to Fridericia’s formula (QTcF). It is either machine-read or manually over-read. The specific formula used to determine eligibility for an individual participant in this study will be Fridericia’s formula. An electrocardiogram (ECG) will be obtained in subjects at screening to confirm subject eligibility.

ECGs will also be obtained in triplicate (i.e., each ECG assessment obtained 5 minutes apart) prior to and following SL-172154 ITI and *the reported QTc should be based on the average of triplicate ECG readings.* Assessment of the QTc interval using the Fridericia (QTcF) correction methods for heart rate will be performed at the following time points: cycle 1, day 1 at predose and 1 hour and 4 hours after ITI of SL-172154 is given. These planned post ITI time points are subject to change based on emerging PK data and determination of Tmax. ECGs in triplicate will also be collected prior to injection of SL-172154 on cycle 2, day 1. ECG measurements should be obtained with the subject in a supine position having rested in this position for at least 10 minutes prior to testing. Triplicate ECGs should be performed prior to blood drawn for clinical, PK/ADA or biomarker labs or measurement of vital signs at each of the time points specified. Local ECG machines available at the clinical site should be used for all ECG assessments specified by the protocol.

6.3.6 Laboratory Assessments

6.3.6.1 Clinical Labs Performed Locally

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

Clinical Labs Performed at the Local Laboratory	
Hematology	**Clinical Chemistry**
Hemoglobin Hematocrit Platelet Count Red Blood Cell Count White Blood Cell Count Automated WBC Differential (absolute number and percent): Neutrophils Lymphocytes Monocytes Eosinophils Basophils	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 Aspartate aminotransferase Alanine aminotransferase Alkaline phosphatase
Blood Type and Screen	**Serum/Urine Pregnancy Test**
ABO and D Group (ABO/Rh) Antibody screen Direct antiglobulin test Phenotype/Genotype minor antigens: Rh C/c E/e, K, Jk, Fy and MNSs	β-human chorionic gonadotropin
Coagulation	**Antiviral Testing**
Prothrombin time and International- normalized ratio Activated partial thromboplastin time Fibrinogen D-Dimer	Hepatitis B: HBsAg / HBV core Ab Hepatitis C: HCV Ab / HCV RNA viral load

6.3.6.2 Central Labs

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
PK/Immunogenicity[a]
Pharmacokinetics (SL-172154 serum concentration) Anti-drug antibodies
Flow Cytometry[a]
Immunophenotyping Panels
Tumor IHC[a]
PD-L1 expression CD47 and CD40 expression Changes in immune infiltrate such as 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.

6.3.6.3 Ad Hoc Labs for SAEs

Ad hoc labs should be collected as noted if injection-related reaction/CRS or an immune-related serious adverse event (irSAE) 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 Coagulation panel C reactive protein Ferritin	Pharmacokinetics (SL-172154 serum concentration) Anti-drug antibodies 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. If an event of injection-related reaction/CRS or an irSAE occurs, these specific biomarker samples should be collected as soon as possible.

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

6.3.6.4 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.

6.3.6.5 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 table in Section 6.1.

6.4 Pharmacokinetics

6.4.1 Intensive PK Sampling in Dose Escalation

Intensive serial PK samples will be collected for all subjects enrolled. 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 2 day 2, only predose samples will be collected for ADA and PK analyses. Refer to supplementary tables provided in Section 6.1.1 for details.

6.5 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.

6.6 Pharmacodynamic/Biomarker Assessments

Blood samples and tumor tissue will be collected from all subjects in this study for pharmacodynamic/biomarker research as specified in the SOA and supplementary table (Section 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 and fresh and archival tumor tissue collection during the study will be provided.

6.6.1 Pharmacodynamic Assessments in Blood

6.6.1.1 Cytokine and Chemokine Analysis

The levels of serum proteins such as cytokines and chemokines will be measured as noted in Section 6.3.6.2. Levels of serum cytokines/chemokines may provide context to AEs observed in subjects following ITI of SL-172154 and may act as pharmacodynamic markers of activity.

