Protocol Title: An Open-Label, Phase 1b Study of SL-172154 (SIRPα-Fc-CD40L) Administered with Either Pegylated Liposomal Doxorubicin or Mirvetuximab Soravtansine in Subjects with Platinum-Resistant Ovarian Cancers

Short Title: Phase 1b Study of SL-172154 Administered with Combination Agent(s) in Subjects with Ovarian Cancers

Protocol Identifying Number: SL03-OHD-105

Version Number: 3.0

Study Phase: Phase 1b

Investigational New Drug (IND) Sponsor: Shattuck Labs

Legal Registered Address:

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Regulatory Agency Identifier Number(s)

IND: 142568

EudraCT: 2022-000698-17

Approval Date: 25 Jun 2024

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LIST OF ABBREVIATIONS

Ab	Antibody
ADA	Anti-drug antibodies
ADC	Antibody drug conjugate
ADL	Activities of daily living
AE	Adverse event
AIBW	Adjusted ideal body weight
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANA	Anti-nuclear antibody
ANC	Absolute neutrophil count
APC	Antigen-presenting cell
aPTT	Activated partial thromboplastin time
AR	Adverse reaction
ARC	Agonist redirected checkpoint
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	Area under the serum concentration time curve
AUC_{last}	Area under the serum concentration time curve, time 0 to the last quantifiable concentration
$AUC_{0\text{-}inf}$	Area under the serum concentration time curve from time 0 extrapolated to infinity
$AUC_{0\text{-}t}$	Area under the serum concentration time curve, time 0 to time = t
$\%AUC_{ext}$	Percentage of $AUC_{0\text{-}inf}$ due to extrapolation from T_{last} to infinity
AUC_{tau}	The area under the serum concentration time curve, over the dosing interval
BCVA	Best corrected visual acuity
β-hCG	Beta-human chorionic gonadotropin
BID	Twice a day
BP	Blood pressure
BRCA	Breast cancer gene
C	Cycle
CBC	Complete blood count
CBR	Clinical benefit rate
CD	Cluster of differentiation
C1D1	Cycle 1 Day 1
CFR	Code of Federal Regulations
cGAS/STING	Cyclic guanine monophosphate – adenosine monophosphate synthase/stimulator of interferon genes
CI	Confidence Interval
CL	Clearance
C_{max}	Maximum observed concentration

C_{min}	Minimum observed concentration
CMP	Clinical monitoring plan
CNS	Central nervous system
CPAP	Continuous positive airway pressure
CR	Complete response
CrCl	Creatinine clearance
CRO	Clinical research organization
CRS	Cytokine release syndrome
CRT	Calreticulin
CT	Computed tomography
CTCAE	Common terminology criteria for adverse event
CTLA-4	Cytotoxic T cell lymphocyte-associated antigen 4
CYP	Cytochrome P
D	Day
DAT	Direct antiglobulin test
DC	Dendritic cells
DL	Dose level
DLT(s)	Dose-limiting toxicity(ies)
DNA	Deoxyribonucleic acid
DoR	Duration of response
ECD	Extracellular domain
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EIOP	Elevated intraocular pressure
EMA	European Medicines Agency
EOC	Epithelial ovarian cancer
EOI	End of infusion
EPO	Erythropoietin
ESMO	European Society for Medical Oncology
ETFE	Ethylene tetrafluoroethylene
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FOLR1	Folate receptor 1
FRα	Folate receptor alpha
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice

GCSF	Granulocyte colony stimulating factor
GLP	Good Laboratory Practice
H1/H2	Histamine 1/ Histamine 2
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HR	Heart rate
HRD	Homologous recombination deficiency
HSR(s)	Hypersensitivity reaction(s)
IB	Investigator's brochure
IBW	Ideal body weight
IC	Investigator's choice
ICF	Informed consent
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFNγ	Interferon gamma
IHC	Immunohistochemistry
IL	Interleukin
ILD	Interstitial lung disease
IM	Intramuscular
IND	Investigational new drug
INR	International normalized ratio
IOP	Intra-ocular pressure
IP	Investigational product
irAE	Immune-related adverse event
IRB	Institutional Review Board
IRR(s)	Infusion-related reaction(s)
ITT	Intent-to-treat
IV	Intravenous
IVIG	IV immunoglobulin
K_D	Receptor off-rate constant
LLOQ	Lower limit of quantification
LVEF	Left ventricular ejection fraction
mAb(s)	Monoclonal antibody(ies)
MAD	Maximum administered dose
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities

MIRV	Mirvetuximab soravtansine
MMF	Mycophenolate mofetil
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mTPI-2	Modified toxicity probability interval
MUGA	Multigated acquisition scan
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
ORR	Objective response rate
OS	Overall survival
PARP	Poly ADP-ribose polymerase
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PET	Positron Emission Tomography
PFS	Progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PLD	Pegylated liposomal doxorubicin
PLT	Platelet
PO	Orally
PR	Partial response
PRN	As needed
PROC	Platinum-resistant ovarian cancer
PS2+	Scoring method based on membrane stain intensity level of 2 or greater
PT	Prothrombin time
PTV	Post-treatment visit
q	Every
Q3W	Every 3 weeks
RANKL	Receptor activator of nuclear factor kappa B ligand
RBC	Red blood cell
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic acid
RO	Receptor Occupancy
RP2D	Recommended Phase 2 dose
RR	Respiratory rate
RSI	Reference safety information
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction

SD	Stable disease
SFU	Survival follow-up
SIRPα	Signal regulatory protein alpha
SL-172154	SIRPα-Fc-CD40L
SLM	Study Lab Manual
SMC	Safety Monitoring Committee
SmPC	Summary of product characteristics
SOA	Schedule of Assessments
SPM	Study Pharmacy Manual
SQ	Subcutaneous
SUSAR	Suspected unexpected serious adverse reaction
T	Temperature
t½	Terminal elimination half-life
TAM	Tumor-associated macrophages
TEAE	Treatment-emergent adverse event
T_{last}	Time of last observed quantifiable concentration
T_{max}	Time of maximum observed concentration
TME	Tumor microenvironment
TNF	Tumor necrosis factor
TRAF	Tumor necrosis factor receptor-associated factor
TSH	Thyroid stimulating hormone
TTR	Time to response
ULN	Upper limit of normal
USPI	United States Prescribing Information
V_z	Volume of distribution
WBC	White blood cell
λ_z	Terminal elimination rate constant

Trademark Information

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Agonist Redirected Checkpoint (ARC™)	FluroTec®
	TruEdge®
	Flip-off®
	Durezol®

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)/Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard(s) to the trial subjects. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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

Principal Investigator:

Print/Type Name	Signature

Date: _____

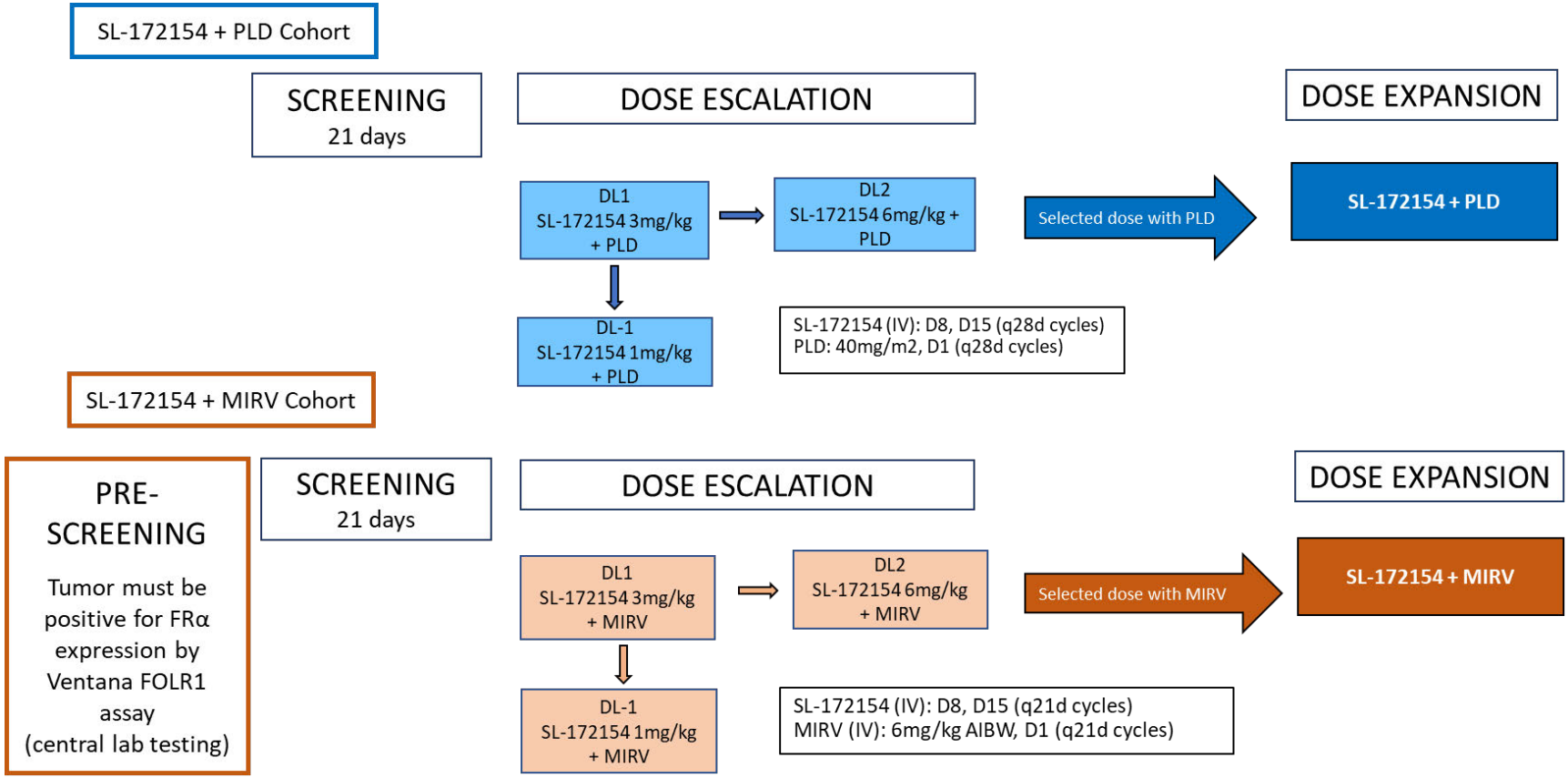
KEY TRIAL CONTACTS

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

Sponsor Signatory:

STUDY SCHEMA

Figure 1. Study Schema



Abbreviations: AIBW = adjusted ideal body weight; D = day; DL = dose level; FOLR1 = folate receptor 1; FRα = folate receptor alpha; IV = intravenous; MIRV = mirvetuximab soravtansine; PLD = pegylated liposomal doxorubicin

Doses explored in SL03-OHD-105 will not exceed the highest dose determined to be safe and tolerable in the monotherapy dose escalation study SL03-OHD-101.
Positive FRα expression is defined as ≥ 25% of tumor cells positive for FRα by Ventana FOLR1 assay by central testing.

PROTOCOL SYNOPSIS

Sponsor	Shattuck Labs
Product Name	SL-172154
Other Names	SIRPα-Fc-CD40L recombinant fusion glycoprotein
Protocol Title	An Open-Label, Phase 1b Study of SL-172154 (SIRPα-Fc-CD40L) Administered with Either Pegylated Liposomal Doxorubicin or Mirvetuximab Soravtansine in Subjects with Platinum-Resistant Ovarian Cancers
Protocol Number	SL03-OHD-105
Clinical Phase	Phase 1b
Planned Sample Size	Approximately 102 subjects
Planned Number of Sites and Countries	Approximately 30 to 40 clinical sites United States, Canada, United Kingdom, Spain
Recruitment Duration:	14 months
Study Duration	25 months

Background and Rationale

The investigational product, SL-172154, is a novel fusion protein consisting of human signal regulatory protein alpha (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. SL-172154 not only inhibits the cluster of differentiation (CD)47/SIRPα axis but it also augments cross presentation of antigens by antigen-presenting cells (APC) to T cells through the costimulatory role of CD40L, thus bridging innate and adaptive immunity. *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 (K_D values of 0.628 nM and 4.74 nM, respectively) as well as a slow off rate, 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.

Ovarian, fallopian tube, and primary peritoneal cancers, collectively known as epithelial ovarian cancer (EOC), are the most lethal gynecological cancer. The current standard-of-care front-line treatment for advanced EOC patients consists of combination carboplatin and paclitaxel chemotherapy before or after debulking surgery and results in high response rates. Further progress has recently been made by incorporating molecularly targeted agents into treatment paradigms. The use of PARP (poly ADP-ribose polymerase) inhibitors into front-line maintenance and recurrent, platinum-sensitive settings, as well as bevacizumab in all lines of therapy, have improved patient outcomes [Liu, 2014] [Herzog, 2017]. Unfortunately, most patients eventually relapse with disease that is platinum-resistant which is defined by relapse between 0 to 6 months after the last platinum dose. Outcomes for patients with platinum-resistant EOC remain particularly poor, with low response rates to non-platinum chemotherapy (e.g., 11.8% in the AURELIA trial; [Pujade-Lauraine, 2014]), median progression-free

survival (PFS) of 3 to 4 months, and median overall survival less than 1 year [Davis, 2014]. Furthermore, subsequent lines of systemic therapy are often associated with cumulative toxicities and limited tolerability in patients. For these reasons, the development of novel therapies for use in the platinum-resistant setting is critical.

Ovarian and related cancers were selected for investigation in both the Phase 1a first-in-human dose escalation study of SL-172154 monotherapy (SL03-OHD-101) and for this Phase 1b study of SL-172154 (SL03-OHD-105) due to the fact that these histologies have a high percentage of tumors with detectable CD47 expression (TCGA data; [Wang, 2015; Brightwell, 2016]). A tissue microarray of 265 tissues from patients with ovarian, primary peritoneal, and fallopian tube cancers were analyzed by immunohistochemical analysis for CD47 expression; expression was detected in 210 of 265 cases (79%). Furthermore, CD47 is a tumor associated antigen with higher levels of expression in epithelial ovarian cancer cells compared with normal ovarian cells [Li, 2017]. Finally, ovarian cancer is characterized by peritoneal metastasis which is facilitated by a crosstalk between tumor cells and other cells in the TME, including a high percentage of tumor associated macrophages. This rationale is supported by the results of a Phase 1 study of an anti-CD47 antibody, Hu5F9-G4 (magrolimab), in which monotherapy activity was reported in 2 (partial responses) out of 13 patients with ovarian cancer [Sikic, 2019]. Given that the APC is hypothesized to be the primary target of SL-172154, the unique immune contexture of ovarian and related cancers in conjunction with their high tumor CD47 expression makes these histologies particularly suitable for clinical investigation.

It is likely that a combinatorial approach to overcoming immune suppression will be required to provide benefit from immune-targeting agents in EOCs [Leary, 2021]. SL-172154 potentiates macrophage phagocytosis when combined with agents that induce immunogenic tumor cell death (see SL-172154 investigator's brochure [IB]). Initiation of these cell death pathways makes tumor cells more visible to APCs, such as macrophages and dendritic cells, resulting in enhanced phagocytotic activity. We hypothesize that combining SL-172154 with cytotoxic agents may concurrently 1) inhibit the CD47/SIRPα checkpoint; 2) enhance stimulation of phagocytosis by induction of prophagocytic proteins on tumor cells, and 3) augment antigen presentation by APCs to T cells via costimulation of the CD40L/CD40 pathway.

Preclinical data have demonstrated that pegylated liposomal doxorubicin (PLD) induces immunogenic cell death as evidenced by increased extracellular ATP levels, secreted HMGB1, induction of calreticulin (CRT) and CRT translocation to the plasma membrane [Solari, 2020] thus increasing infiltration of active T cells. Similarly, doxorubicin has also been shown to further promote immune priming by enhancing antigen presentation [Zitvogel, 2013] and modifying the suppressive microenvironment by increasing the infiltration of active T cells [Hao, 2018]. In preclinical murine studies using subcutaneous CT26 colorectal carcinoma tumors, mSIRPα-Fc-CD40L (intraperitoneal) in combination with doxorubicin (intravenous) resulted in greater tumor growth inhibition in comparison to either monotherapy treatment. This synergistic activity may be due to chemotherapy-induced tumor cell death resulting in increased tumor visibility to APCs (e.g., macrophages and dendritic cells) and subsequent enhanced phagocytosis activity mediated by mSIRPα-Fc-CD40L.

There are no highly effective therapies in the platinum-resistant EOC population, although non-platinum agents have demonstrated modest antitumor efficacy in a subset of these patients. PLD is commonly used in clinical practice for the treatment of platinum-resistant ovarian cancer (PROC; [Davis, 2014]). Single-agent PLD has been extensively studied in this patient population, demonstrating an objective response rate (ORR) of 10 to 20%, median PFS of 2.1 to 3.7 months, and overall survival (OS) ranging from 8.4 to16.8 months [Gordon, 2001; Lawrie, 2013; Pujade-Lauraine, 2021]. Taken together, these observations suggest that combination of anthracyclines with SL-172154 may provide added clinical benefit relative to either agent alone.

Folate receptor alpha (FRα) is a glycosylphosphatidylinositol-anchored cell surface protein encoded by the folate receptor 1 (FOLR1) gene. FRα internalizes folate, which is an essential cofactor for one-carbon transfer reactions that are required for deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis, cell growth, and proliferation. Published studies have demonstrated FRα overexpression by immunohistochemistry (IHC) in various epithelial tumors, particularly the serous and endometrioid histologic subtypes of ovarian and endometrial cancers [Garin-Chesa, 1993; Allard, 2007; Dainty, 2007; Brown Jones, 2008; Kalli, 2008; Scorer, 2010; Crane, 2012; Ab, 2015]. Because of its tumor-specific expression and capacity to internalize small and large molecule ligands, FRα has emerged as a biologically rational target for antibody drug conjugate (ADC) therapy. ADCs combine the specificity of a monoclonal antibody (mAb) to tumor antigens with the extraordinary cytotoxicity of maytansine derivatives, which are potent anti-microtubule agents that target proliferating cells. Mirvetuximab soravtansine (MIRV) consists of the chimeric anti-FRα mAb M9346A attached via a cleavable linker to the cytotoxic maytansinoid, DM4.

The internalization of MIRV leads to the apoptosis of target ovarian tumor cells that overexpress FRα. The hypothesis that combining MIRV with SL-172154 may increase the macrophage-mediated phagocytosis of these apoptotic cells is supported by *in vitro* phagocytosis assays using human monocyte-derived macrophages and human ovarian cancer cell lines. These assays demonstrated that SL-172154 or MIRV stimulated macrophage-mediated phagocytosis of KB, IGROV1, and OV90 ovarian cancer cells, and the combination of the two agents further enhanced phagocytic activity. Interestingly, in MESOV ovarian cancer cells (which express low levels of FRα and high levels of CD47 and calreticulin), SL-172154 alone stimulated phagocytosis whereas MIRV alone did not and combining the two agents enhanced phagocytosis above that seen with SL-172154 alone. These data suggest that SL-172154 may broaden the activity of MIRV to tumor cells expressing low FRα levels.