6.6.1.2 PBMC for Immunophenotyping

Protein expression of phenotypic markers as well as absolute quantitation of phenotypic populations will be assessed by flow cytometry. The composition and change of T and B cells, NK cells, and monocytes in the peripheral blood may provide insights into the mechanism of action of SL-172154 and serve as biomarkers for immune response.

6.6.2 Pharmacodynamic Assessment of Tumor Tissue

6.6.2.1 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. 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. The screening biopsy is used to evaluate the immune status of the tumor before SL-172154 treatment, while the on-treatment biopsies are used to characterize changes in the TME in response to drug administration. Immunohistochemistry (IHC) analyses will be performed on these fresh tumor samples. Changes in the immune infiltrate of the tumor at the different biopsy time points will be assessed by visualizing and assessing the phenotype of cells in the TME 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.

Biopsy Collection

For subjects assigned to the dose escalation cohort, a baseline and two on-treatment biopsies should be obtained from the same injected lesion. For subjects assigned to the pharmacodynamic cohort, a baseline and two on-treatment biopsies should be obtained from both an injected lesion and a non-injected lesion. The same tumor lesion should be biopsied at the baseline and on-treatment time points to allow for direct comparison. The tumor biopsies should be obtained at the time points noted in the SOA. The time interval for the on-treatment biopsy may be changed by the Sponsor if emerging data indicates that a different time point would be more suitable.

Depending on the location of the lesion, biopsies can be performed by either full thickness punch biopsy or core needle biopsy based on investigator judgment. The same modality of biopsy should be performed at all time points. If punch biopsies are being performed on a lesion, it is necessary to obtain two punch biopsies up to 6 mm diameter each or the equivalent. If core needle biopsies are being performed on a lesion, three core needle biopsies should be obtained. Biopsies should be performed per institutional standards. Biopsy tissue should be fixed in formalin and paraffin embedded and the entire block must be submitted. Please refer to the SLM for further instructions.

Information regarding the timing of the biopsy, the location and measurement of the lesion(s) that is biopsied and its injected vs non-injected status will be collected. Documentation of the lesion at the time of biopsy will be obtained either by digital photography or image-based documentation. For ultrasound, CT or MRI-guided biopsies, all relevant treatment planning radiological images (e.g., biopsy needle in lesion images) may be centrally collected and should be made available to

the Sponsor or designated central imaging vendor. These images will be used to confirm the lesions that were biopsied by their injected vs non-injected status.

- Where possible lymph node biopsies should be avoided as reliable measurements of tumor infiltrating lymphocytes (or their activation) in a background of (non-tumor) lymphoid tissue is challenging.
- Attempt to select RECIST v1.1 target lesions for biopsy when the lesion is ≥ 2 cm in longest diameter and/or biopsy of the lesion is not expected to impact or alter the size of the lesion and the lesion's subsequent evaluation by RECIST v1.1
- If biopsies and response assessment are to be performed at the same visit, biopsies should always be performed after response assessments so that biopsy associated trauma or swelling does not confound response assessment.
- If biopsies and ITIs are being performed on the same day, please try to biopsy the lesion from one side and inject IP distant to the biopsy site to minimize leakage of the IP.
- If feasible, biopsy material should be collected after disease progression has been confirmed, ideally on lesions that have progressed.

Safety Considerations for Biopsy Collection

Only punch biopsies or percutaneous biopsies will be performed on subjects. No laparoscopic, endoscopic or open surgical procedures will be performed solely to obtain a biopsy for this protocol. Surgical, laparoscopic or endoscopic biopsies are permitted ONLY when obtained incidentally to a clinically necessary procedure and not for the sole purpose of the clinical trial. Excisional or endoscopic biopsy tissue that was obtained for a medically indicated procedure can be used for analysis.

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 an anatomical site 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.

For the dose escalation and pharmacodynamic cohort, subjects must undergo baseline and on-treatment biopsies of injected lesions. These lesions should be biopsied directly or with the use of ultrasound guidance in a manner similar to the ITI. For the pharmacodynamic cohort, subjects must also undergo baseline and on-treatment biopsies of a non-injected lesion. The use of imaging to facilitate biopsies of these non-injected lesions is permitted and 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.

6.6.2.2 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 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 an adequate sample was collected via punch biopsy or core needle biopsy. Please notify the sponsor if archival tissue will be used as the baseline biopsy.

6.7 Assessment of Anti-tumor Activity

The primary analysis of anti-tumor activity is according to RECIST v1.1. Tumor size changes will also be assessed in the injected lesion(s) and in the non-injected lesion(s) as available. The same method of assessment and the same technique used to characterize each identified and reported lesion at baseline should be used throughout. Disease assessment will be performed at baseline and at the following intervals until disease progression is confirmed: every 6 weeks through week 54, and every 12 weeks thereafter until year 2, and every 24 weeks until study conclusion. Refer to Section 8 for additional details. Treatment beyond progression is permitted provided the subject meets protocol specified criteria (see Section 8.2). All subjects will be followed for PD unless they withdraw consent.

6.8 SL-172154 Administration by Intratumoral Injection

6.8.1 Baseline Lesion Identification

At baseline, all subjects assigned to the dose escalation cohort will be required to have a minimum of one lesion that meets the following criteria:

- One target lesion that is measurable per RECIST v 1.1 and
- Can be safely injected as determined by the site investigator and
- Amenable to tumor biopsy collection.

At baseline, all subjects assigned to the pharmacodynamic cohort will be required to have a minimum of 2 lesions:

- Lesion 1: One target lesion that is measurable per RECIST v 1.1 and can be safely injected as determined by the site investigator and amenable to tumor biopsy collection
- Lesion 2: One lesion that remains non-injected and is amenable to tumor biopsy collection.

It is preferable for both cohorts to identify at least 2 lesions at baseline. In order to assess response in an injected lesion, 1 lesion must be measurable by RECIST v.1.1 and accessible for injection. In order to assess anenestic or bystander response, the second lesion should be measurable per RECIST v1.1 and be non-injected.

6.8.2 Definition of Lesion Injectability

ITI of SL-172154 must be able to be conducted by direct visualization, palpation or by ultrasound guidance. Injections of deep or visceral lesions or injections by MRI or CT guidance are not permitted. Non-nodal lesions must measure ≥ 1 cm in the longest diameter and nodal lesions must measure ≥ 1.5 cm in the longest diameter to be considered injectable. Injectable lesions cannot exceed 6 cm in the longest diameter. Measurements may be made based upon clinical or radiologic examination.

Tumor lesions must be located in an anatomic location where SL-172154 can be safely injected as determined by the investigator. Lesions should not be in close proximity to critical structures (e.g., major blood vessels, nerve bundle, trachea or a major airway tract) as determined by the investigator. Lesions that are associated with large fistulas, that are primarily ulcerated, cystic or necrotic, or in high-risk locations such as peristomal, at the oral commissure or near the orbital cavity should be avoided**.**

6.8.3 General Instructions for Injection

- Tumor injections may be performed by any trained practitioner including physicians, advanced practice providers or nurses.
- Administration of conscious sedation to the subject for the ITI procedure is permissible if the treating physician determines that the risk-benefit is appropriate.
- Lesions identified for injection should be prepared per facility guidelines.
- Lesions may be pre-treated with topical anesthetic agents. Local anesthetic should NOT be instilled into the lesion prior to ITI of SL-172154.
- Injections may be performed using standard supplies as per institutional guidelines permitted that these supplies meet compatibility requirements with the IP. The size of the syringe selected must allow for accurate measurement and instillation of drug product. To minimize morbidity and limit drug product leakage, the smallest gauge needle should be used that is appropriate for a given lesion location.
- If biopsies and ITI are being performed on the same day, please attempt to biopsy the lesion from one side and then inject IP distant to the biopsy site to minimize leakage of the IP.
- If biopsies and response assessment are to be performed at the same visit, biopsies should always be performed after response assessments so that biopsy associated trauma or swelling does not confound response assessment.
- SL-172154 should be injected along multiple different tracks within the lesion in order to obtain as wide a dispersion as clinically feasible.