Single-agent MIRV has recently been studied in a randomized, open-label Phase 3 trial comparing MIRV and investigator's choice (IC) chemotherapy in patients with platinum-resistant EOC who had received 1 to 3 prior lines of therapy and whose tumors were positive for FRα. While the primary endpoint, PFS, did not reach statistical significance in either the intent-to-treat (ITT) or the FRα high population, superior outcomes for MIRV over chemotherapy were observed in all secondary endpoints in the FRα high population, including improved ORR (24% versus 10%), CA-125 responses, and patient-reported outcomes. Importantly, confirmed responses were seen across FRα levels, with a confirmed ORR in the ITT population being higher for MIRV than for IC chemotherapy (22% versus 12%, P= 0.015) and correlated with improved CA-125 responses (51% versus 27%, P < 0.001). These data suggest that MIRV is generating a cytotoxic signal even in ovarian tumors expressing medium and low levels of FRα expression. It is hypothesized that this pro-phagocytic signal from MIRV could synergize with SL-172154 in platinum-resistant ovarian cancer patients whose tumors express low, medium or high levels of FRα expression and potentially result in clinically meaningful durable responses that are greater than observed with either monotherapy treatment.

Taken together, these data suggest that both PLD and MIRV are appropriate to combine with SL-172154 in this phase 1b trial in patients with platinum-resistant EOC, a population with high unmet need.

SL03-OHD-105 is designed as a Phase 1b open-label trial to evaluate the safety, pharmacokinetic (PK), pharmacodynamic (PD), and preliminary efficacy of SL-172154 administered as add-on therapy to background treatment with either PLD or MIRV in subjects with ovarian and related cancers. PLD is commonly used in clinical practice in this patient population, with well-described safety, PK and PD profiles. MIRV is being investigated for the treatment of PROC patients with efficacy, safety and PK profiles reported. Each component is anticipated to have activity on distinct targets, and PLD or MIRV combined with SL-172154 has the potential to further bridge innate and adaptive immunity, thus

potentially improving treatment outcomes without increasing toxicity. Anticipated overlapping toxicities are minimal when combining SL-172154 with PLD (infusion-related reactions [IRRs], fatigue, nausea, constipation, diarrhea and cytopenias) or with MIRV (IRR, low grade fatigue, nausea, diarrhea and cytopenias).

Upon identification of the SL-172154 dose in each of the combination regimens during dose escalation, a dose expansion cohort will enroll additional subjects to receive either PLD or MIRV with the selected SL-172154 dose.

Study Objectives

Primary Objective(s)	**Outcome Measures**
To evaluate the safety and tolerability of SL-172154 administered with pegylated liposomal doxorubicin (PLD) or mirvetuximab soravtansine (MIRV) in subjects with platinum-resistant ovarian, primary peritoneal, or fallopian tube cancer	• Incidence and severity of adverse events (AE) per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 5.0 • Change from baseline in laboratory values per NCI-CTCAE, version 5.0 • AEs leading to discontinuation • Maximum tolerated dose (MTD) of SL-172154 in each combination regimen based on the rate of dose-limiting toxicities (DLTs), or the Maximum Administered Dose (MAD) of SL-172154
To select the recommended Phase 2 dose (RP2D) for SL-172154 administered with PLD or MIRV in subjects with platinum-resistant ovarian, primary peritoneal, or fallopian tube cancer	• Number and occurrence of DLTs as defined in the protocol • Available pharmacokinetic (PK) parameters • Available pharmacodynamic (PD) effects • Safety • Anti-tumor activity
Secondary Objectives	**Outcome Measures**
To assess preliminary evidence of anti-tumor activity of SL-172154 when administered with PLD or MIRV (overall as well as subgroups with high (PS2+ ≥ 75%), medium (PS2+ ≥ 50% and < 75%), or low (PS2+ ≥ 25% and < 50%) tumor FRα expression) in subjects with platinum-resistant ovarian, primary peritoneal, or fallopian tube cancer.	• ORR based on investigator assessment by Response Evaluation Criteria in Solid Tumors (RECIST v1.1) • Clinical benefit rate (CBR) • Time to response (TTR) • Duration of response (DoR) • PFS based on investigator assessment
To evaluate immunogenicity to SL-172154 or MIRV during and after treatment of SL-172154 administered with PLD or MIRV in subjects with platinum-resistant ovarian, primary peritoneal, or fallopian tube cancer	• Number/proportion of subjects with positive or negative anti-drug antibody (ADA) titer • Number/proportion of subjects with neutralizing anti-drug antibodies • ADA duration • Transient vs. persistent ADA
To assess the pharmacokinetic profile of SL-172154 when administered with PLD or MIRV in subjects with platinum-resistant	• Maximum observed concentration (C_{max}), time at which the maximum concentration is observed (T_{max}), and minimum observed concentration (C_{min}) following single and multiple doses of SL-172154

ovarian, primary peritoneal, or fallopian tube cancer	• Area under the serum concentration-time curve (AUC) • Terminal elimination half-life (t½), Clearance (CL) and Volume of Distribution (V_z), as data permit
To assess the pharmacokinetic profile of MIRV when administered with SL-172154 in subjects with platinum-resistant ovarian, primary peritoneal, or fallopian tube cancer	• PK exposure evaluation of MIRV, total antibody, and payload (DM4 and S-methyl DM4)
Exploratory Objectives	**Outcome Measures**
To identify and assess pharmacodynamic biomarkers associated with ovarian cancer or the mechanism of action of SL-172154, PLD, or MIRV following treatment with SL-172154 administered with PLD or MIRV in subjects with platinum-resistant ovarian, primary peritoneal, or fallopian tube cancer	• Changes from baseline in select cytokines • Changes in immune cell subsets • CD47 and CD40 expression • Target-associated regulatory networks • Genomic alterations which may correlate with drug safety or efficacy
To explore the association of biological/clinical endpoints with PK parameters of SL-172154 administered with PLD or MIRV in subjects with platinum-resistant ovarian cancer, primary peritoneal, or fallopian tube cancer	• To assess the relationship between SL-172154 PK parameters and the anti-tumor activity and safety of SL-172154, if feasible
Estimate overall survival (OS)	• OS: time from first dose to death

Study Design

Study SL03-OHD-105 is an open-label, multicenter, Phase 1b trial designed to evaluate the safety, PK, PD effects, and preliminary anti-tumor activity of SL-172154 administered as add-on therapy to background treatment with either PLD or MIRV in subjects with platinum-resistant ovarian, primary peritoneal, or fallopian tube cancers. The study will consist of dose escalation followed by dose expansion.

Subjects with histologically confirmed epithelial ovarian cancer or primary peritoneal or fallopian tube cancer of high-grade histology who are platinum-resistant are eligible. For the SL-172154 + MIRV cohort, the subject's tumor must be positive for FRα expression as defined by central testing using the Ventana FOLR1 Assay.

All subjects (dose escalation and dose expansion) will receive SL-172154 administered with PLD or with MIRV until documented disease progression, unacceptable toxicity or intolerance, withdrawal of consent, investigator's decision to discontinue treatment, or lost to follow-up.

Study SL03-OHD-105 will initially enroll subjects to one of two dose escalation cohorts: SL-172154 + PLD or SL-172154 + MIRV. The SL-172154 starting dose of 3.0 mg/kg is supported by safety data from the SL03-OHD-101 study in which 4 subjects receiving 1.0 mg/kg and 6 subjects receiving 3.0 mg/kg of SL-172154 once-weekly have cleared the DLT evaluation period with no DLTs reported. Five subjects were enrolled at 10 mg/kg dose level and 1 DLT has been reported in this group.

The initial SL-172154 dose escalation cohorts in Study SL03-OHD-105 are:

- SL-172154 (3.0 mg/kg, intravenous(ly) (IV); Days 8 and 15 of each 28-day cycle) administered with PLD (40 mg/m^2, IV, Day 1 of each 28-day cycle)
- SL-172154 (3.0 mg/kg, IV; Days 8 and 15 of each 21-day cycle) administered with MIRV (6.0 mg/kg adjusted ideal body weight [AIBW], IV; Day 1 of each 21-day cycle)

During dose escalation, subjects will be enrolled in sequential cohorts of approximately 3 subjects and evaluated for DLT during the first cycle of therapy (i.e., DLT evaluation period). Treatment will be administered in 28-day (PLD cohorts) or 21-day (MIRV cohorts) cycles until disease progression, unacceptable toxicity, or withdrawal of consent. Dose escalation of SL-172154 with each of the combination regimens will continue until a safe dose of SL-172154 when administered with the assigned combination agent (e.g., PLD or MIRV) is identified. The dose escalation cohorts will utilize the modified Toxicity Probability Interval (mTPI-2) design [Guo, 2017] with target DLT rate of 30% for the maximum tolerated dose (MTD).

In selecting the dose of SL-172154 to be evaluated in the respective combination regimen dose expansion cohort, the totality of the data from the dose escalation phase including the safety of the combination and PD activity will be considered. Upon identification of the selected SL-172154 dose administered with PLD, a dose expansion cohort will enroll approximately 20 subjects (including subjects from dose escalation at the same dose level) to further evaluate the safety and efficacy of the study treatment. The same patient population will be enrolled in both the dose escalation and dose expansion portion of the study.

Upon identification of the selected SL-172154 dose administered with MIRV, a dose expansion cohort will enroll approximately 70 subjects whose tumor is FRα-positive (including subjects from dose escalation at the same dose level) to further evaluate the safety and efficacy of the study treatment. All subjects with FRα-positive tumors will be enrolled and retrospectively binned by FRα expression subgroups (high, medium, or low) in the study analysis. The same patient population will be enrolled in both the dose escalation and dose expansion portion of the study.

The planned sample size is approximately 102 subjects, depending on the number of dose levels evaluated in dose escalation for each of the combination. Approximately 24 subjects will be enrolled in dose escalation cohorts (12 subjects in PLD cohorts and 12 subjects in MIRV cohorts) and approximately 78 subjects will be enrolled in the dose expansion cohorts (an additional 14 subjects at the selected dose in PLD cohort and additional 64 subjects at the selected dose in MIRV cohort).

NOTE: The planned sample sizes may be revised if additional dose levels are evaluated or if more subjects (i.e., subjects available for dosing beyond the number required in a cohort) are enrolled than anticipated. The actual number of subjects to be enrolled for each combination dose escalation will depend upon the number of dose levels evaluated and the number of DLTs observed for each dose level and related dose escalation/stay/de-escalation decision.

Treatment Schedules

All subjects will receive the assigned study treatment until disease progression, unacceptable toxicity, withdrawal of consent, investigator's decision to discontinue treatment, or lost to follow-up.

For all subjects in all cohorts, premedication as prophylaxis for IRR with dexamethasone (8 mg IV), an antipyretic and antihistamines should be administered at least 30 minutes prior to each SL-172154 administration. For subjects enrolled to receive MIRV, premedication with antipyretic, antihistamine, and dexamethasone will be administered at least 30 minutes prior to each MIRV administration. The infusion rate of SL-172154 may change based on final drug volume needed for administration, safety, and tolerability of the infusion for the subject and/or observed safety findings during the study or

SL-172154 development program. Additional doses and/or schedules or intermediate doses may be explored based on emerging safety, PK and PD data.

DOSE ESCALATION: SL-172154 + PLD

Dose Level[a]	SL-172154 Dose[b] [D8 and 15 in each 28d cycle]	SL-172154 Infusion[c]	Pegylated liposomal doxorubicin (PLD)
-1[d]	1.0 mg/kg	60 min ± 10 min	PLD (40 mg/m^2) IV administered on Day 1 of each 28-day cycle Administer first dose on study (C1D1) as 1 mg/min IV infusion; after Cycle 1, if tolerated, PLD can be delivered as a 1-hour infusion.
1 (Starting Dose)	3.0 mg/kg	120 min ± 15 min	
2	6.0 mg/kg	180 min ± 15 min	

Abbreviations: AIBW = adjusted ideal body weight; C1D1 = Cycle 1 Day 1; D = day; IV = intravenously; mTPI-2 = modified toxicity probability interval; PLD = pegylated liposomal doxorubicin

a. Doses explored in SL03-OHD-105 will not exceed the highest dose determined to be safe and tolerable in the monotherapy dose escalation study SL03-OHD-101.
b. The actual body weight in kilograms (kg) will be used for SL-172154 dose calculation in all subjects whose body weight is ≤ 100 kg. For subjects with body weight > 100 kg, the dose to be administered should be the same as that calculated for a subject weighing 100 kg.
c. Infusion time may change based on final drug volume needed for administration, safety and tolerability of the infusion for the subject and/or observed safety findings during the study. Please refer to the Study Pharmacy Manual (SPM) for details.
d. SL-172154 dose level -1 at 1.0 mg/kg will be evaluated if 3.0 mg/kg is not safe per mTPI-2.

DOSE ESCALATION: SL-172154 + MIRV

Dose Level[a]	SL-172154 Dose[b] [D8 and 15 in each 21d cycle]	SL-172154 Infusion[c]	Mirvetuximab (MIRV)[e]
-1[d]	1.0 mg/kg	60 min ± 10 min	6.0 mg/kg AIBW, IV administered on Day 1 of each 21-day cycle Administer first dose on study (C1D1) at rate of 1 mg/min; after 30 min increase rate to 3.0 mg/min if well tolerated. If well-tolerated after 30 min at 3.0 mg/min, infusion rate may be increased to 5.0 mg/min. Subsequent infusions should be delivered at the tolerated rate.
1 (Starting Dose)	3.0 mg/kg	120 min ± 15 min	
2	6.0 mg/kg	180 min ± 15 min	

Abbreviations: AIBW = adjusted ideal body weight; C1D1 = Cycle 1 Day 1; D = day; IV = intravenously; MIRV = mirvetuximab soravtansine; mTPI-2 = modified toxicity probability interval

a. Doses explored in SL03-OHD-105 will not exceed the highest dose determined to be safe and tolerable in the monotherapy dose escalation study SL03-OHD-101.
b. The actual body weight in kilograms (kg) will be used for SL-172154 dose calculation in all subjects whose body weight is ≤ 100 kg. For subjects with body weight > 100 kg, the dose to be administered should be the same as that calculated for a subject weighing 100 kg.

c. Infusion time may change based on final drug volume needed for administration, safety, and tolerability of the infusion for the subject and/or observed safety findings during the study. Please refer to the Study Pharmacy Manual (SPM) for details.
d. SL-172154 dose level -1 at 1.0 mg/kg will be evaluated if 3.0 mg/kg is not safe per mTPI-2.
e. Administer premedication at least 30 min prior to the start of MIRV infusion.

The SL-172154 dose in combination with either PLD or MIRV that is selected in dose escalation will be used in the respective dose expansion cohort. The same schedule and infusion duration for SL-172154 as well as for the combination agent (either PLD or MIRV) that was utilized during dose escalation will be used in dose expansion.

Definition of Dose-Limiting Toxicity

Protocol-defined DLT criteria are applicable to the dose escalation portion of the study. The determinant period for DLT is the first cycle of treatment (i.e., 28 days for PLD cohorts, 21 days for MIRV cohorts); however, there is provision in the criteria below for AEs that occur beyond this period to be considered in the determination of the RP2D. All toxicities except for cytokine release syndrome (CRS) and ocular AEs will be graded as per NCI CTCAE v5. CRS will be graded per the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading Criteria for CRS; ocular AEs for the MIRV cohort will be graded per the tables provided in the Appendix. AEs clearly related to the underlying disease, disease progression, intercurrent illness, or concomitant medications are not considered DLTs. AEs that are clearly related to PLD or MIRV only do not have to be considered DLTs, unless the investigator considers the AE to be exacerbated by SL-172154. DLT is defined as an event considered related or possibly related to SL-172154 and meets one of the following criteria:

- Any death not clearly related to underlying disease or intercurrent illness
- Elevations in liver transaminases (aspartate aminotransferase [AST], alanine aminotransferase [ALT]) or total bilirubin:
    - In subjects who enroll with AST/ALT/total bilirubin ≤ upper limit of normal (ULN), AST or ALT elevation of > 8x ULN **or** total bilirubin > 5x ULN.
    - In subjects who enroll with AST/ALT/total bilirubin > ULN, AST or ALT elevation of > 8x baseline **or** total bilirubin > 5x baseline.
    - Evidence of Hy's Law (AST or ALT > 3x ULN [or baseline*] with concurrent increase in total bilirubin > 2x ULN [or baseline*] without evidence of cholestasis or alternative explanation such as disease progression or viral hepatitis.

      **ULN or baseline dependent on value at enrollment as described above*.
- Any AE that requires permanent discontinuation of SL-172154
- Any Grade 3 or greater AE except for those listed below:
    - Grade 3 fatigue lasting ≤ 7 days
    - Grade 3 anemia
    - Grade 3 or 4 neutropenia not associated with fever (temperature > 38.5°C) 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 anorexia, nausea, vomiting or diarrhea provided that it does not require tube feeding, total parenteral nutrition, or require or prolong hospitalization
- Grade 3 laboratory abnormalities which resolve to Grade 1 or baseline within 72 hours with or without intervention
- Grade 3 hypertension that can be controlled (i.e., systolic BP < 140 mmHg and diastolic BP < 90 mmHg) with medical therapy
- Grade 3 or 4 amylase and/or lipase abnormalities that are not associated with clinical signs/symptoms or finding on imaging consistent with pancreatitis
- 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
- Vitiligo or alopecia of any grade

Other toxicities may be considered a DLT as determined by the investigator in conjunction with the Safety Monitoring Committee (SMC).

Eligibility Criteria

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

Inclusion Criteria

Subjects must meet <u>all</u> of the following criteria:

1. Subject has voluntarily agreed to participate by giving written informed consent in accordance with ICH/GCP guidelines and applicable local regulations.
2. Age ≥ 18 years.
3. **[PLD Cohort]** Subject has a histologically confirmed diagnosis of high grade EOC (including primary peritoneal cancer or fallopian tube cancer).

   NOTE: Non-epithelial tumors and ovarian tumors with low malignant potential are excluded.
4. [**PLD Cohort**] Subject must have platinum-resistant disease, defined as radiologic disease progression within 180 days (6 months) following the last administered dose of platinum therapy.

   NOTE: Progression should be calculated from the date of the last administered dose of platinum therapy to the date of the radiographic imaging showing progression.

   NOTE: Subjects who are primary platinum refractory, defined by progressing during or within 1 month of upfront platinum therapy, are excluded.
5. **[PLD Cohort]** Subjects may have received any number of prior lines of therapy for EOC; however, they may not have received more than 1 prior line of systemic anticancer therapy for platinum-resistant disease.

   Lines of therapy are defined in this study as:

- Adjuvant ± neoadjuvant is considered 1 line of therapy.
- Maintenance therapy (e.g., bevacizumab, PARP inhibitors) will be considered part of the preceding line of therapy (i.e., not counted independently).
- Therapy changed due to toxicity in the absence of progression will be considered part of the same line (i.e., not counted independently).
- Hormonal therapy will be counted as a separate line of therapy unless it was given as maintenance.

6. **[MIRV Cohort]** Subject has a histologically confirmed diagnosis of high grade serous EOC including primary peritoneal cancer or fallopian tube cancer).

   NOTE: non-epithelial tumors and ovarian tumors with low malignant potential are excluded.

7. **[MIRV Cohort]** Subject must have platinum-resistant disease as defined by:

   - Subjects who have only had 1 line of platinum-based therapy must have received at least 4 cycles of platinum, must have had a response (complete response/remission [CR] or partial response/remission [PR]) and then progressed between > 3 months and ≤ 6 months after the date of the last dose of platinum.
   - Subjects who have received 2 or 3 lines of platinum therapy must have progressed on or within 6 months after the date of the last dose of platinum.

   NOTE: Progression should be calculated from the date of the last administered dose of platinum therapy to the date of the radiographic imaging showing progression.

   NOTE: Subjects who are platinum refractory during front-line treatment are excluded [primary platinum-refractory disease, defined as disease that did not respond to (CR or PR) or has progressed within 3 months of the last dose of first-line platinum-containing chemotherapy].

8. **[MIRV Cohort]** Subjects must have received at least 1 but no more than 3 prior systemic lines of anticancer therapy.

   Lines of therapy are defined in this study as:

   - Adjuvant ± neoadjuvant is considered 1 line of therapy.
   - Maintenance therapy (e.g., bevacizumab, PARP inhibitors) will be considered part of the preceding line of therapy (i.e., not counted independently).
   - Therapy changed due to toxicity in the absence of progression will be considered part of the same line (i.e., not counted independently).
   - Hormonal therapy will be counted as a separate line of therapy unless it was given as maintenance.

9. [**MIRV Cohort**] Willing to provide an archival tumor tissue block or slides or undergo procedure to obtain new biopsy using a low-risk, medically routine procedure for IHC confirmation of FRα positivity.
10. [**MIRV Cohort**] Subject's tumor must be positive for FRα expression defined as PS2+ ≥ 25% by the Ventana FOLR1 Assay.
11. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.
12. Measurable disease by RECIST v1.1 using radiologic assessment.

13. Laboratory values must meet the following criteria:

Laboratory parameter	Threshold value
Absolute neutrophil count (ANC)	≥ 1.5 x 10^9/L without GCSF in prior 10 days or long-acting WBC growth factors in prior 20 days
Platelet count	≥ 100 x 10^9/L without platelet transfusion in prior 10 days
Hemoglobin (Hgb)	≥ 9.0 g/dL without packed RBC transfusion in the prior 7 days
Creatinine clearance (CrCl)	≥ 30 milliliter (mL)/min (using modified Cockcroft-Gault formula)
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
Serum albumin **[MIRV cohort only]**	≥ 2 g/dL
Left ventricular ejection fraction (LVEF) **[PLD cohort only]**	> 50% by echocardiography/MUGA scan

14. Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test within 4 days of the first dose of study treatment. FCBP must use 2 highly effective methods of contraception starting at least 14 days prior to the first dose of study treatment, throughout the study, and for at least 6 months after the last dose of PLD or at least 3 months after the last dose of SL-172154 or MIRV, or for the duration required by local regulatory guidance, whichever is longer.
15. Subjects must have stabilized or recovered (Grade 1 or baseline) from all prior anti-cancer therapy-related toxicities. NOTE: Grade 2 alopecia is acceptable for either cohort; Grade 2 sensory neuropathy **[PLD Cohort only]** or Grade 1 sensory neuropathy **[MIRV Cohort only]** is acceptable.
16. **[MIRV Cohort only, Dose Expansion only]** Willing to consent to 1 mandatory pretreatment and 1 on-treatment tumor biopsy, unless there is excessive risk from the procedure as determined by the investigator.

Exclusion Criteria

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

1. Prior treatment with a SIRPα targeting agent, anti-CD47 agent or CD40 agonist.
2. **[PLD Cohort]** Prior treatment with doxorubicin or PLD.
3. **[MIRV Cohort]** Prior treatment with MIRV or another FRα-targeting agent.
4. Any anti-cancer therapy within the time intervals noted below prior to first dose (Day 1) of study treatment:

Therapy	Washout Period
Chemotherapy	4 weeks or 5 half-lives, whichever is shorter
Hormonal therapy	4 weeks or 5 half-lives whichever is shorter
PD-1/L1 inhibitor and other immunotherapies not otherwise specified	4 weeks or 5 half-lives whichever is shorter
Tumor vaccine	4 weeks
Cell-based therapy	8 weeks
Other mAbs or biologic therapies	4 weeks or 5 half-lives whichever is shorter
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

5. Concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment is prohibited. Concurrent use of hormones for non-cancer-related conditions is acceptable.
6. Receipt of live attenuated vaccine (including live attenuated vaccines for COVID-19) within 28 days of the first dose of study treatment.
7. Current or prior use of systemic immunosuppressive medication within 7 days prior to first dose of study treatment. The following are exceptions to this exclusion criterion:
   - Intranasal, inhaled, topical, injected (e.g., intra-articular injection) or local steroid or immunosuppressive medication.
   - Steroids as premedication for hypersensitivity reactions (HSRs) (e.g., CT scan premedication).
8. **[MIRV Cohort]** Requires use of folate-containing supplements (e.g., folate deficiency)
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, history of multiple sclerosis (MS) or other demyelinating disease and/or Lambert-Eaton syndrome (paraneoplastic syndrome). Exceptions include controlled Type I diabetes, vitiligo, alopecia areata or hypo/hyperthyroidism.
10. Ongoing or active infection (e.g., no systemic antimicrobial therapy for treatment of infection within 5 days of D1 of study treatment).
11. Known severe hypersensitivity to the active drug substance or to any of the excipients for the agents to be administered or known hypersensitivity to Chinese hamster ovary cell products.

Prior severe hypersensitivity to monoclonal antibodies **[MIRV Cohort only]** or liposomal preparations **[PLD Cohort only]**.

12. Severe gastrointestinal conditions such as clinical or radiological evidence of bowel obstruction within 4 weeks prior to study entry.
13. Clinically significant or uncontrolled cardiovascular disease including any of the following:
    - Myocarditis
    - Unstable angina within 6 months from first dose of study treatment
    - Acute myocardial infarction within 6 months from first dose of study treatment
    - 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 block without a pacemaker, circulatory collapse requiring vasopressor or inotropic support, or arrhythmia requiring therapy)
    - History of hemorrhagic or ischemic stroke within 6 months prior to enrollment
    - Prior anthracycline-related cardiotoxicity or prior anthracycline exposure approaching the lifetime limit **[PLD cohort only]**
14. [**MIRV Cohort**] History of cirrhotic liver disease (Child-Pugh Class B or C)
15. [**MIRV Cohort**] Active or chronic corneal disorders, history of corneal transplantation, or active ocular conditions requiring ongoing treatment/monitoring, such as uncontrolled glaucoma, wet age-related macular degeneration requiring intravitreal injections, active diabetic retinopathy with macular edema, macular degeneration, presence of papilledema, and/or monocular vision.
16. Previous clinical diagnosis of noninfectious interstitial lung disease (ILD), including noninfectious pneumonia.
17. 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 first dose of study treatment and no longer require steroids.
18. Women who are pregnant or breast feeding, or who plan to become pregnant or breast feed while receiving study treatment.
19. 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.
20. 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 the study treatment.
21. Has undergone allogeneic stem cell transplantation or organ transplantation.
22. Known history or positive test for human immunodeficiency virus (HIV), 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 RNA).

NOTE: *Hepatitis B virus (HBV)*: Subjects who are hepatitis B core antibody [HBcAb] positive, but HBsAg negative are eligible for enrollment. *HCV*: Subjects who are HCV Ab positive, but HCV RNA negative are eligible for enrollment.
Safety Oversight
Study progress and safety will be reviewed throughout the conduct of the study. During the study while subjects are receiving treatment with SL-172154, SMC meetings will be held to review relevant data with the investigators or designees during both dose escalation and dose expansion. These meetings will be held once a month (or more frequently if required) during dose escalation to share safety data and communicate results of ongoing analyses provided subjects have been enrolled and data are available to be reviewed. All available safety, PK, PD, 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 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. As dose escalation proceeds, the SMC will take into account data from Study SL03-OHD-105 as well as other knowledge obtained for SL-172154, including data from the monotherapy SL-172154 dose escalation in Study SL03-OHD-101. Safety and PK data from Study SL03-OHD-101 will be shared with the SMC for SL03-OHD-105. Doses explored in SL03-OHD-105 will not exceed the highest dose cleared for safety in SL03-OHD-101. All dose escalation or safety decisions made by the SMC will be documented in writing with copies maintained at each site and in the Trial Master File at the Contract Research Organization.
Statistics
The safety evaluation for each combination regimen will be based on the All-Treated Population defined as all subjects who received at least one dose of study treatment. Frequency tables by dose levels will be used to describe safety and tolerability parameters such as: AEs, SAEs, fatal AEs, and AEs leading to discontinuation of SL-172154, PLD or MIRV. Changes in toxicity grade for laboratory parameters will also be summarized. AEs will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ classification. All AEs except CRS and ocular AEs will be graded according to the NCI CTCAE v5.0. CRS will be graded per the ASTCT Consensus Grading Criteria for CRS; ocular AEs for the MIRV cohort will be graded per the tables provided in the Appendix. The DLT evaluation will be based on the DLT-evaluable population. The DLT-evaluable population for SL-172154 + PLD and SL-172154 + MIRV is defined as all subjects enrolled in the dose escalation cohorts who receive at least 50% scheduled doses of SL-172154 and one dose of PLD or MIRV and complete the post-treatment visit (PTV) through the DLT evaluation period or experience any DLT during the DLT evaluation period. DLTs will be summarized by dose level for each of the combination dose escalation cohorts. The MTD will be estimated using isotonic regression. Continuous toxicity monitoring based on the Pocock-type stopping boundary [Ivanova, 2005] will be used for the rate of AEs leading to treatment discontinuation within each of the dose expansion cohorts. Anti-tumor activity data will be summarized by dose level and for all subjects for each combination regimen, respectively, 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 ORR and CBR based on investigator-assessed response per RECIST v1.1 will be estimated along with a 95% confidence interval using the exact probability method. Duration of response and time to response will be evaluated, using the Kaplan-Meier method, for the subgroup of

subjects with a confirmed response. The Kaplan-Meier method will be used to estimate the PFS/OS curve and PFS/OS rate at timepoints of interest.

SL-172154 PK parameters will be summarized and analyzed using appropriate statistical methods. The relationship between PK exposure parameters and ADA, safety, efficacy, and PD endpoints may be explored, as data permit, using appropriate graphical and statistical methods. PD biomarkers values will be summarized descriptively by dose level for each combination regimen. The effect of ADA and neutralization capacity on the PK, PD, safety and efficacy will be explored, as data permit, using appropriate graphical and statistical methods.

Plasma concentrations for MIRV will also be summarized. All concentration data will be determined using validated assays. The immunogenic potential of MIRV will also be assessed.

1. BACKGROUND AND STUDY RATIONALE

1.1 Bridging Innate and Adaptive Immunity via Concurrent Targeting of CD47 and CD40

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 [Oldenborg, 2000; Blazar, 2001; Yamao, 2002; Olsson, 2005; Yi, 2015]. The anti-phagocytic activity of CD47/signal regulatory protein α (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 [K. Liu, 2015]. Specifically, inhibition of SIRPα signaling in CD8α+ DCs has been shown to enhance sensing of phagocytosed tumor mitochondrial deoxyribonucleic acid (DNA), 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 [K. Liu, 2015; Xu, 2018]. Increased antigen priming of CD8α+ DC in the presence of CD47/SIRPα inhibition dramatically enhances tumor rejection in multiple preclinical 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 antigen-presenting cells (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 CD40L, expressed by resting CD8α+ (but not CD8α negative) DCs, is an important signal for enhancing the antigen cross-presenting activity of exogenous antigen by DCs to CD8+ T cells [Bennett, 1998; Schoenberger, 1998; O'Connell, 2000; Delamarre, 2003; Yasumi, 2004]. Interestingly, activation of tumor necrosis factor receptor-associated factor (TRAF) signaling downstream of CD40 ligation has also been shown to facilitate a type I interferon response via STING activation, but STING activation does not appear to be essential for the anti-tumor immune response to CD40 stimulation [Byrne, 2016; Yao, 2016]. Despite the potentially context-dependent role of a type I interferon response, anti-tumor immunity to CD40 agonists remained dependent upon batf3 positive DCs and CD8+ T cells [Byrne, 2016]. These data indicate that, like CD47/SIRPα, the CD40/CD40L axis appears capable of bridging innate and adaptive

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

1.2 Ovarian Cancer

Ovarian, fallopian tube, and primary peritoneal cancers, collectively known as epithelial ovarian cancer (EOC), are the most lethal gynecological cancer with greater than 185,000 yearly deaths worldwide. EOCs are the fifth most common cause of cancer mortality in women [Bray, 2018]. Patients are initially considered to have platinum-sensitive disease if they respond to first-line platinum and taxane based chemotherapy and experience a relapse-free period of greater than 6 months following the last dose of platinum therapy. The current standard-of-care frontline treatment for advanced EOC patients consists of combination carboplatin and paclitaxel chemotherapy before or after debulking surgery and results in high response rates. Further progress has recently been made by incorporating molecularly targeted agents into treatment paradigms. The use of PARP (poly ADP-ribose polymerase) inhibitors into front-line maintenance and recurrent, platinum-sensitive settings, as well as bevacizumab in all lines of therapy, have improved patient outcomes [J. Liu, 2014; Herzog, 2017]. However, most patients eventually relapse with disease that is platinum-resistant, which is defined by relapse between 0 to 6 months after the last platinum dose. Outcomes for patients with platinum-resistant EOC remain particularly poor, with low response rates to non-platinum chemotherapy (e.g., 11.8% in the AURELIA trial; [Pujade-Lauraine, 2014]), median progression-free survival (PFS) of 3 to 4 months, and median overall survival less than 1 year [Davis, 2014]. Furthermore, subsequent lines of systemic therapy are often associated with cumulative toxicities and limited tolerability in patients. For these reasons, the development of novel therapies for use in the platinum-resistant setting is critical.

1.3 CD47 and CD40 Targeting in Ovarian Cancer

Ovarian and related cancers were selected for investigation in the Phase 1a first-in-human dose escalation study of SL-172154 (SL03-OHD-101) and this Phase 1b study of SL-172154 (SL03-OHD-105) due to the fact that these histologies have a high percentage of tumors with detectable CD47 expression (TCGA data; [Wang, 2015; Brightwell, 2016]). A tissue microarray of 265 tissues from patients with ovarian, primary peritoneal, and fallopian tube cancers were analyzed by immunohistochemical analysis for CD47 expression and expression was detected in 210 of 265 cases (79%). Furthermore, CD47 is a tumor-associated antigen with higher levels of expression in epithelial ovarian cancer cells compared with normal ovarian cells [Li, 2017]. High CD47 expression is associated with poor response to primary therapy in ovarian cancer [Brightwell, 2016]. Finally, ovarian cancer is characterized by peritoneal metastasis which is facilitated by crosstalk between tumor cells and other cells in the tumor microenvironment (TME). Tumor-associated macrophages (TAMs) constitute over 50% of cells within the peritoneal TME and malignant ascites and are potential targets for therapy [Gupta, 2018]. This rationale is supported by the results of a Phase 1 study of an anti-CD47 antibody, Hu5F9-G4, in which monotherapy activity was reported in 2 (partial responses) out of 13 patients with ovarian cancer [Sikic, 2019]. Given that the APC is hypothesized to be the primary target of SL-172154, the unique immune contexture of ovarian and related cancers in conjunction with their high tumor CD47 expression makes these histologies particularly suitable for clinical investigation.

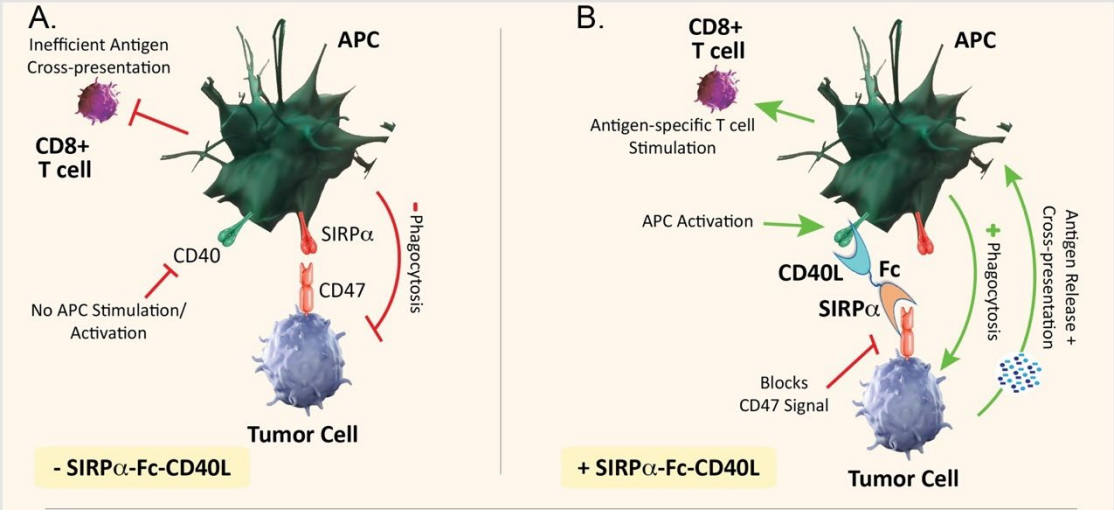
1.4 SL-172154

1.4.1 Mechanism of Action

The apparently non-overlapping roles of CD47/SIRPα and CD40/CD40L in bridging innate and adaptive cancer immunotherapy suggests that the two pathways could be complimentary or synergistic in combination and have the potential to improve survival in patients with ovarian and related cancers. In an attempt to improve upon current paradigms, Shattuck Labs has developed a bifunctional fusion protein 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. Superior preclinical activity compared to the separate administration of two individual antibodies against identical targets were reported [de Silva, 2020]. As a result, Shattuck sought to develop a SIRPα-Fc-CD40L ARC™ fusion protein as a means to target these pathways with a single compound. Tumor-expressed CD47 can provide a "do not eat me" signal to APCs, including macrophages and DCs, through the binding of SIRPα [Figure 2A]. SIRPα-Fc-CD40L (SL-172154) can relieve this inhibitory signal through blockade of CD47 with the SIRPα domain of the ARC, while simultaneously providing a co-stimulatory signal via CD40 [Figure 2B]. This enhances tumor phagocytosis, APC activation, increased antigen processing/presentation, and induction of an antitumor antigen-specific CD8+ T cell response.