6.8.4 Prioritization of Lesions for Injection

- It is strongly recommended that baseline lesion selection and the prioritization of lesions for injection are discussed on an ongoing basis with the multidisciplinary care team.
- Prioritization of lesions for injection should favor larger lesions over smaller lesions and symptomatic lesions over asymptomatic lesions.
- Dosing of SL-172154 will proceed using a flat dose and fixed volume format (see Section 3.4 for additional details). The entire drug dose must be instilled into one to three tumor lesions at a given ITI time point in order to ensure that the toxicity assessment can be accurately ascribed to a specific drug dosage. A maximum of three lesions can be injected at any dosing time point.

- If multiple lesions are being injected at a given time point, the drug product should be split between the lesions based on the relative size of each lesion. A minimum of 0.5 mL of SL-172154 should be instilled into any given lesion.
- Dosing may continue as per the specified interval until all clinically feasible lesions are injected at least once and then lesions that were previously injected may be re-injected.
- A previously injected lesion that is stable or responding may be reinjected until the lesion has completely resolved or as long as clinically feasible. At the time of complete resolution of a lesion, no further injections should be administered into the lesion with the complete resolution, however other lesions can be injected if clinically feasible.
- A previously injected lesion that is progressing may be re-injected if the benefit-risk ratio of continuing therapy is justified and all criteria for re-injection are met.
- New lesions that develop during the study which meet all of the criteria for being injectable, may be considered for injection.

6.8.5 Documentation of Intratumoral Injections

- At baseline, all lesions that are selected for ITI must be recorded via digital photography or by image-based documentation (if using ultrasound). Photographs should include a close-up view of the index lesion and an anatomical location view of the index lesion area(s). Two exposures for each location and lesion will be taken. **Refer to the Site Imaging Manual for complete instructions**.
- All lesions undergoing ITI must be documented. Documentation of the needle tip on or within the lesion at the time of injection will be obtained either by digital photography or image-based documentation. For ultrasound guided injections, all relevant treatment planning radiological images (e.g., needle in lesion images, ultrasound images clearly marking the lesion to be injected) may be centrally collected and should be made available to the Sponsor or designated central imaging vendor, for collection, storage, and possible future central re-analysis. These images will be used to confirm the lesions that were injected vs non-injected in order to assess the local and anenestic or bystander response to therapy.

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. 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 PD 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 study therapy 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/study therapy. 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 observation period of an AE starts at the time of signing informed consent and includes baseline or washout periods, even if no study treatment has been administered. The definition of an AE is 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. An AE is also 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 (SL-172154). 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.

Event	Definition
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 6.3.6.3 above if injection-related reaction/CRS or an irSAE 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 AR (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 phase 1 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). Findings 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.
- 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 v5.0 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 activities of daily living (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 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 IP 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 IP 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 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 PD 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, 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 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 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.

Event	Reporting Procedures
	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 in the SRM***. 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 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

7.7 Study Halting Rules

Administration of IP will be halted if a fatal SAE is reported to the Sponsor related to SL-172154. 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) 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. Additionally, periodic safety reviews will be undertaken by the SMC. Based on the 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. Tumor response will be defined by RECIST v1.1 criteria according to the schedule outlined in the SOA. All participants who underwent the first disease assessment at the 6-week time point or progress or die before to the first 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 response assessments. More frequent response assessments may be performed at the discretion of the investigator. If study treatment is withdrawn for reasons other than disease progression, response 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 Response Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline, on-treatment and during follow-up.

Tumor lesions will only be considered measurable by clinical examination when they are superficial and dimensions are accurately assessed using calipers or a ruler (e.g., skin nodules). For skin lesions, documentation by color photography including a ruler to estimate the size of the lesion, is required at all timepoints. Investigators will also provide a clinical description of the externally visible target lesion(s) at baseline and at each tumor assessment, as well as comments on any changes in the lesion(s) since the previous assessment. **Please refer to the Site Imaging Manual for complete instructions**. When lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective. Furthermore, radiologic imaging will be essential in the evaluation of tumor lesions that have subdermal components that cannot be adequately assessed by digital medical photography.