The preclinical data supporting the translational study of SL-172154 in human subjects with cancer is described in detail in the Investigator's Brochure (IB). The mechanism of action, *in vitro* and *in vivo* pharmacology, toxicokinetics, summary of clinical data, and the rationale for investigation are briefly summarized below.

Figure 2. SIRPα-Fc-CD40L (SL-172154) Mechanism of Action



A. Tumor expressed CD47 can bind SIRPα and suppress APCs (i.e., macrophages and DCs)
B. SIRPα-Fc-CD40L directly induces APC activation through CD40 stimulating an antigen-specific CD8 T cell response.

1.4.2 Summary of Nonclinical Data

A brief summary of the nonclinical data is provided in the following section. SIRPα-Fc-CD40L has demonstrated functional activity both *in vitro* and *in vivo* [de Silva, 2020]. Detailed information is presented in the SL-172154 IB.

1.4.3 *In Vitro* Pharmacology Studies

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 (K_D values of 0.628 nM and 4.74 nM, respectively) as well as a slow off rate, indicating a longer on target resident time. This longer resident time could be of benefit in the 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.

Tumor-macrophage engulfment assays were performed to determine if SL-172154 similarly potentiates phagocytosis of tumor cells by macrophages in combination with ADCC-competent antibodies including rituximab, cetuximab, trastuzumab, an anti-CD38 antibody, an anti-SLAM-F7 antibody, and an anti-BCMA antibody. Generally, across the antibodies and tumor cell lines, macrophage mediated phagocytosis was enhanced with the Sl-172154/antibody combination in comparison to Sl172154 alone or antibody alone.

In other tumor-macrophage engulfment assays, both calreticulin and Fc receptor engagement was demonstrated to be required for efficient phagocytosis of CD20+ B-cell lymphoma cells by the combination of Sl-172154 and rituximab. Addition of a calreticulin-blocking peptide confirmed the importance of Fc interactions for Fc-competent targeting antibodies and provided evidence that the initiation of phagocytosis by Sl-172154 was driven by the SIRPα domain [de Silva, 2020].

1.4.4 *In Vivo* Pharmacology

It has been previously reported that CD47 blockade *in vivo* leads to rapid upregulation of CD86 and MHC-II on splenic CD8α+ DCs [Yi, 2015]. In mice given a single intravenous (IV) injection of the murine surrogate of SL-172154 (mSIRPα-Fc-CD40L), rapid and durable activation and proliferation of both CD4+ and CD8+ splenic DCs was observed, which matched the duration of activation observed with murine CD40 antibodies [de Silva, 2020]. Furthermore, CD40 stimulation had a more prolonged effect on the same DC populations.

In preclinical murine studies using subcutaneous CT26 colorectal carcinoma tumors, mSIRPα-Fc-CD40L given via intraperitoneal injection enhanced tumor control and rejection of both primary and re challenge tumors. These data suggest that mSIRPα-Fc-CD40L elicits an antitumor response and programs a durable immunological memory response. The decrease in tumor size associated with mSIRPα-Fc-CD40L was statistically significant compared to vehicle, murine anti-CD40, murine anti-CD47, and anti-CD47/anti-CD40 in combination. Approximately 63% of mSIRPα-Fc-CD40L treated mice rejecting the initial tumor and 60% rejected the subsequent tumor re-challenge. In comparison, in the anti-CD40/anti-CD47 combination group, 33% rejected the primary tumor, and neither of the 2 animals available for assessment rejected the secondary tumor. Additionally, in CT26 tumor-bearing mice, immune profiling for antigen-specific CD8+ T cells by flow cytometry demonstrated that anti-tumor activity of mSIRPα-Fc-CD40L was accompanied by an expansion of antigen-specific CD8+ T cells. To characterize the mediators of the antitumor response, mice were depleted of CD8+ cells, CD4+ cells or both, followed by mSIRPα-Fc-CD40L treatment. The tumor growth inhibition of mSIRPα-Fc-CD40L was most significantly impacted by depletion of CD8+ T cells suggesting that the *in vivo* antitumor activity of mSIRPα-Fc-CD40L is heavily dependent on CD8+ T cells.

1.4.5 Toxicology Studies in Non-Human Primates

Two repeat IV dose studies in cynomolgus monkeys, utilizing once-weekly administration, of up to 5 weeks in duration evaluated SL-172154 doses of 0 (vehicle), 0.1, 1, 10, and 40 mg/kg. Dose-dependent receptor occupancy was observed with up to > 90% CD40 receptor occupancy on PBMCs and up to ~80% CD47 receptor occupancy on erythrocytes. Following IV administration of SL-172154, transient and reversible decreases in platelets (minimal to moderate) and lymphocytes (mild) were observed. Additionally, the increased splenic weight and lymphoid cellularity observed in the Good Laboratory Practice (GLP) study are consistent with a pharmacological effect; these findings were reversed following the 4-week off-dose period.

While SL-172154 was shown to bind to CD47 receptors on monkey erythrocytes *in vivo*, 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. SL-172154's lack of hemolysis of erythrocytes is likely because it does not engage effector Fc gamma receptors unlike CD47 targeting antibodies such as Hu5F9-G4 (magrolimab) [Sikic, 2019].

The principal SL-172154-related toxicity finding in the GLP toxicology study was the occurrence of dose-dependent infusion-related reactions (IRRs) at 10 mg/kg (2 of 6 animals) and 40 mg/kg (6 of 10 animals) during the third or fourth doses of SL-172154. These IRRs were coincident with the emergence of anti-drug antibodies (ADA) and complement activation. ADA

was present in all SL-172154-treated monkeys by Day 15 (Dose 3) and complement activation is commonly associated with the presence of ADA. Emergence of ADA in the non-human primate studies was expected given that SL-172154 is based on human amino acid sequences which have 82% identity to the corresponding cynomolgus sequences.

In the GLP toxicity study in cynomolgus monkeys, there were no findings in the safety pharmacology endpoints assessing the central and peripheral nervous systems, respiratory system, or cardiovascular system.

1.4.6 Toxicokinetic Studies

In two studies in cynomolgus monkeys, systemic exposure, as evaluated by C_{max} and AUC, increased in a greater than dose-proportional manner on Day 1. Clearance of SL-172154 from serum decreased as the dose increased, suggesting a saturable clearance mechanism. In the GLP Study, the mean terminal elimination half-life (t½) on Day 1 was approximately 0.4 hours following a 1.0 mg/kg dose, and approximately 1 hour after the 10 and 40 mg/kg doses. Potential explanations for rapid drug clearance include an antigen sink due to the ubiquitous expression of CD47 on peripheral blood cells (i.e., RBC, platelets, and PBMCs), target-mediated uptake at early time points with trafficking of cells (e.g., PBMCs), and binding of drug to peripheral tissues. In both studies, compared to Day 1, systemic exposure to SL-172154 following multiple once-weekly IV infusions was reduced on Day 29, with the decrease appearing more marked in the GLP toxicity study compared to the dose-range finding study. As all monkeys were positive for ADA by Day 15 (Dose 3) in both studies, the production of ADA to SL-172154 was likely the primary factor contributing to the lower serum SL-172154 concentrations observed on Day 29 compared to Day 1.

1.4.7 Summary of Clinical Data for SL-172154

A brief summary of the clinical data is provided for Study SL03-OHD-101. Detailed information is presented in the current SL-172154 IB. As of the data cut-off of 12 September 2022, SL-172154 has been administered IV as monotherapy to 26 subjects with ovarian cancer.

Study SL03-OHD-101 is a Phase 1, first-in-human, open-label, multicenter, dose escalation study to investigate the safety, pharmacokinetic (PK), pharmacodynamic (PD), and clinical activity of SL-172154 administered to subjects with platinum-ineligible ovarian, fallopian tube, or primary peritoneal cancers. SL-172154 was administered on two schedules. In dosing Schedule 1, SL-172154 was administered on Days 1, 8 and 15 of a 28-day cycle and then every 2 weeks (Days 1 and 15) in 28-day cycles starting at Cycle 2. In dosing Schedule 2, SL-172154 was administered weekly (i.e., Days 1, 8, 15 and 22 in 28-day cycles). Twenty-six subjects were enrolled into 6 dose cohorts where SL-172154 was administered as a 30, 60 or 120-minute infusion in ascending doses of 0.1 mg/kg (n=3, Schedule 1), 0.3 mg/kg (n=3, Schedule 1), 3.0 mg/kg (n=2, Schedule 1), 0.3 mg/kg (n=3, Schedule 2), 1.0 mg/kg (n=4, Schedule 2), 3.0 mg/kg (n=6, Schedule 2), and 10 mg/kg (n=5, Schedule 2). Subjects treated with IV SL-172154 from 0.1mg/kg through 3.0 mg/kg cleared the 28-day dose-limiting toxicity (DLT) evaluation period with no DLTs. 1 DLT (Grade 3 alanine aminotransferase [ALT] increased) has been reported in the 10 mg/kg cohort.

Most subjects (96%) reported adverse events (AEs) with the most frequently (> 20% of subjects) reported AEs being IRR (17 subjects, 65%), fatigue (11 subjects, 42%), nausea (9 subjects, 35%), constipation (6 subjects, 23%) and diarrhea (6 subjects, 23%). AEs considered related to

SL-172154 per investigator assessment were reported in 23 subjects (89%), with the most common (> 15% of subjects) being IRR, fatigue, nausea and decreased appetite. IRRs are further described in Section 1.7.1. Eleven subjects (42%) reported at least one Grade 3/4 AE. Of the Grade 3/4 AEs, anemia, aspartate aminotransferase (AST) increased, ALT increased, back pain, thrombocytopenia, IRR, muscular weakness (all in 1 subject), and lymphopenia (2 subjects) were considered to be related to SL-172154. There were 6 subjects with serious adverse events (SAEs), none of which were considered drug-related. No Grade 5 AEs have been reported and no AEs led to permanent discontinuation of SL-172154.

The PK parameters for SL-172154 have been estimated in 23 subjects receiving 0.1 mg/kg (n=3), 0.3 mg/kg (n=6), 1.0 mg/kg (n=4), 3.0 mg/kg (n=5) and 10 mg/kg (n=5) in Study SL03-OHD-101. For doses > 0.1 mg/kg that have been evaluated, serum SL-172154 concentrations were above the lower limit of quantification (LLOQ) for 2 to 25 hours after the start-of-infusion. Following a dose of ≥ 1.0 mg/kg, concentrations appear to decline in a weakly biphasic manner. In general, serum SL-172154 C_{max} and AUC_{last} values increased with increasing dose, with evidence of non-linearity noted by a positive relationship between dose-normalized exposure versus the administered dose. Additionally, marked variability in C_{max} and AUC values at dose levels ≥ 1.0 mg/kg was noted, which is most likely due to dosing interruption secondary to infusion-related reactions. Clearance and volume of distribution decreased as a function of dose between 1.0 mg/kg and 3.0 mg/kg. For doses ≥ 0.3 mg/kg, geometric mean values indicated a short serum half-life (less than 1 hour). Preliminary evidence of decreasing clearance with increasing dose may be due to target mediated drug disposition. In general, subject serum concentrations and exposure (i.e., C_{max}, AUC) were within the same magnitude on Cycle 1, Days 1 and 15 and Cycle 2, Day 1, indicating no accumulation and no time-dependence on SL-172154 PK. Also, serum SL-172154 C_{max} and AUC_{last} values increased with increasing dose in a greater than dose proportional manner. Clearance was similar between Cycle 1, Day 15 and Cycle 2, Day 1. The volume of distribution after repeat dosing was lower than that following a single dose.

In summary, SL-172154 has demonstrated an AE profile that has been manageable and acceptable in the context of benefit-risk. As of the data cut-off, no clinically significant findings were identified from the two ongoing clinical trials. One DLT at the 10 mg/kg dose has been observed and no AE led to permanent drug discontinuation as of the data cut-off date for the SL03-OHD-101 study.

Hematologic toxicities have been reported with Fc-active CD47 antibodies or SIRPα-Fc fusion proteins, while hepatotoxicity and cytokine release syndrome (CRS) have been reported with CD40 agonist antibodies. Of note, no event of CRS has been noted in the clinical trial as of 23 April 2022. Treatment-related Grade 3 ALT/AST elevations were reported in one subject treated at 10 mg/kg. The ALT/AST elevations normalized with withholding of treatment. Overall, the benefit-risk profile of SL-172154 supports the continued investigation of SL-172154 in subjects with advanced cancer.

1.5 Rationale for Combination Therapies

SL-172154 is a novel Fc-fusion protein consisting of human SIRPα and CD40L (SIRPα–Fc-CD40L). SL-172154 not only inhibits CD47/SIRPα axis but it also augments cross presentation of antigens by APC to T cells through the costimulatory role of CD40L, thus bridging innate and adaptive immunity. SL-172154 potentiates macrophage phagocytosis when

combined with agents that induce immunogenic tumor cell death [SL-172154 IB]. It is likely that a combinatorial approach to overcoming immune suppression will be required to provide benefit from immune-targeting agents in EOCs [Leary, 2021]. Cytotoxic agents initiate a cascade of events by initiating tumor cell apoptosis, thus providing an 'eat me' signal and exposing neighboring macrophages to tumor antigens. In this context, SL-172154 blocks the SIRPα/CD47 'do not eat me' axis and simultaneously provides a co-stimulatory signal to the macrophages within the tumor microenvironment, enhancing their ability to process tumor antigens and present them to CD8+ T cells. In preclinical studies, the combination of these 'eat me' and 'do not eat me blocking' signals synergize and further increase macrophage mediated phagocytosis of tumor cells.

1.5.1 Rationale for SL-172154 Administered with Pegylated Liposomal Doxorubicin (PLD)

Preclinical data has demonstrated that pegylated liposomal doxorubicin (PLD) induces immunogenic cell death as evidenced by increased extracellular ATP levels, secreted HMGB1, induction of calreticulin (CRT) and CRT translocation to the plasma membrane [Bezu, 2015; Solari, 2020]. Similarly, doxorubicin has been shown to further promote immune priming by enhancing antigen presentation [Zitvogel, 2013] and modifying the suppressive microenvironment by increasing infiltration of active T cells [Hao, 2018]. Thus, combining SL-172154 with PLD may concurrently 1) enhance stimulation of phagocytosis by induction of prophagocytic proteins and inhibition of the CD47/SIRPα checkpoint along with 2) augmentation of antigen presentation by APC to T cells via costimulation of the CD40L/CD40 pathway.

In preclinical murine studies using subcutaneous CT26 colorectal carcinoma tumors, mSIRPα-Fc-CD40L (intraperitoneal) in combination with intravenous doxorubicin resulted in enhanced antitumor response. Combination therapy of mSIRPα-Fc-CD40L with paclitaxel or doxorubicin both resulted in greater tumor growth inhibition in comparison to either monotherapy control. At Day 18, the mean tumor size was smaller in each combination therapy group with statistical significance achieved for the combination with doxorubicin (p=0.0195). While 25% of mSIRPα-Fc-CD40L + doxorubicin treated animals completely rejected the tumor implants, there were no complete rejections noted in the mSIRPα-Fc-CD40L + paclitaxel group. This synergistic activity may be due to chemotherapy-induced tumor cell death resulting in increased tumor visibility to APCs (e.g., macrophages and dendritic cells) and subsequent enhanced phagocytosis activity mediated by mSIRPα-Fc-CD40L.

There are no highly effective therapies in the platinum-resistant/refractory population, although non-platinum agents have demonstrated modest antitumor efficacy in a subset of these patients. PLD is a standard of care option for the treatment of platinum-resistant ovarian cancer (PROC; [Davis, 2014]) and is therefore appropriate to combine with SL-172154 in this Phase 1b trial. Single-agent PLD has been extensively studied in this patient population, demonstrating an objective response rate (ORR) of 10 to 20%, median PFS of 2.1 to 3.7 months, and overall survival (OS) ranging from 8.4 to 16.8 months [Gordon, 2001; Lawrie, 2013; Pujade-Lauraine, 2021]. Based on the proposed mechanism of action, we hypothesize that that combination of PLD with SL-172154 may provide added clinical benefit relative to either agent alone.

1.5.2 Rationale for SL-172154 Administered with Mirvetuximab Soravtansine (MIRV)

Folate receptor alpha (FRα) is a glycosylphosphatidylinositol-anchored cell surface protein encoded by the folate receptor 1 (FOLR1) gene. FRα internalizes folate, which is an essential cofactor for one-carbon transfer reactions that are required for DNA and ribonucleic acid (RNA) synthesis, cell growth, and proliferation. Published studies have demonstrated FRα overexpression by immunohistochemistry (IHC) in various epithelial tumors, particularly the serous and endometrioid histologic subtypes of ovarian and endometrial cancers [Garin-Chesa, 1993; Allard, 2007; Dainty, 2007; Brown Jones, 2008; Kalli, 2008; Scorer, 2010; Crane, 2012; Ab, 2015]. Several additional studies have validated FRα as a target in serous EOC. First, quantitative polymerase chain reaction studies show ubiquitous FRα mRNA expression in serous EOC [Hoskins, 1998; Hough, 2001; Hanker, 2012] and high levels of FRα mRNA correlate with poor response to chemotherapy and decreased disease-free survival [Chen, 2012]. Second, it has been demonstrated that recurrent tumors retain FRα expression comparably to primary tumors as shown by serial biopsy sampling and IHC [Kalli, 2008; Crane, 2012]. Third, studies with FRα-specific imaging agents have demonstrated real-time FRα expression at primary and metastatic tumor sites [Garin-Chesa, 1993; Fisher, 2008; van Dam, 2011; Garcia, 2013; Gaillard, 2018]. Because of its tumor-specific expression and capacity to internalize small and large molecule ligands, FRα has emerged as a biologically rational target for antibody drug conjugate (ADC) therapy. ADCs combine the specificity of monoclonal antibody (mAb) to tumor antigens with the extraordinary cytotoxicity of maytansine derivatives, which are potent antimicrotubule agents that target proliferating cells. MIRV consists of the chimeric anti-FRα mAb M9346A attached via a cleavable linker to the cytotoxic maytansinoid, DM4.

The internalization of MIRV leads to the apoptosis of target ovarian tumor cells that overexpress FRα. The hypothesis that SL-172154, by blocking the SIRPα/CD47 axis, would increase the macrophage-mediated phagocytosis of these apoptotic cells is supported by *in vitro* phagocytosis assays using human monocyte-derived macrophages and human ovarian cancer cell lines. These assays demonstrated that individually, SL-172154 and MIRV stimulated macrophage-mediated phagocytosis of KB, IGROV1, and OV90 ovarian cancer cells, and the combination of the two agents further enhanced the phagocytic activity.

Interestingly, in MESOV ovarian cancer cells (which express low levels of FRα and high levels of CD47 and calreticulin), SL-172154 alone stimulated phagocytosis whereas MIRV alone did not; combining the two agents enhanced phagocytosis above that seen with SL-172154 alone. These data suggest that SL-172154 may broaden the activity of MIRV to tumor cells expressing low FRα levels.

Single-agent MIRV has recently been studied in a randomized, open-label Phase 3 comparing MIRV and investigator's choice (IC) chemotherapy in patients with platinum-resistant EOC who had received 1 to 3 prior lines of therapy and whose tumors were positive for FRα. While the primary endpoint, PFS, did not reach statistical significance in either the intent-to-treat (ITT) or the FRα high population, superior outcomes for MIRV over chemotherapy were observed in all secondary endpoints in the FRα high population including improved ORR (24% versus 10%), CA-125 responses, and patient-reported outcomes. Importantly, confirmed responses were seen across FRα levels, with a confirmed ORR in the ITT population being higher for MIRV than for IC chemotherapy (22% versus 12%, P=0.015) and correlated with improved CA-125 responses (51% versus 27%, P< 0.001). These data indicate that MIRV was generating a cytotoxic signal even in ovarian tumors expressing medium and low levels of FRα expression. The *in vitro*

phagocytosis data demonstrates that SL-172154 can synergize with this cytotoxic signal. Thus, by increasing tumor phagocytosis and programming a durable immunologic memory response, SL-172154 may enhance MIRV anticancer effects, including in tumors expressing lower FRα levels. MIRV demonstrated a more manageable safety profile than chemotherapy with fewer treatment-related Grade ≥ 3 AEs, and fewer events leading to dose reduction and treatment discontinuation in comparison with chemotherapy [Moore, 2021]. Two additional phase 3 studies for MIRV in PROC are ongoing (IMGN853-0416 and IMGN853-0417). Taken together, these data suggest that both PLD and MIRV are appropriate to combine with SL-172154 in this Phase 1b trial in patients with platinum-resistant EOC, a population with high unmet need.

1.6 Dose and Schedule Rationale

1.6.1 Pegylated Liposomal Doxorubicin (PLD)

The approved dose of PLD in the US, Canada, and Europe is 50 mg/m^2 administered IV every 4 weeks; however, 40 mg/m^2 every 4 weeks is commonly used in clinical practice and in clinical trials [Gordon, 2001]. This latter dose is associated with significantly reduced frequencies of AEs, particularly hand-foot syndrome, and a lower frequency of dose reductions with a similar ORR [Markman, 2000]. The dose of 40 mg/m^2 was used in the AURELIA study which formed the basis of approval of bevacizumab in platinum-resistant ovarian cancer [Pujade-Lauraine, 2014]. In Study SL03-OHD-105, the PLD dose will be 40 mg/m^2 administered every 4 weeks.

1.6.2 Mirvetuximab Soravtansine (MIRV)

The selection of the Phase 2 dose of 6.0 mg/kg adjusted ideal body weight (AIBW) IV every 3 weeks (Q3W) was based on data obtained from Study IMGN853-0401, a first-time-in-human study designed to establish the maximum tolerated dose (MTD) and determine the recommended Phase 2 dose (RP2D) of MIRV when administered IV as a single-agent in adult patients with FRα-positive solid tumors who have relapsed or are refractory to standard therapies. This dose and schedule were deemed well tolerated in patients with PROC, based on the results from 243 patients who received MIRV in Study IMGN853-0403. In addition, this full dose and schedule of MIRV was able to be combined with full doses of each of the combination agents in Study IMGN853-0402. Therefore, 6.0 mg/kg AIBW IV Q3W was chosen for evaluation in Study SL03-OHD-105 of subjects with platinum-resistant ovarian cancer. For more information, please see the MIRV IB.

1.6.3 SL-172154

In Study SL03-OHD-101, SL-172154 monotherapy was administered on two schedules. In dosing Schedule 1, SL-172154 was administered on Days 1, 8 and 15 of a 28-day cycle and then every 2 weeks (Days 1 and 15) in 28-day cycles starting at Cycle 2. In dosing Schedule 2, SL-172154 was administered weekly (i.e., Days 1, 8, 15 and 22 in 28-day cycles). As of 12 September 2022, 26 subjects have been enrolled into 6 dose cohorts where SL-172154 was administered as a 30, 60 or 120-minute infusion in ascending doses of 0.1 mg/kg (n=3, Schedule 1), 0.3 mg/kg (n=3, Schedule 1), 3.0 mg/kg (n=2, Schedule 1), 0.3 mg/kg (n=3, Schedule 2), 1.0 mg/kg (n=4, Schedule 2), 3.0 mg/kg (n=6, Schedule 2), or 10 mg/kg (n=5, Schedule 2). Across these dose levels, SL-172154 has been well tolerated on both schedules with one DLT noted in the 10 mg/kg cohort.

The starting dose of 3.0 mg/kg in SL03-OHD-105 is supported by safety data from the Study SL03-OHD-101 study (Section 1.4.7) in which 4 subjects receiving 1.0 mg/kg and 6 subjects receiving 3.0 mg/kg of SL-172154 once-weekly have cleared the DLT evaluation period with no DLTs reported. 1 DLT (Grade 3 ALT increased) was reported in 1 of the 5 DLT-evaluable subjects in the 10 mg/kg cohort.

For Study SL03-OHD-105, a less intense schedule of SL-172154 administration will be explored with each of the combination agents. SL-172154 will be administered by IV infusion on Days 8 and 15 in combination with PLD (40 mg/m^2, IV, Day 1 of each 28-day cycle) or MIRV (6.0 mg/kg AIBW, IV, Day 1 of each 21-day cycle). This dosing schedule was empirically selected. PLD or MIRV dosing will be staggered with SL-172154, with the assumption that peak tumor concentrations and maximal cytotoxicity for PLD or MIRV occur within 3 to 7 days postinfusion [Northfelt, 1996; Harrington, 2001; Gabizon, 2002; Charrois, 2003] [Al-Saden, 2018; Brand, 2018; Heo, 2019]. Therefore, SL-172154 is provided on Days 8 and 15 of each cycle at a point when peak concentrations of the cytotoxic agent are beginning to wane and immune cells have infiltrated the tumor microenvironment in the setting of tumor cell destruction and phagocytosis of cell debris [Heath, 2021]. It is hypothesized that during this window, tumor cell phagocytosis, antigen processing and presentation by APCs can be maximized by SL-172154. Another important consideration is that concurrent dosing of MIRV or PLD with SL-172154 may ablate macrophages and immune effector populations by exposing them to high concentrations of the cytotoxic agent [Takayama, 2020].

1.7 Potential Risks and Benefits of SL-172154

1.7.1 Potential Risks

Potential risks to subjects in the study are addressed by vigilant monitoring and safety guidelines as outlined below. The risks (evaluation of safety and tolerability) and potential benefits (evaluation of anti-tumor activity) of SL-172154 monotherapy administered IV are being assessed in the Phase 1 first-in-human clinical trial, SL03-OHD-101, in subjects with relapsed, refractory ovarian cancer and provide relevant safety information for this study. Therefore, the assessment of potential safety concerns is based on (1) the published safety profiles of other CD40 agonists and CD47-SIRPα targeting agents; (2) preclinical toxicology data from cynomolgus monkeys; and (3) emerging safety data from the SL03-OHD-101 study (Section 1.4.7).

Adverse events reported with other CD47-SIRPα targeting agents and CD40 agonists: Anti-CD47 monoclonal antibodies and SIRPα-Fc fusion proteins have been evaluated in patients with hematologic malignancies and solid tumors. AEs that have been observed include anemia, hemagglutination, hyperbilirubinemia, lymphopenia, thrombocytopenia, neutropenia, elevation of hepatic transaminases, fatigue, headache, fever, and IRRs [Chao, 2019; Sikic, 2019; Eladl, 2020]. A common AE reported with CD40 agonist monoclonal antibodies was transient IRRs characterized by fever, rigors, chills, and other symptoms such as headache and back pain. Rare events of CRS were noted. Other AEs include 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 CD47-targeted agents or CD40

antibodies but remain a potential concern [Vonderheide, 2001; Vonderheide, 2007; Vonderheide, 2013a; Vonderheide, 2013b; Nowak, 2015; Chao, 2019; Sanborn, 2019; Eladl, 2020].

Toxicities observed with SL-172154 in preclinical toxicology studies in cynomolgus monkeys: The underlying etiology of the SL-172154-related effects observed in cynomolgus monkeys is most likely due to a combination of both the pharmacologic activity of the molecule and immunologic reactions to SL-172154 administration. The following are potential contributory factors to the dose-dependent IRRs observed in monkeys during or following the third to the fifth dose of SL-172154: (1) development of ADA and downstream complement activation; (2) elevations in serum cytokines; and (3) postdose changes in peripheral blood lymphocyte counts. Emergence of ADA in cynomolgus monkeys was expected given that SL-172154 is based on human amino acid sequences which have 82% identity to the corresponding cynomolgus sequences. 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.

Safety profile of SL-172154 in the context of PLD: The combination of SL-172154 and PLD has not previously been studied in humans. The most common AE (> 20%) reported with PLD in patients with ovarian cancer includes asthenia, fatigue, fever, anorexia, nausea, vomiting, stomatitis, diarrhea, constipation, hand-foot syndrome, rash, neutropenia, thrombocytopenia, and anemia [DOXIL USPI, 2019]. Serious, life-threatening, and fatal IRRs can occur with PLD. Across multiple studies of PLD monotherapy in various solid tumors, 11% of patients had IRRs with the majority of infusion-related events occurred during the first infusion. Doxorubicin hydrochloride can cause myocardial damage, including acute left ventricular failure. The risk of cardiotoxicity is 11% when the lifetime cumulative anthracycline dose (not limited to PLD) approaches 450 to 550 mg/m^2. Complete information for PLD to be used in Study SL03-OHD-105 may be found in the current PLD prescribing information (i.e., Doxil USPI, Caelyx product monograph, or Caelyx SmPC).

Fatigue and IRRs have been reported following administration with CD47-SIRPα targeting agents as well as with CD40 agonist monoclonal antibodies. In addition, IRRs, fatigue, nausea, constipation and diarrhea are the most frequently reported AEs associated with IV SL-172154 monotherapy in the SL03-OHD-101 study (Section 1.4.7). Thus, potential overlapping toxicities between SL-172154 and PLD include IRRs, fatigue, nausea, constipation, diarrhea and cytopenias. It is not expected that SL-172154 would exacerbate any other toxicities commonly observed with PLD in this patient population.

Safety profile of SL-172154 in the context of MIRV: The combination of SL-172154 and MIRV has not previously been studied in humans. Safety information for MIRV is summarized in the reference safety information (RSI) provided in the MIRV IB. Single-agent MIRV safety data are available for 599 patients, which includes 137 patients treated with single-agent 6.0 mg/kg MIRV in the expansion phase of Study IMGN853-0401, 243 patients treated with single-agent 6.0 mg/kg MIRV in the pivotal stage of Study IMGN853-0403, 112 patients treated with single-agent 6.0 mg/kg MIRV in Study IMGN853-0416, and 106 patients treated with single-agent 6.0 mg/kg MIRV in Study IMGN853-0417. All-causality, treatment-emergent adverse events (TEAEs) by preferred term observed in > 10% of patients treated with monotherapy MIRV in Study IMGN853-0401 (expansion phase) were diarrhea, vision blurred, AST increased, nausea, vomiting, headache, dry eye, keratopathy, decreased appetite, ALT increased, and peripheral neuropathy. The majority of TEAEs were Grade ≤ 2. The nature,

frequency, and severity of TEAEs were consistent with the safety profile of MIRV, and there were no clinically significant differences between the EOC and endometrial cohorts. The most common Grade ≥ 3 TEAEs were vomiting and abdominal pain (8 patients each, 5.8%) and fatigue and dehydration (7 patients each, 5.1%). There was no clinically significant difference in either the nature or severity of Grade ≥ 3 TEAEs experienced by patients in the EOC and endometrial cancer cohorts. Complete information for MIRV to be used in Study SL03-OHD-105 may be found in the MIRV IB and Elahere USPI.

Thus, potential overlapping toxicities between SL-172154 and MIRV include IRR, fatigue, nausea, diarrhea and cytopenias. It is not expected that SL-172154 would exacerbate any other toxicities commonly observed with MIRV in this patient population.

Potential risks of SL-172154 administration in SL03-OHD-105 study

The potential risks noted below are based on observations in the SL-172154 toxicology studies, the Phase 1 clinical studies (as of 12 September 2022), or select toxicities reported with other CD47 or CD40-targeted agents. The RSI for SL-172154 is provided in the SL-172154 IB.

1) IRRs and CRS: In Study SL03-OHD-101, 17 of the 26 total subjects (65.4%) had 44 treatment-related IRR events. Twelve subjects (46.2%) had IRR events that led to infusion interruption. The median number of IRR events per subject was 2 with a range of 1 to 9. All treatment-related IRR events were Grade 1 or 2, except for 1 subject dosed with 3.0 mg/kg on Schedule 1 who had a Grade 3 event. No IRR was deemed to be serious. All IRR events resolved with no sequelae. Symptomatic manifestations of the IRR events variably include fever, chills, rigors, back pain, rash, hyper/hypotension, tachycardia, nausea, and visual symptoms. Most of the IRRs were reported to be relatively short in duration and occurred during the infusion or immediately postinfusion. No delayed IRRs were noted. Collectively, the frequency of subjects experiencing IRR events increased with increasing dose. However, at all dose levels IRR events were readily managed with temporary interruption of the infusion, treatment medications potentially including steroids, and/or slowing the rate of SL-172154 infusion at re-start; the majority of subjects received premedications (such as diphenhydramine, famotidine or other available histamine 2 (H2) receptor antagonist, and acetaminophen) prior to their next dose. Subjects receiving 10 mg/kg SL-172154 received primary prophylactic premedication beginning on Cycle 1 Day 1. All subjects received their full scheduled dose and no subjects have discontinued dosing of SL-172154 secondary to IRR. The constellation of symptoms, signs, and timing of the IRR events have not been consistent with CRS. This is supported by the absence of a significant IL-6 or TNFα response in subjects who have experienced IRR.

   The steps taken to minimize the risks associated with IRRs and CRS include administration in an outpatient oncology clinic or inpatient setting by experienced health care providers, mandatory premedication prior to SL-172154 administration for IRR prophylaxis, lengthening the SL-172154 infusion duration in Study SL03-OHD-105, management guidelines (e.g., SL-172154 infusion adjustments/interruptions, rescue treatments), and extended monitoring when indicated. Recommendations to identify and manage IRRs and CRS are outlined in the Toxicity Management Guidelines section of the protocol (Section 3.7.1).

2) Immunogenicity: 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 SL03-OHD-105 will 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 and neutralization may be characterized.

3) Hematologic toxicity: Anemia and thrombocytopenia have been reported with CD47 targeted agents that have an active Fc-domain (e.g., magrolimab, TTI-621, TTI-622). Interference with crossmatch has been reported with some CD47 targeted agents (e.g., magrolimab, ALX-148). G3/4 hematologic toxicities have only been noted in the 10mg/kg dose level of SL-172154 and include lymphopenia (2/5 subjects), anemia (1/5 subjects) and thrombocytopenia (1/5 subjects) and all were considered treatment-related. The subject with anemia had a baseline medical condition of anemia. Following the data-cut off, there has been one event of G3 neutropenia in the 3.0 mg/kg dose level. In Study SL03-OHD-105, complete blood counts (CBCs) will be assessed frequently during treatment to monitor for hematologic toxicity. Supportive therapy will be provided according to standard medical practice; dose modifications for hematologic toxicity for each agent will follow according to recommendations provided in the protocol and product information for PLD or MIRV. To date, hemolysis has not been observed in SL03-OHD-101. The absence of hemolytic anemia is likely due to the inactive Fc domain of SL-172154 [Chow, 2019]. To investigate the possible risk of interference with pretransfusion testing due to SL-172154, blood phenotyping, type and screen (ABO/Rh), and direct antiglobulin test (DAT) was performed before and following exposure to SL-172154 in SL03-OHD-101. No interference with pretransfusion testing (as evidenced by ability to resolve crossmatch) has been observed in subjects treated to date in SL03-OHD-101.

4) Immune-Related Adverse Events (irAEs): As experience with CD47 and CD40 targeted agents has expanded, it has become apparent that the typical irAEs described with cytotoxic T cell lymphocyte-associated antigen 4 (CTLA-4) and PD-1 inhibitors are not being observed with these agents. irAEs have not been reported in the current safety profile of SL-172154. Nevertheless, it is unknown if irAEs resulting from a breakdown of self-tolerance could occur with SL-172154 administration with PLD or with MIRV.

In summary, this Phase 1 study has taken the following precautions to minimize potential risks: (1) the study is being conducted at centers that have extensive experience with this class of agents and the management of associated toxicities; (2) the starting dose of SL-172154 is a dose that has been safely administered to patients with ovarian cancer; (3) patients treated at each SL-172154 dose level would be observed for the duration of the DLT assessment period to confirm tolerability of the combination dose; (4) increasing the SL-172154 infusion duration time, (5) administration of SL-172154 in an oncology treatment center/hospital allows for close monitoring of subjects for AEs and for timely action; (6) guidelines for management of AEs based on established guidelines [Lee, 2014; Haanen, 2017; Puzanov, 2017; Rosello, 2017b; Brahmer, 2018; Porter, 2018; Lee, 2019] are provided in the protocol; and (7) a Safety Monitoring Committee (SMC) will meet at least monthly (or as data warrant) during dose escalation to review emerging toxicities and assess the impact of these toxicities on study conduct; the SMC will continue with ongoing review of safety data during dose expansion. As dose escalation in SL03-OHD-105 will be informed by data from SL03-OHD-101, safety and PK data from SL03-OHD-101 will be shared with the SMC for SL03-OHD-105 to ensure that the SMC is fully informed of the IV SL-172154 monotherapy data. Doses explored in SL03-OHD-105 will not exceed the highest dose cleared for safety in SL03-OHD-101.

1.7.2 Potential Benefits

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 clinical benefits of SL-172154 in combination with either PLD or MIRV in subjects with platinum-resistant ovarian, primary peritoneal, or fallopian tube cancers are unknown as no clinical trials have been conducted to date.