All subjects will undergo radiologic imaging studies, preferably by contrasted CT scan, of the chest, abdomen and pelvis and all other sites of known disease at baseline and at the following intervals until disease progression: every 6 weeks until week 54 and every 12 weeks thereafter until year 2 and every 24 weeks until study conclusion. PET-CT, MRI, and/or bone scan should be performed as clinically indicated. In the event of a CR or PR, confirmatory scans should be performed in at least 4 weeks (>28 days) and preferably at the next disease assessment that is approximately 6 weeks later. Contrast enhanced imaging is required unless the subject is precluded from receiving contrast (e.g., hypersensitivity, renal impairment). If biopsies and scans for response assessment are to be performed on the same lesion, biopsies should always be performed after response assessments so that biopsy associated trauma or swelling does not confound response assessment.

All copies of scans and digital photographs taken for response assessment should be collected and stored at the site. The Sponsor may request that all of these images be sent to a designated central imaging vendor for collection, storage and possible future central re-analysis. Images may be used to assess the local and anenestic or bystander response to therapy.

Treatment beyond progression will be permitted provided the subject meets protocol specified criteria in Section 8.2. If subjects discontinue investigational therapy prior to PD, 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] (Section 16.5). Response of target and non-target lesions will be collected and analyzed by their injected or non-injected status in order to determine if anenestic or bystander responses are observed.

Regarding target lesion selection, when more than one measurable tumor lesion is present at baseline, all lesions up to a maximum of 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesion selection will not be capped at a maximum of 2 lesions per organ e.g., if there are 3 cutaneous/subcutaneous measurable lesions, all 3 lesions can be selected as target lesions.

Given the relatively high rate of secondary primary malignancies in subjects with CSCC, new lesions must be carefully assessed to determine if they represent a second primary. A new CSCC will be considered as PD if the lesion is > 5 mm, can be clearly documented as not being previously present, and cannot be managed with standard therapy (such as surgical excision or topical palliation). Biopsy may be clinically indicated to confirm CSCC prior to determination of PD.

8.2 Criteria for Treatment Beyond Initial Progression

Subjects will be permitted to continue IP beyond initial PD 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 PD by providing a separate written informed consent.

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

- Develops clinical symptoms or signs such that the benefit-risk ratio of continuing therapy is no longer justified
- Meets any of the criteria for discontinuation of IP (see Section 3.7)
- Experiences rapid PD 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 5 for dose escalation decision rules based on the total number of subjects evaluable for DLT and the number of DLTs observed.

Table 5: 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 18 subjects. This sample size assumes evaluation of four dose levels with approximately 12 subjects treated in the dose escalation cohorts and approximately 6 subjects in the pharmacodynamic cohort. The goal is to enroll approximately 6 subjects at the potential RP2D, including subjects in dose escalation and the pharmacodynamic cohort. 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 during cycle 1 and complete the safety follow-up through the 21-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 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/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. Changes in toxicity grade for clinical chemistry and hematology will be summarized. Change from baseline QTcF will also be summarized. 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.

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 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. The ORR 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. Change from baseline diameter for each individual injected and non-injected lesion will be provided. DOR and TTR 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 curve and PFS 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 6, as data permit.

Table 6: Serum SL-172154 PK Parameters

Cmax	Maximum observed concentration
Tmax	Time of maximum observed concentration
AUC0-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).
AUC0-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).
AUC0-inf	Area under the serum concentration time curve from time 0 extrapolated to infinity, calculated as AUClast + Clast/terminal elimination rate constant (λz). Reliability of AUC0-inf values is contingent on the percent of the total area obtained by extrapolation: AUC0-inf values with <20% of the total area coming from Clast/λz are considered acceptable. Any exceptions to the above procedures will be clearly documented/justified in the PK report.
AUCtau	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).
%AUCext	Percentage of AUC0-inf due to extrapolation from Tlast to infinity
t½	Terminal elimination half-life, estimated using the equation [ln(2)/λz]
CL	Clearance; calculated as Dose/AUC0-inf
Vz	Volume of distribution; calculated as Dose/(λz * AUC0-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 data analysis will be based on the pharmacodynamic population. Pharmacodynamic biomarkers values will be summarized descriptively by dose level 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 or his/her legally authorized representative 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 will contain a separate section 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

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. Additionally, periodic safety reviews will be undertaken by the SMC. Based on the 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. The SMC 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. 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 Sponsor will remain in constant contact with the clinical sites during the enrollment period to ensure that cohort enrollment is completed as per protocol. Investigators will be informed about available openings for enrollment on the trial and will be asked to pre-screen subjects to determine their potential for eligibility to avoid over-enrollment. Enrollment will be offered to all sites and slots filled based on the mTPI-2 design method.