SL-172154 targets both the CD40/CD40L and the SIRPα/CD47 axes. There are currently no reported multitargeted agents or trials for CD47 inhibitors in combination with CD40 agonists. High expression of CD47 is reported across ovarian and related cancers in a large percentage of tumors (~80%) demonstrating detectable CD47 expression (TCGA data; [Wang, 2015; Brightwell, 2016] and CD47 is a tumor associated antigen in this cancer type [Li, 2017].

As a monotherapy, CD47 inhibitors have demonstrated relatively low response rates and tumor responses have only been observed with Fc-competent agents [Chow, 2019]. Magrolimab demonstrated an ORR of 10% in relapsed/refractory acute myeloid leukemia (AML)/ myelodysplastic syndrome (MDS) patients [Sallman, 2019] and 15% (2/13) of ovarian cancer patients [Sikic, 2019]. Sporadic clinical responses have also been reported in patients with relapsed, refractory non-Hodgkin's lymphoma (NHL) treated with TTI-622 monotherapy [Patel, 2020].

Magrolimab in combination with avelumab reported stable disease in 56% of patients (N=18 platinum-resistant or refractory ovarian cancer) who had at least one response evaluation, with an unconfirmed partial response (PR) reported in one of these patients [Lakhani, 2020]. Multiple combination studies with CD47 inhibitors have also been tested in other hematologic and solid tumor malignancies. Magrolimab in combination with azacitidine has demonstrated activity in MDS and AML, with a complete response (CR) rate of 50% in previously untreated patients with MDS (n=24), and 42% in previously untreated patients with AML (n=43) [Sallman, 2019; Sallman, 2020]. The combination appears to compare favorably with historical data from azacitidine monotherapy [Fenaux, 2009; DiNardo, 2020]. Additionally, activity signals have been reported in patients with relapsed refractory NHL treated with magrolimab [Advani, 2018] or ALX-148 in combination with rituximab [Kim, 2020] as well as ALX-148 plus trastuzumab in HER2+ gastric/gastroesophageal junction tumors [Chow, 2019]. Taken together, these data indicate that CD47 inhibitors combined with chemotherapy or ADCP-competent antibodies demonstrate encouraging signals relative to historical data for the contributing components.

Several different CD40 agonistic antibodies have been studied in early phase trials [Beatty, 2017]. Sporadic responses in solid and hematologic malignancies including renal cell cancer, melanoma, diffuse large B cell lymphoma and Hodgkin's lymphoma have been noted with monotherapy CD40 agonists. The CD40 agonist, dacetuzumab, demonstrated monotherapy responses (1 CR and 5 PRs among n=50 subjects) in diffuse large B cell lymphoma [Advani, 2009]. However, a critical component that is believed to mediate the anti-tumor effect is the presence of tumor antigen, which is necessary for CD40-activated APCs to induce antigen-specific T cell adaptive immunity. This is the hypothesis for several other ongoing clinical trials combining CD40 agonists with vaccines and chemotherapy [Beatty, 2017].

1.8 Study Rationale

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 checkpoint inhibition. 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 coordinated manner, potentially leading to a more potent and durable anti-tumor response.

The investigation of SL-172154 in ovarian and related cancers is supported by the following factors: (1) mechanism of action of SL-172154, (2) high levels of CD47 expression, (3) enhanced tumor growth inhibition with mSIRPα-Fc-CD40L in combination with doxorubicin in preclinical murine xenograft models, and (4) potentiation of phagocytic activity when SL-172154 was combined with MIRV with the potential to broaden the activity of MIRV into FRα medium and low tumors.

SL03-OHD-105 is designed as a Phase 1b open-label trial to evaluate the safety, PK, PD, and preliminary efficacy of SL-172154 administered with either PLD or MIRV in subjects with platinum-resistant ovarian and related cancers. PLD is commonly used in clinical practice in this patient population, with well-described safety, PK and PD profiles. MIRV is being investigated for the treatment of PROC patients with efficacy, safety and PK profiles reported. Each component is anticipated to have distinct mechanisms of activity, and both PLD and MIRV have the potential to bridge innate and adaptive immunity when combined with SL-172154, thus potentially improving treatment outcomes without increasing toxicity. Anticipated overlapping toxicities are minimal when combining SL-172154 with PLD (IRRs, fatigue, nausea, constipation, diarrhea and cytopenias) or with MIRV (IRR, fatigue, nausea, diarrhea and cytopenias). The possible benefits of each of the combination regimens proposed in this trial outweigh the potential risks in the patient population proposed for enrollment in SL03-OHD-105.

Upon identification of the SL-172154 dose for each of the combination regimens from dose escalation groups, dose expansion cohorts will enroll additional subjects to receive either PLD or MIRV with the selected SL-172154 dose.

2. STUDY OBJECTIVES AND OUTCOME MEASURES

Objective	Outcome Measure
Primary Objectives	
To evaluate the safety and tolerability of SL-172154 administered with pegylated liposomal doxorubicin (PLD) or mirvetuximab soravtansine (MIRV) in subjects with platinum-resistant ovarian, primary peritoneal, or fallopian tube cancer	• Incidence and severity of adverse events (AE) per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 5.0 • Change from baseline in laboratory values per NCI-CTCAE, version 5.0 • AEs leading to discontinuation • Maximum tolerated dose (MTD) of SL-172154 in each combination regimen based on the rate of dose-limiting toxicities (DLTs) or the Maximum Administered Dose (MAD) of SL-172154
To select the recommended Phase 2 dose (RP2D) for SL-172154 administered with PLD or MIRV in subjects with platinum-resistant ovarian, primary peritoneal, or fallopian tube cancer	• Number and occurrence of DLTs as defined in the protocol • Available pharmacokinetic (PK) parameters • Available pharmacodynamic (PD) effects • Safety • Anti-tumor activity
Secondary Objectives	
To assess preliminary evidence of anti-tumor activity of SL-172154 when administered with PLD or MIRV (overall as well as subgroups with high (PS2+ ≥ 75%), medium (PS2+ ≥ 50% and < 75%), or low (PS2+ ≥ 25% and < 50%) tumor FRα expression) in subjects with platinum-resistant ovarian, primary peritoneal, or fallopian tube cancer	• ORR based on investigator assessment by Response Evaluation Criteria in Solid Tumors (RECIST v1.1) • Clinical benefit rate (CBR) • Time to response (TTR) • Duration of response (DoR) • PFS based on investigator assessment
To evaluate immunogenicity to SL-172154 or MIRV during and after treatment of SL-172154 administered with PLD or MIRV in subjects with platinum-resistant ovarian, primary peritoneal, or fallopian tube cancer	• Number/proportion of subjects with positive or negative ADA titer • Number/proportion of subjects with neutralizing anti-drug antibodies • ADA duration • Transient vs. persistent ADA
To assess the pharmacokinetic profile of SL-172154 when administered with PLD or MIRV in subjects with platinum-resistant ovarian, primary peritoneal, or fallopian tube cancer	• Maximum observed concentration (C_{max}), time at which the maximum concentration is observed (T_{max}), and minimum observed concentration (C_{min}) following single and multiple doses of SL-172154 • Area under the serum concentration-time curve (AUC) • Terminal elimination half-life ($t_{½}$), Clearance (CL) and Volume of Distribution (V_z), as data permit

Objective	Outcome Measure
To assess the pharmacokinetic profile of MIRV when administered with SL-172154 in subjects with platinum-resistant ovarian, primary peritoneal, or fallopian tube cancer	• PK exposure evaluation of MIRV, total antibody, and payload (DM4 and S-methyl DM4)
Exploratory Objectives	
To identify and assess pharmacodynamic biomarkers associated with ovarian cancer or the mechanism of action of SL-172154, PLD, or MIRV following treatment with SL-172154 administered with PLD or MIRV in subjects with platinum-resistant ovarian, primary peritoneal, or fallopian tube cancer	• Changes from baseline in select cytokines • Changes in immune cell subsets • CD47 and CD40 expression • Target-associated regulatory networks • Genomic alterations which may correlate with drug safety or efficacy
To explore the association of biological/clinical endpoints with PK parameters of SL-172154 administered with PLD or MIRV in subjects with platinum-resistant ovarian, primary peritoneal, or fallopian tube cancer	• To assess the relationship between SL-172154 PK exposure and the anti-tumor activity and safety of SL-172154, if feasible
Estimate overall survival (OS)	• OS: time from first dose to death

3. STUDY DESIGN

3.1 Description of Study Design

Study SL03-OHD-105 is an open-label, multicenter, Phase 1b trial designed to evaluate the safety, PK, PD effects, and preliminary anti-tumor activity of SL-172154 administered with either PLD or MIRV in subjects with platinum-resistant ovarian, primary peritoneal, or fallopian tube cancers. The study will consist of dose escalation followed by dose expansion for each of the combination regimens (see Figure 1).

Subjects eligible for enrollment to the SL-172154 + PLD cohort will have histologically confirmed epithelial ovarian cancer, or primary peritoneal or fallopian tube cancer, and be platinum-resistant (defined as radiologic disease progression within 180 days [6 months] following the last administered dose of platinum therapy). Subjects may have received any number of prior lines of therapy for EOC; however, they may not have received more than 1 prior line of systemic therapy for platinum-resistant disease.

Subjects eligible for enrollment to the SL-172154 + MIRV cohort will have histologically confirmed high grade serous epithelial ovarian cancer, or primary peritoneal or fallopian tube cancer, and a tumor positive for FRα expression (PS2+ $\geq$ 25%) as defined by the Ventana FOLR1 Assay. Subjects must have received at least 1, but no more than 3, prior systemic lines of anticancer therapy. In addition, subjects must have platinum-resistant disease, defined as either having progressed between > 3 months and $\leq$ 6 months following the last administered dose of platinum therapy if the subject had only 1 line of therapy OR having progressed on or within 6 months after the last dose of platinum therapy if the subject had received 2 or 3 prior lines of platinum therapy.

Study SL03-OHD-105 will initially enroll subjects to dose escalation cohorts to receive 1 of 2 combination regimens (SL-172154 + PLD or SL-172154 + MIRV). In the initial cohort of each

combination regimen, SL-172154 (3.0 mg/kg starting dose, IV) will be administered on Day 8 and Day 15 with either PLD (40 mg/m^2, IV, Day 1 of each 28-day cycle) or MIRV (6.0 mg/kg AIBW, IV, Day 1 of each 21-day cycle). For each combination regimen, subjects will be enrolled in sequential cohorts of approximately 3 subjects and evaluated for DLTs (Section 3.5) during the first cycle of therapy, which is the DLT evaluation period (28 days for the PLD cohort; 21 days for the MIRV cohort). The planned dose escalation of SL-172154 is outlined in Table 1 (PLD Cohort) and Table 2 (MIRV Cohort) for each of the combination regimens. The dose escalation cohorts 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 based on mTPI-2 model are outlined in Section 9.1.1. Dose escalation of SL-172154 in each of the combination regimens will continue until a safe dose of SL-172154 administered with either PLD or MIRV is identified.

In selecting the dose of SL-172154 to be evaluated in the dose expansion cohort of each combination regimen, the totality of the data from the dose escalation phase will be considered, including safety of the combination and PD activity. Upon identification of the selected SL-172154 dose administered with PLD, a dose expansion cohort will enroll up to approximately 20 subjects (including subjects from dose escalation at the same dose level) to further evaluate the safety and efficacy of the study treatment. Similarly, upon identification of the selected SL-172154 dose administered with MIRV, a dose expansion cohort will enroll up to approximately 70 subjects (including subjects from dose escalation at the same dose level) to further evaluate the safety and efficacy of the study treatment. The same patient population will be enrolled in both the dose escalation and dose expansion portion of the study for each of the combination regimens.

For all subjects in all cohorts, premedication as prophylaxis for IRR with dexamethasone (8 mg IV), an antipyretic and antihistamines should be administered at least 30 minutes prior to each SL-172154 administration. For dosage and schedule of prophylactic premedications, please see Section 5.1.1. For subjects enrolled to receive MIRV, premedication with an antipyretic, antihistamine, and dexamethasone will be administered at least 30 minutes prior to each MIRV administration as described in Section 5.3.2.1.

Throughout the treatment period for all subjects, an ongoing review of available safety data will be undertaken by a SMC as described in Section 7.8. All subjects (dose escalation and dose expansion) will receive SL-172154 administered with either PLD or MIRV until documented disease progression, unacceptable toxicity or intolerance, withdrawal of consent, or the subject meets other criteria for discontinuation (whichever occurs first) as defined in Section 3.1.1.

3.1.1 Sample Size

The planned sample size is approximately 102 subjects, depending on the number of dose levels evaluated in dose escalation for each of the combinations. Approximately 24 subjects will be enrolled in dose escalation cohorts (12 subjects in PLD cohorts and 12 subjects in MIRV cohorts) and approximately 78 subjects will be enrolled in the dose expansion cohorts (an additional 14 subjects at the selected dose in PLD cohort and additional 64 subjects at the selected dose in MIRV cohort). See Section 9.1.4 for more details.

3.2 Dose Escalation

Subjects with platinum-resistant ovarian, primary peritoneal, or fallopian tube cancer will be enrolled in dose escalation cohorts to receive either SL-172154 with PLD or SL-172154 with MIRV. For the MIRV cohort, subjects must have a tumor that is positive for FRα expression as defined by the Ventana FOLR1 Assay. Subjects can be enrolled to only 1 of the combination regimens in this study.

3.2.1 SL-172154 Administered with Pegylated Liposomal Doxorubicin (PLD)

SL-172154 (3.0 mg/kg starting dose) will be administered by IV infusion on Days 8 and 15 of each 28-day cycle. Premedication as prophylaxis for IRR with dexamethasone (8 mg IV), an antipyretic and antihistamines should be administered at least 30 minutes prior to each SL-172154 administration as described in Section 5.1.1. PLD (40 mg/m^2, IV) will be administered on Day 1 of each 28-day cycle. Administer the first dose (Cycle 1 Day 1) of PLD as a 1 mg/min infusion; after Cycle 1, if tolerated, PLD can be delivered as a 1-hour infusion. Premedication (any agent except steroid) as prophylaxis for nausea and vomiting with PLD may be administered per institutional guidelines.

The planned dose escalation of SL-172154 is outlined in Table 1; additional doses and/or schedules may be explored based on emerging safety, PK and PD data. SL-172154 doses explored in SL03-OHD-105 will not exceed the highest dose determined to be safe and tolerable in the monotherapy dose escalation study SL03-OHD-101.

Subjects will be enrolled in cohorts of approximately 3 subjects into sequential dose levels of SL-172154 administered with PLD and evaluated for DLT during the 28-day DLT evaluation period. DLT criteria are defined in Section 3.5. Treatment will be administered in 28-day cycles until at least one of the study treatment discontinuation criteria is met (Section 3.1.1). During therapy, management of PLD-related toxicity should follow the guidelines provided in the current PLD label, or local guidelines and are described in Section 3.7.2. Subjects will be followed according to the Schedule of Assessments (SOA) in Section 6.1.

The safety as well as available PK, PD, and efficacy data from these subjects will inform the dose of SL-172154 selected to be further evaluated in dose expansion when administered in combination with PLD to subjects with platinum-resistant ovarian, primary peritoneal, or fallopian tube cancer.

Table 1 SL-172154 Dose Escalation Plan When Administered with PLD

Dose Level[a]	SL-172154 Dose[b] [D8 and 15 in each 28d cycle]	SL-172154 Infusion[c]	Pegylated liposomal doxorubicin (PLD)
-1[d]	1.0 mg/kg	60 min ± 10 min	PLD (40 mg/m^2) IV administered on Day 1 of each 28-day cycle Administer first dose on study (C1D1) as 1 mg/min IV infusion; after Cycle 1, if tolerated, PLD can be delivered as a 1-hour infusion
1 (Starting Dose)	3.0 mg/kg	120 min ± 15 min	
2	6.0 mg/kg	180 min ± 15 min	

Abbreviations: AIBW = adjusted ideal body weight; C1D1 = Cycle 1 Day 1; D = day; IV = intravenously; mTPI-2 = modified toxicity probability interval; PLD = pegylated liposomal doxorubicin

a. Doses explored in SL03-OHD-105 will not exceed the highest dose determined to be safe and tolerable in the monotherapy dose escalation study SL03-OHD-101.
b. The actual body weight in kilograms (kg) will be used for SL-172154 dose calculation in all subjects whose body weight is ≤ 100 kg. For subjects with body weight > 100 kg, the dose to be administered should be the same as that calculated for a subject weighing 100 kg.
c. Infusion time may change based on final drug volume needed for administration, safety and tolerability of the infusion for the subject and/or observed safety findings during the study. Please refer to the Study Pharmacy Manual (SPM) for details.
d. SL-172154 dose level -1 at 1.0 mg/kg will be evaluated if 3.0 mg/kg is not safe per mTPI-2.

3.2.2 SL-172154 Administered with Mirvetuximab Soravtansine (MIRV)

SL-172154 (3.0 mg/kg starting dose) will be administered by IV infusion on Day 8 and Day 15 of 21-day cycles. Premedication as prophylaxis for IRR with dexamethasone (8 mg IV), an antipyretic and antihistamines should be administered at least 30 minutes prior to each SL-172154 administration as described in Section 5.1.1. MIRV (6.0 mg/kg AIBW, IV) will be administered on Day 1 of each 21-day cycle. Premedication with antipyretic, antihistamine, and dexamethasone will be administered at least 30 minutes prior to each MIRV administration as described in Section 5.3.2.1. Prophylactic use of eye drops with MIRV administration is described in Section 5.3.2.2.

The planned dose escalation of SL-172154 is outlined in Table 2; additional doses and/or schedules or intermediate doses may be explored based on emerging safety, PK, and PD data. SL-172154 doses explored in SL03-OHD-105 will not exceed the highest dose determined to be safe and tolerable in the monotherapy dose escalation study SL03-OHD-101.

Subjects will be enrolled in cohorts of approximately 3 subjects into sequential dose levels of SL-172154 administered with MIRV and evaluated for DLT during the 21-day DLT evaluation period. DLT criteria are defined in Section 3.5. Treatment will be administered in 21-day cycles until at least one of the study treatment discontinuation criteria is met (Section 3.1.1). During therapy, management of MIRV-related toxicity should follow the guidelines provided in Section 3.7.3 and the MIRV IB or the current USPI, as applicable. Subjects will be followed according to the SOA in Section 6.2.

The safety as well as available PK, PD, and efficacy data from these subjects will inform the dose of SL-172154 selected to be further evaluated in dose expansion when administered in combination with MIRV to subjects with platinum-resistant ovarian, primary peritoneal, or fallopian tube cancer.

Table 2 SL-172154 Dose Escalation Plan When Administered with MIRV

Dose Level[a]	SL-172154 Dose[b] [D8 and D15 in each 21d cycle]	SL-172154 Infusion[c]	Mirvetuximab soravtansine (MIRV)[e]
-1[d]	1.0 mg/kg	60 min ± 10 min	6.0 mg/kg AIBW, IV administered on Day 1 of each 21-day cycle Administer first dose on study (C1D1) at rate of 1 mg/min; after 30 min increase rate to 3.0 mg/min if well tolerated. If well-tolerated after 30 min at 3.0 mg/min, infusion rate may be increased to 5.0 mg/min. Subsequent infusions should be delivered at the tolerated rate.
1 (Starting dose)	3.0 mg/kg	120 min ± 15 min	
2	6.0 mg/kg	180 min ± 15 min	

Abbreviations: AIBW = adjusted ideal body weight; C1D1 = Cycle 1 Day 1; D = day; IV = intravenously; MIRV = mirvetuximab soravtansine; mTPI-2 = modified toxicity probability interval

a. Doses explored in SL03-OHD-105 will not exceed the highest dose determined to be safe and tolerable in the monotherapy dose escalation study SL03-OHD-101.
b. The actual body weight in kilograms (kg) will be used for SL-172154 dose calculation in all subjects whose body weight is ≤ 100 kg. For subjects with body weight > 100 kg, the dose to be administered should be the same as that calculated for a subject weighing 100 kg.
c. Infusion time may change based on final drug volume needed for administration, safety, and tolerability of the infusion for the subject and/or observed safety findings during the study. Please refer to the Study Pharmacy Manual (SPM) for details.
d. SL-172154 dose level -1 at 1.0 mg/kg will be evaluated if 3.0 mg/kg is not safe per mTPI-2.
e. Administer premedication at least 30 min prior to the start of MIRV infusion (see Section 5.3.2.1 for details).

3.3 Dose Expansion

The goal of the dose expansion cohort is to further evaluate the safety, PD effects, and efficacy of the regimen at the dose identified in the dose escalation part of the study. Enrollment to the dose expansion cohort for each combination regimen will not commence until the SL-172154 dose has been selected for the combination with PLD or MIRV.

3.3.1 SL-172154 Administered with PLD

Subjects with platinum-resistant ovarian, primary peritoneal, or fallopian tube cancer will be enrolled to receive SL-172154 and PLD at the dose identified in the dose escalation part of the study. Premedication as prophylaxis for IRR with dexamethasone (8 mg IV), an antipyretic and antihistamines should be administered at least 30 minutes prior to each SL-172154 administration as described in Section 5.1.1. Approximately 14 subjects will be enrolled in the dose expansion cohort. The goal is to enroll approximately 20 subjects at the potential RP2D for this combination regimen, including subjects in dose escalation and dose expansion that have received the same dose of SL-172154. Treatment will be administered in 28-day cycles until at least one of the study treatment discontinuation criteria is met (Section 3.1.1). Alternate dose level(s) may be evaluated at the discretion of the Sponsor based on emerging clinical or nonclinical data in the SL-172154 program.

3.3.2 SL-172154 Administered with MIRV

Subjects with platinum-resistant ovarian, primary peritoneal, or fallopian tube cancer whose tumors are positive for FRα expression (PS2+ ≥ 25%) as defined by the Ventana FOLR1 Assay will be enrolled to receive SL-172154 and MIRV at the dose identified in the dose escalation part of the study. Premedication as prophylaxis for IRR with dexamethasone (8 mg IV), an antipyretic and antihistamines should be administered at least 30 minutes prior to each SL-172154 administration as described in Section 5.1.1. In addition, premedication as prophylaxis for IRR with antipyretic, antihistamines, and dexamethasone should be administered at least 30 minutes prior to each MIRV administration as described in Section 5.3.2.1. Approximately 64 subjects will be enrolled in the MIRV dose expansion cohort. Approximately 70 subjects will be enrolled in this MIRV cohort which is anticipated to include approximately 20 subjects at the potential SL-172154 RP2D in either dose escalation or dose expansion for each of the following three tumor FRα expression subgroups: high (PS2+ ≥ 75%), medium (PS2+ ≥ 50% and < 75%), and low (PS2+ ≥ 25% and < 50%). This estimation is based on the anticipated frequency of patients with high grade serous ovarian cancer who fall into each of these FRα expression subgroups. If this distribution is not achieved in any subgroup, approximately 10 additional subjects may be enrolled in this dose expansion cohort in order to achieve these subject numbers. Treatment will be administered in 21-day cycles until at least one of the study treatment discontinuation criteria is met (Section 3.1.1). Alternate dose level(s) or treatment schedule(s) may be evaluated at the discretion of the Sponsor based on emerging clinical or nonclinical data in the SL-172154 program.

3.4 Selection of Recommended Phase 2 Dose

If an MTD is not observed, the MAD would then be the highest dose of SL-172154 administered as specified in the protocol. Selection of the recommended dose for SL-172154 for further study in combination with PLD and in combination with MIRV will be based upon the totality of the safety, tolerability, PK, PD, and efficacy data in subjects treated with each of the regimens in dose escalation and dose expansion cohorts. The RP2D is a dose of SL-172154 that can be safely administered with standard of care doses of PLD or with the recommended dose of MIRV. In addition, preliminary efficacy of each of the combination regimens will be assessed to determine whether either or both of the regimens warrant further evaluation in a Phase 2 study.

3.5 Definition of Dose-Limiting Toxicity

Protocol-defined DLT criteria are applicable to the dose escalation portion of the study. The determinant period for DLT is the first cycle of treatment (i.e., 28 days for PLD cohorts, 21 days for MIRV cohorts); however, there is provision in the criteria below for AEs that occur beyond this period to be considered in the determination of the RP2D. All toxicities except for CRS and ocular AEs will be graded as per NCI CTCAE v5. CRS will be graded per the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading Criteria for CRS (described in Section 3.7.1.2); ocular AEs for the MIRV cohort will be graded per the tables provided in the Appendix Section 16.6. AEs clearly related to the underlying disease, disease progression, intercurrent illness, or concomitant medications are not considered DLTs. AEs that are clearly related to PLD or MIRV only do not have to be considered DLTs, unless the investigator considers the AE to be exacerbated by SL-172154. DLT is defined as an event considered related or possibly related to SL-172154 and meets one of the following criteria:

- Any death not clearly related to underlying disease or intercurrent illness
- Elevations in liver transaminases (aspartate aminotransferase [AST], alanine aminotransferase [ALT]) or total bilirubin:
    - In subject who enroll with AST/ALT/total bilirubin ≤ upper limit of normal (ULN), AST or ALT elevation of > 8x ULN **or** total bilirubin > 5x ULN.
    - In subjects who enroll with AST/ALT/total bilirubin > UNL, AST or ALT elevation of > 8x baseline **or** total bilirubin > 5x baseline.
    - Evidence of Hy's Law (AST or ALT > 3x ULN [or baseline*] with concurrent increase in total bilirubin > 2x ULN [*or baseline] without evidence of cholestasis or alternative explanation such as disease progression or viral hepatitis.

      **ULN or baseline dependent on value at enrollment as described above*.
- Any AE that requires permanent discontinuation of SL-172154
- Any Grade 3 or greater AE **except** for those listed below:
    - Grade 3 fatigue lasting ≤ 7 days
    - Grade 3 anemia
    - Grade 3 or 4 neutropenia not associated with fever (temperature > 38.5°C) 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 anorexia, nausea, vomiting, or diarrhea, provided that it does not require tube feeding, total parenteral nutrition, or require or prolong hospitalization
    - Grade 3 laboratory abnormalities which resolve to Grade 1 or baseline within 72 hours with or without intervention
    - Grade 3 hypertension that can be controlled (i.e., systolic BP < 140 mmHg and diastolic BP < 90 mmHg) with medical therapy
    - Grade 3 or 4 amylase and/or lipase abnormalities that are not associated with clinical signs/symptoms or finding on imaging consistent with pancreatitis
    - 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
    - Vitiligo or alopecia of any grade

Other toxicities may be considered a DLT as determined by the investigator in conjunction with the SMC.

3.6 Concomitant Medications, Treatments, and Procedures

Investigators may prescribe concomitant medications or treatments deemed necessary to provide supportive care except for prohibited medications (Section 3.6.1). Best supportive care should be

provided (including antibiotics, bisphosphonates, receptor activator of nuclear factor kappa B ligand (RANKL) inhibitors, nutritional support, correction of metabolic disorders, hydration, optimal symptom control, and pain management including palliative radiotherapy) for all subjects when clinically indicated. The Medical Monitor should be consulted prior to starting palliative radiotherapy and prior to restarting study treatment after the completion of radiotherapy.

Subjects receiving recombinant erythropoietin (EPO) or darbepoetin-α before study start may continue to receive pretreatment doses. Primary prophylactic use of erythropoietic and granulocyte growth factors initiated during the first cycle of therapy is not permitted. In subsequent cycles, the use of erythropoietic and granulocyte growth factors in accordance with American Society of Clinical Oncology (ASCO) guidelines may be implemented at the discretion of the investigator.

Use of anticoagulant agents is allowed as clinically indicated.

Use of intranasal, inhaled, topical, injected (e.g., intra-articular injection) or local steroid or immunosuppressive medication is permitted. Temporary use of systemic corticosteroids (e.g., prior to computed tomography [CT] to prevent contrast allergies, premedication prior to each dose of MIRV administration) is acceptable.

Primary prophylaxis of nausea and vomiting using all agents except a steroid is permitted for PLD according to institutional guidelines.

For subjects enrolled in a MIRV cohort, an antiemetic (e.g., 5-HT3 serotonin receptor antagonists such as palonosetron, granisetron, or ondansetron) medication is recommended before each MIRV dose; additional antiemetics and/or antidiarrheal (e.g., loperamide) medications may be used any time at the discretion of the investigator.

COVID-19 vaccines (except for live attenuated vaccines for COVID-19) are permitted during the study. If administered, COVID-19 vaccines should not be administered on the same day as any of the study medications; please discuss with the Medical Monitor regarding the timing of COVID-19 vaccine administration during this study.

3.6.1 Prohibited Medications or 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 the study:

- Any investigational anti-cancer therapy not described in this protocol
- Any concurrent therapy for anticancer intent (other than study medications), including radiotherapy (except palliative radiotherapy after consultation with the Sponsor Medical Monitor), or systemic therapy including chemotherapy, hormonal or hormonal suppression therapy, immunotherapy, or biologic therapy.
- Steroid and immunosuppressive medication usage: data indicate that corticosteroids have an adverse effect on T cell function and that they inhibit and damage lymphocytes [Schleimer, 1984]. Furthermore, as with all immunotherapies intended to augment cell-mediated immunity, there is a risk that concomitant immunosuppressives such as

steroids will counteract the intended benefit of the proposed SL-172154 therapy. Therefore, the use of steroids during this trial is as follows:

- Therapeutic use: Subjects who require immunosuppressive medications (e.g., corticosteroids) for management of irAE or IRRs that the investigator assesses as possibly related or related to SL-172154 should be managed per Toxicity Management Guidelines in Section 3.7.1.1.
- Steroid premedication for CT-contrast allergies is permitted.
- Steroid premedication prior to each dose of MIRV administration and SL-172154 administration for IRR prophylaxis is permitted.
- Primary prophylactic use of steroids for nausea/vomiting is not permitted.
- Non-steroidal, systemic immunosuppressive medications are not permitted.
- If steroids are required for managing any specific conditions, please contact the Medical Monitor.

- **[MIRV Cohort]** Folate-containing supplements
- Live attenuated vaccines (including live attenuated vaccines for COVID-19) during the study and through 30 days after the last dose of SL-172154.

3.6.2 Medications to be used with Caution

Please refer to the current listing of drugs that are cytochrome P450 (CYP450) substrates, including CYP3A4, CYP2D6 and P-glycoprotein (P-gp) substrates, at: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-1.

SL-172154

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 CYP450 enzymes including CYP3A4 activity [Evers, 2013]. Although not tested clinically, a drug-drug interaction may occur with the co-administration 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.

PLD

Doxorubicin is a major substrate of CYP3A4 and CYP2D6, and P-gp. Clinically significant interactions have been reported with inhibitors of CYP3A4 (e.g., ketoconazole, erythromycin, ciprofloxin), CYP2D6 (e.g., paroxetine, fluoxetine, and/or P-gp (e.g., verapamil), resulting in increased concentration and clinical effect of doxorubicin.

Inducers of CYP3A4 (e.g., phenobarbital, phenytoin, St. John's Wort) and P-gp inducers may decrease the concentration of doxorubicin. If possible, avoid concurrent use of doxorubicin with strong inhibitors and strong inducers of CYP3A4, CYP2D6, or P-gp.

MIRV

In vitro metabolism studies demonstrated that DM4 is predominantly metabolized by thiol s-methyltransferase to form S-methyl DM4, which is further metabolized into sulfoxide methyl-DM4. As S-methyl DM4 has been shown to be primarily metabolized by CYP3A, its exposure could potentially be increased in the presence of strong CYP3A inhibitors. Drinking greater than one serving (250 mL) of grapefruit juice per day should be avoided.

Both DM4 and S-methyl DM4 are substrates for MDR1 efflux transporter. Their exposure could potentially increase in the presence of MDR1 efflux transporter. *In vitro* metabolism data also indicates that DM4 is a time-dependent inhibitor of CYP3A4. The risk of a significant *in vivo* drug-drug interaction caused by inhibition of CYP3A4 or MDR1 is unknown. Treatment of patients with concomitant medications that are inhibitors of MDR1, sensitive substrates of CYP3A or are CYP3A substrates with a narrow therapeutic index should be used with caution and carefully monitored. Please consult with the Medical Monitor if further guidance is needed.

3.7 Toxicity Management Guidelines

All AEs should be assessed using NCI-CTCAE v5.0 criteria. CRS will be graded per the ASTCT Consensus Grading Criteria for CRS (described in Section 3.7.1.2). Ocular AEs for MIRV will be graded per the tables in Appendix Section 16.6. These guidelines are not meant to be prescriptive, and investigators should always use clinical judgement. 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, the possibility of an immune-related AE should be considered.

Every effort should be made to administer study treatment on the planned dose and schedule. If PLD or MIRV dosing is delayed, SL-172154 should also be delayed so that the dosing interval between PLD or MIRV and SL-172154 can be preserved. This will result in the cycle being delayed. If an SL-172154 dose is not given, the dose should be considered skipped, and the cycle should not be delayed. Please consult with the Medical Monitor if further guidance is needed.

3.7.1 Toxicity Management Guidelines for SL-172154

The toxicity management guidelines provided in this section represent general guidance for AEs that are considered by the investigator to be possibly related or related to treatment with SL-172154.

Table 3 describes the dose levels to be used for dose reductions due to AEs that are considered by the investigator to be possibly related or related to treatment with SL-172154. Only one level dose reduction is permitted for AE management and then SL-172154 administration should be held. Investigators always have the option to perform a more conservative dose modification if clinically indicated (i.e., dose interruption as opposed to dose reduction). Any AE deemed to be related to SL-172154 that requires a dose hold of more than 28 days will result in permanent discontinuation of SL-172154.

Table 3 SL-172154 Dose Levels for Dose Reductions

Starting SL-172154 Dose Level (mg/kg)	Dose Level Reduction (mg/kg)
1.0	Interrupt SL-172154 until toxicity resolves to ≤ Grade 1 or baseline and then restart at same dose level or discontinue. Reduction of SL-172154 below 1.0 mg/kg will not be permitted.
3.0	1.0 mg/kg
6.0	3.0 mg/kg

3.7.1.1 Management of Infusion-Related Reactions [SL-172154]

General Guidance for Infusion-Related Reactions (IRRs) [Rosello, 2017a]	
IRRs have been temporally related to SL-172154 administration. Subjects must be closely monitored for signs and symptoms of IRRs with prompt institution of treatment. Appropriate drugs and medical equipment to treat hypersensitivity reactions (HSRs), IRRs, and CRS must be immediately available, and study personnel must be trained to recognize and treat these toxicities. Premedication for IRR prophylaxis with dexamethasone (8 mg IV), an antipyretic and antihistamines should be administered at least 30 minutes prior to each SL-172154 administration as outlined in Section 5.1.1. Additional premedication with dexamethasone one day prior to SL-172154 infusion is not required but can be optionally given. The dose and administration method of prophylactic premedication can be modified at the Investigator's discretion. Subjects should be notified that symptoms may occur during the first infusion and for up to several hours afterwards or with subsequent infusions. In the SL03-OHD-101 study, IRRs occurred during the infusion or within 2 hours after the end of infusion. Instruct subjects to contact their physician if symptoms or signs of an IRR occur. If **IRR events** occur, ad hoc labs should be collected as noted in Section 6.5.9.1.	
Severity	**Management**
Grade 1	• Infusion interruption not indicated. • Vital signs should be measured after the onset of an IRR approximately every 15 minutes through the completion of the infusion followed by approximately every 15 minutes for one hour after completion of the SL-172154 infusion and then approximately every 30 minutes for the second hour after completion of the SL-172154 infusion. • Monitor subjects with close observation in an outpatient or inpatient setting until recovery from symptoms
Grade 2	• Temporarily interrupt SL-172154. • Vital signs should be measured after the onset of an IRR approximately every 15 minutes through the completion of the infusion followed by approximately every 15 minutes for one hour after completion of the SL-172154 infusion and then approximately every 30 minutes for the second hour after the completion of the SL-172154 infusion. • Begin IV infusion of normal saline and treat symptoms as indicated and per institutional guidelines, e.g., with antipyretic and antihistamines; consider opioids (e.g., meperidine) for rigors, leukotriene inhibitor, bronchodilator therapy, or corticosteroids as appropriate. • Monitor subjects with close observation in an outpatient or inpatient setting until recovery from symptoms. Consider if admission to hospital is necessary.

General Guidance for Infusion-Related Reactions (IRRs) [Rosello, 2017a]	

	• Restart the infusion after resolution of symptoms. Based on the severity of symptoms, reduce the rate to ≤50% of the rate at which the reaction occurred.
	• If symptoms recur, then no further SL-172154 will be administered at this visit.
	• Subsequent Infusions:
	  ○ If the Grade 2 IRR signs and symptoms were not severe, the investigator may administer the next two infusions at the current dose but at ≤50% rate. If the symptoms do not recur, the infusion rate may be increased back to the original rate stated in the protocol.
	  ○ If the Grade 2 IRR signs and symptoms were severe, the investigator may reduce the SL-172154 dose for the next two infusions to 1 mg/kg. If the symptoms do not recur, SL-172154 dose may be increased back to 3 mg/kg at ≤50% of the original rate. If tolerated, the rate may be increased back to the original rate stated in the protocol.