Dose escalation decisions will be made based on the DLTs observed at the current dose level with guidance provided by the mTPI-2 design as stated in the study protocol. All dose escalation and safety decisions will be documented in writing with copies maintained at each site and the Trial Master File at the CRO.

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.

United States 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 (e.g., FDA, European Medicines Agency, Health Canada, 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 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 will be maintained in the regulatory file. All deviations must be addressed in study source documents, 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.

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16. APPENDICES

16.1 mTPI-2 Dose Escalation Scenarios

See Table 5 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 5 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 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 or males of reproductive potential must agree to avoid becoming pregnant or avoid impregnating a partner, respectively. Female or males 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 subjects 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

- Male Subjects: The following contraception methods may be used by female partners and requires use of a male condom for the male subject:
  - diaphragm with spermicide
  - cervical cap with spermicide (nulliparous women only)
  - contraceptive sponge (nulliparous women only)
  - hormonal contraceptives including oral contraceptive pill (estrogen/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:
Devine BJ. Case Number 25 Gentamicin Therapy: Clinical Pharmacy Case Studies. Drug Intell. Clin Pharm. 1974;8:650-655.
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16.5 RECIST 1.1

16.5.1 RECIST 1.1 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 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesion selection will not be capped at a maximum of 2 lesions per organ. 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 10) 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 PD, 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 PD (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 PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

16.6 Summary of Changes for Amendment 01

Minor Editorial Changes

- Title page and all page headers have edits to denote revised version number /date of amendment 01
- Updated Table of Contents
- Updated Abbreviations to include definitions for ECG, QTcF, QTcB
- New Appendix added to summarize changes made for Amendment 01
- Footnotes to SOA table in Section 6.1 modified to accommodate insertion of new footnote q

1. Revised section 5.1.4 Monitoring Dose Administration to specify that subjects must be monitored for injection-related reactions and cytokine-release syndrome for a minimum of 6 hours following intratumoral injection of SL-172154.
   - New text (provided in italics) added as follows to Section 5.1.4: *All subjects must be observed for at least 6 hours after the injection.*
   - Schedule of Assessments (SOA) Table in Section 6.1: New text (provided in italics) added to footnote m as follows: *All subjects must be observed for at least 6 hours at the center after each intratumoral injection of SL-172154.*

2. The protocol is modified to include ECG monitoring at Tmax after the first dose. In addition, a predose ECG assessment on cycle 2 day 1 has been added for safety purposes after repeated dosing as no accumulation of SL172154 is expected.
   - Inclusion Criterion #9 revised in Synopsis/Section 4.1: ECG assessment inclusion criterion #9 specifies baseline QTcF interval requirement for study eligibility as ≤ 480 milliseconds
   - ECG assessments added to the SOA Table in Section 6.1 at screening, cycle 1, day 1, and cycle 2, day 1. A new footnote q added with the new text (provided in italics) as follows:

     Electrocardiogram (ECG): *Local ECG machines available at the site should be used. A single ECG will be collected during screening to determine eligibility. ECGs will be obtained in triplicate for assessment of QT/QTc as outlined below (See Section 6.3.5 for additional details).*

     - *Cycle 1, Day 1: Predose and 1 hour and 4 hours after ITI SL-172154*
     - *Cycle 2, Day 1: Predose only*

   - A new Section 6.3.5 entitled Electrocardiogram Monitoring for QTc Evaluation is now included.
   - New text (provided in italics) was added to Section 9.2.4 Safety Analyses as follows: *Change from baseline QTcF will also be summarized.*

3. The maximum number of target lesions assessed per RECIST v1.1 will be 10 lesions instead of 5 lesions.

- 5 target lesions changed to 10 target lesions in Section 8.1.1 in the second paragraph and in Appendix 16.5.1 in the fifth paragraph (2 locations)