Recurrent Grade 2	• If the Grade 2 IRR recurred after reducing the dose to 1 mg/kg and the signs and symptoms are severe, permanently discontinue SL-172154

Grade 3	• Immediately discontinue infusion of SL-172154
	• Vital signs should be measured after the onset of an IRR approximately every 15 minutes for one hour after discontinuation of SL-172154 infusion and then approximately every 30 minutes for hours 2 and 3 after the discontinuation of the SL-172154 infusion.
	• Begin IV infusion of normal saline and treat symptoms as indicated and per institutional guidelines e.g., epinephrine, bronchodilators, diphenhydramine, famotidine or other available H2 receptor antagonist, corticosteroids, consider opioids (e.g., meperidine) for rigors, oxygen, fluids, vasopressors, etc. 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 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 the subject has completely recovered, carefully consider if it is safe for the subject to receive SL-172154 at the next scheduled dose with premedication and dose reduction.
	  ○ Reduce the SL-172154 dose for the next two infusions to 1 mg/kg at ≤ 50% of the rate stated in the protocol. These two subsequent infusions of SL-172154 (after an event of Grade 3 event of IRR) must be administered in an inpatient or outpatient setting with prolonged observation for a minimum of 12 hours after the completion of the infusion.
	  ○ If symptoms do not recur at 1 mg/kg SL-172154 dose, subsequent infusions may be administered at the original rate stated in the protocol. If no further symptoms, the SL-172154 dose may be re-escalated to 3 mg/kg but administered at ≤ 50% of the rate stated in the protocol.

Recurrent Grade 3	• If the Grade 3 IRR recurred, permanently discontinue SL-172154

General Guidance for Infusion-Related Reactions (IRRs) [Rosello, 2017a]	
Grade 4	• Permanently discontinue SL-172154. • Admit to hospital for close observation until resolution of symptoms. • Vital signs should be measured after the onset of an IRR approximately every 15 minutes for one hour after discontinuation of SL-172154 infusion and then approximately every 30 minutes for hours 2 and 3 after the completion of the SL-172154 infusion. • Manage severe IRRs per institutional standards (e.g., epinephrine, diphenhydramine, famotidine or other available H2 receptor antagonist, corticosteroids, consider opioids (e.g., meperidine) for rigors, bronchodilators, oxygen, fluids etc.). Epinephrine is the drug of choice in an anaphylactic reaction and its administration should not be delayed.

3.7.1.2 Management of Cytokine Release Syndrome

CRS will be graded using the ASTCT Consensus Grading Criteria for CRS (Table 4).

Table 4 ASTCT Consensus Grading Criteria for CRS [Lee, 2019]

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[1]	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressor (excluding vasopressin)
		And/Or[2]		
Hypoxia	None	Requiring low-flow nasal cannula[3] or blow-by	Requiring low-flow nasal cannula[3], facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

Abbreviations: ASTCT = American Society for Transplantation and Cellular Therapy; CPAP = continuous positive airway pressure; BiPAP = bilevel positive airway pressure
Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

1. Fever is defined as temperature ≥ 38°C not attributable to any other cause. In subjects who have CRS and receive antipyretic or anti-cytokine therapy, such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
2. CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.
3. Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/minute.

General Guidance for Cytokine Release Syndrome (CRS) [Lee, 2014; Lee, 2019; BREYANZI® USPI, 2021; Porter, 2018]	
Cytokine release syndrome (CRS) is a non-antigen specific, systemic inflammatory response that occurs as result of high-level immune activation with concomitant elevations of cytokines (e.g., IL-6, IL-10, TNF-α, IL-2, interferon gamma [IFNɣ]). CRS can be fatal or have life-threatening reactions. Evaluate for and treat other causes of fever, hypoxia, and hypotension. Determine CRS grade per the ASTCT Consensus Grading criteria for CRS in Table 4 and manage CRS according to this guidance or per institutional guidance. NOTE: CRS may have a similar presentation to a type 1 HSR and may be clinically indistinguishable. Ensure that 2 doses of tocilizumab are available prior to infusion of SL-172154. When tocilizumab is not available, consider using a drug with similar mechanism of action such as anti-IL-6 receptor monoclonal antibodies (e.g., sarilumab) or anti-IL-6 mAbs (e.g., siltuximab). If CRS events occur, ad hoc labs should be collected as noted in Section 6.5.9.1.	
Severity (ASTCT CRS Consensus Grading)	**Management**
Any Grade	• Permanently discontinue SL-172154 if any grade CRS occurs at Cycle 1 Day 2 or later due to ADAs against SL-172154
Grade 1	• Interrupt SL-172154 • Vital signs should be measured approximately every 15 minutes for the first hour after discontinuation of SL-172154 infusion and then approximately every 30 minutes for the second hour. • Monitor subjects with close observation in an outpatient or inpatient setting for 12 hours or until recovery from symptoms. • Maintain IV access. Symptomatic treatment with antipyretic, antiemetics, analgesics, antihistamines (H1/H2 inhibitors) as needed; monitor fluid balance; assess for infection. Consider opioids (e.g., meperidine) for rigors. Regularly evaluate for signs of further deterioration Resume SL-172154 when all symptoms/ clinical features for CRS resolved, and follow the guidelines below: • Subjects who have experienced grade 1 CRS should be hospitalized for the subsequent infusion of SL-172154; subjects should be under prolonged observation for a minimum of 12 hours after the completion of the infusion. • For all subsequent infusions, infuse SL-172154 at the same dose level over at least twice the infusion time. If no recurrence of symptoms, subsequent infusions can be performed in an outpatient setting. • Consider premedication (e.g., antipyretic, antihistamines) per institutional guidelines

General Guidance for Cytokine Release Syndrome (cont.)	
Grade 2	• Interrupt SL-172154 • Vital signs should be measured approximately every 15 minutes for the first hour after discontinuation of SL-172154 infusion and then approximately every 30 minutes for the second hour. • Closely monitor cardiac and other organ function in an outpatient or inpatient setting for 12 hours or until recovery from symptoms. Consider admission to hospital for management of symptoms, evidence of organ dysfunction or administration of therapy. • Monitor subjects with continuous cardiac telemetry and pulse oximetry, closely monitor other organ functions. • Start IV infusion with normal saline. Administer oxygen if needed. Treat with antipyretic, H1/H2 antagonists (diphenhydramine, famotidine, or other available H2 receptor antagonist), and/or corticosteroids and manage per institutional guidelines. o If corticosteroids are initiated, continue corticosteroids for at least 3 doses or until complete resolution of symptoms, and consider corticosteroid taper. • Consider opioids (e.g., meperidine) for rigors. • Consider tocilizumab use for subjects with persistent signs and symptoms after interrupting SL-172154 and after corticosteroid treatment for CSR. o Administer tocilizumab as per your institutional guidelines and local prescribing information. • 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. Resume SL-172154 at one dose level lower when all symptoms/ clinical features for CRS resolved and follow the guidelines below: • Subjects who experience Grade 2 CRS should be hospitalized for the next two subsequent infusions of SL-172154. Subjects should be under prolonged observation for a minimum of 12 hours after the completion of the infusion. • For all subsequent infusions, infuse SL-172154 at least at twice the infusion time. If no recurrence of symptoms, subsequent infusions can be performed in an outpatient setting. • Premedicate with dexamethasone 20 mg, antipyretic, antihistamines (H1/H2 inhibitors), and manage per institutional guidelines.

General Guidance for Cytokine Release Syndrome (cont.)	

Grade 3	• Interrupt SL-172154
	  o Permanently discontinue SL-172154 if CRS does not resolve within 72 hours with management.
	• Vital signs should be measured approximately every 15 minutes for the first hour after discontinuation of SL-172154 infusion and then approximately every 30 minutes for the second hour.
	• Hospitalization required for close monitoring and management of symptoms related to organ dysfunction.
	• Monitor subjects with continuous cardiac telemetry and pulse oximetry. Consider performing an ECHO/MUGA to assess cardiac function.
	• Treat hypotension with IV fluid for blood pressure support and/or pressers. Cryoprecipitate or fresh frozen plasma may be required for coagulopathy. Manage per institutional guidelines.
	• Implement additional management per institutional standards (e.g., epinephrine, diphenhydramine, famotidine or other available H2 receptor antagonist, corticosteroids, bronchodilators, oxygen, fluids, meperidine for rigors, etc.). Epinephrine is the drug of choice in an anaphylactic reaction and its administration should not be delayed.
	• Administer tocilizumab as per your institutional guidelines and local label.
	• Second-line therapies to be considered:
	  o Methylprednisolone 2 mg/kg/day IV. If corticosteroids are initiated, continue corticosteroids for at least 3 doses or until complete resolution of symptoms, and consider corticosteroid taper. 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).
	
	Resume SL-172154 at one dose level lower only when all symptoms/ clinical features of CRS resolve within 72 hours and follow the guidelines below:
	
	• Subjects who experience Grade 3 CRS should be hospitalized for the next two subsequent infusions of SL-172154. Subjects should be under prolonged observation for a minimum of 12 hours after the completion of the infusion.
	• For all subsequent infusions, infuse SL-172154 at least at twice the infusion time. If no recurrence of symptoms, subsequent infusions can be performed in an outpatient setting.
	• Premedicate with dexamethasone 20 mg, antipyretic, antihistamines (H1/H2 inhibitors), and manage per institutional guidelines.
	• If Grade 3 CRS recurs, permanently discontinue SL-172154.

General Guidance for Cytokine Release Syndrome (cont.)	
Grade 4	• Permanently discontinue SL-172154. • Hospitalization required for close monitoring and management of symptoms related to organ dysfunction. • Vital signs should be measured approximately every 15 minutes for the first hour after discontinuation of SL-172154 infusion and then approximately every 30 minutes for the second and third hours. • Consider intensive-care supportive therapy • Monitor subjects with continuous cardiac telemetry and pulse oximetry • Consider performing an ECHO/MUGA to assess cardiac function. • 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. • Implement additional management per institutional standards (e.g., epinephrine, diphenhydramine, famotidine or other available H2 receptor antagonist, corticosteroids, bronchodilators, oxygen, fluids, meperidine for rigors, etc.). Epinephrine is the drug of choice in an anaphylactic reaction and its administration should not be delayed • Administer tocilizumab as per your institutional guidelines and local prescribing information. • Second-line therapies to be considered: o Methylprednisolone 2 mg/kg/day IV. If corticosteroids are initiated, continue corticosteroids for at least 3 doses or until complete resolution of symptoms, and consider corticosteroid taper. 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).

3.7.1.3 Management of Hepatotoxicity

General Guidance for Hepatotoxicity	
Monitor signs, symptoms, and laboratory evidence of liver dysfunction. Evaluate alternative etiologies, including liver function test (LFT) elevations in the setting of IRR and/or CRS; review medications for hepatotoxic drugs and alcohol history; consider performing liver screen: hepatitis A, B, C serology, hepatitis E PCR, antinuclear antibody (ANA)/smooth muscle antibody/liver kidney microsomal antibodies /soluble liver antibody/liver-pancreas antigen/liver cytosol auto-antibodies, iron studies. Consider imaging for progressive disease/thrombosis. Guidelines are based on elevations in ALT, AST, and bilirubin per CTCAE v5.0. Discontinue SL-172154 for Hy's law as follows: AST or ALT ≥ 3 x ULN in the setting of total bilirubin ≥ 2 x ULN without evidence of cholestasis and no other reason can be found to explain the combination of increased aminotransferases and total bilirubin, such as viral hepatitis A, B or C, preexisting or acute liver disease, or another drug capable of causing the observed injury. Grade 3 ALT/AST or bilirubin will be evaluated to determine if events meet the DLT criteria.	
Severity	**Management**
Grade 1	• Continue SL-172154 with close monitoring. • Monitor liver function at least weekly; if liver function is stable, reduce frequency of blood tests

Grade 2	• Monitor liver function approximately every 3 days. If persistent or rising liver chemistries or significant clinical symptoms, hold the next scheduled SL-172154 dose.
	• Consider hepatology consult and liver biopsy is optional.
	• If immune etiology is suspected, start oral prednisone 0.5 to 1 mg/kg/day (or equivalent of methylprednisolone) with 4 week taper. Resume SL-172154 at one dose level lower when toxicity ≤ Grade 1 and corticosteroid taper to ≤ 10 mg/day prednisone or equivalent.
	• For Grade 2 ALT/AST increase that resolves to Grade ≤1 within 7 days, administer next dose at same dose level.
	• For Grade 2 ALT/AST increase that does not resolve to Grade ≤1 within 7 days:
	  ○ Hold/skip the scheduled SL-172154 dose.
	  ○ Resume next dose at the same dose level after ALT/AST elevations resolve to Grade ≤1.

Grade 3	• Hold SL-172154 and monitor liver function approximately every 3 days.
	• Grade 3 ALT/AST increase:
	  ○ Hold/skip the scheduled SL-172154 dose.
	  ○ Resume next dose at one dose level lower after ALT/AST elevations resolve to Grade ≤1
	• Permanently discontinue SL-172154 for liver function test abnormality that meets following criteria in subjects who enroll with AST/ALT/total bilirubin ≤ ULN: AST or ALT > 8 x ULN or total bilirubin > 5 x ULN for greater than 3 days
	• Permanently discontinue SL-172154 for liver function test abnormality that meets following criteria in subjects who enroll with AST/ALT/total bilirubin > ULN: AST or ALT > 8 x baseline or total bilirubin > 5 x baseline for greater than 3 days.

	• If persistent or rising liver chemistries, or significant clinical symptoms and an immune etiology is suspected, start oral prednisone 0.5 to 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. • After careful consultation with hepatology, consider resuming SL-172154 at one dose level lower when toxicity ≤ Grade 1 and corticosteroid taper to ≤ 10 mg/day prednisone or equivalent.
Grade 4	• Permanently discontinue SL-172154. • Consider hospitalization; obtain hepatology consult; assessments as above; monitor liver function daily; consider liver biopsy. • If an immune etiology is suspected, immediately start methylprednisolone 1 to 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.

3.7.1.4 Management of Hematologic AEs

General Guidance for Hematologic Toxicity		
In the event of cytopenia, it is important to use physical exams, complete blood counts (CBCs), serum chemistries including bilirubin fractionation, 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 following SL-172154 administration (e.g., transient decrease in hemoglobin, lymphocytes, neutrophils, monocytes, platelets). The transient declines in peripheral blood counts following SL-172154 administration are thought to be due to margination of cells outside of the circulatory system in response to target engagement (especially CD40), and the cytokines released. In study SL03-OHD-101, recovery was generally observed within 24 hours. 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. No autoimmune cytopenias have been reported to date with SL-172154. In vitro studies showed binding of SL-172154 to CD47 on RBCs, however, there has been no reports of crossmatch interference to date in the clinical trials. The following are recommendations for SL-172154 dosing in the presence of anemia or thrombocytopenia in the setting of combination cytotoxic anti-cancer therapy. Investigators always have the option to perform a more conservative dose modification if clinically indicated.		
Adverse Event	**Severity**	**Management**
Anemia	Grade 1	• Continue SL-172154 with close clinical follow-up and laboratory evaluation
	Grade 2	• Continue SL-172154 with close clinical follow-up and laboratory evaluation
	Grade 3	• Continue SL-172154 with close clinical follow-up and laboratory evaluation.

		• Consider if RBC transfusion is necessary to relieve anemia symptoms or to return subject to an acceptable hemoglobin (Hgb) range per institutional practice. If transfusion is required, recommend completing RBC transfusion at least 2 hours prior to the start of SL-172154 dose. • Determine the etiology of anemia, consider Hematology consult.
	Grade 4	• Hold SL-172154 until AE has reverted to an acceptable hemoglobin (Hgb) range. • Consider RBC transfusion to relieve anemia symptoms or to return subject to an acceptable hemoglobin (Hgb) range per institutional practice. • Determine the etiology of anemia, consider Hematology consult. • Discontinue SL-172154 permanently if no other etiology can be determined and SL-172154 is deemed to be the cause of anemia. Transient decrease in hemoglobin that is associated with SL-172154 infusion may not necessarily require discontinuation of SL-172154. Please consult the Medical Monitor. • If anemia is not due to SL-172154, restart SL-172154 on the next scheduled dosing day at the same dose level.

General Guidance for Hematologic Toxicity (cont.)		
Adverse Event	**Severity**	**Management**
Thrombocytopenia	Grade 1	• Continue SL-172154 with close clinical follow-up and laboratory evaluation
	Grade 2	• Continue SL-172154 with close clinical follow-up and laboratory evaluation
	Grade 3	• Continue SL-172154 with close clinical follow-up and laboratory evaluation. In case of recurrence where SL-172154 deemed to be the cause, reduce dose by one dose level.
	Grade 3 with bleeding or Grade 4	• Hold SL-172154 until AE is ≤ Grade 2. Restart SL-172154 on the next scheduled dosing day at one dose level lower. • Consider platelet transfusion relieve thrombocytopenia symptoms or to return subject to an acceptable platelet count per institutional practice. • Determine the etiology of thrombocytopenia (including chemotherapy), consider Hematology consult. • At the first recurrence of Grade 3 with bleeding or Grade 4, discontinue SL-172154.

3.7.1.5 Management of Other AEs Not Specified

Severity	Dose Modification	Toxicity Management
All Grades	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 modification required.	• Treat accordingly, as per institutional standard
Grade 2	Consider reducing the SL-172154 by one dose level or holding SL-172154 until resolution to ≤ Grade 1 or baseline.	• Treat accordingly, as per institutional standard
Grade 3	Hold SL-172154 until resolution to ≤ Grade 1 or baseline. For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume SL-172154 at one dose level lower. Otherwise, discontinue SL-172154. (Note: For Grade 3 labs, decision to hold should be based on accompanying clinical signs/symptoms, the investigator's clinical judgment, and consultation with the Sponsor).	• Treat accordingly, as per institutional standard
Grade 4	Permanently discontinue SL-172154. (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the investigator's clinical judgment, and consultation with the Sponsor).	• Treat accordingly, as per institutional standard

3.7.2 Toxicity Management Guidelines for PLD

The toxicity management guidelines provided in this section represent general guidance for AEs that are considered by the investigator to be possibly related or related to treatment with PLD. Dose modifications/interruptions or delays and treatment discontinuation of PLD for toxicity management should comply with local institutional guidelines or the current regional prescribing information for management of AEs related to PLD. If the country-specific prescribing information is more conservative, the current local guidelines should be used including the special precautions for patients who reach lifetime maximums of 450 mg/m^2.

In the event of significant toxicity, PLD dosing may be delayed and/or dose reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Table 5 describes the dose reductions to be used for AEs that are considered by the investigator to be possibly related or related to treatment with PLD.

Table 5 PLD Dose Reduction for Management of Toxicities

Dose Level	Dose Level Reduction (mg/kg)
Starting Dose	40 mg/m^2
First Dose Reduction	30 mg/m^2
Second Dose Reduction	20 mg/m^2

3.7.2.1 Management of Hematologic Toxicity [PLD Cohort]

Neutropenia or Thrombocytopenia	PLD Dose Modification
Grade 1	• No dose modification
Grade 2	• Delay PLD until toxicity resolves to ANC 1.5 x 10^9/L, platelets 75 x 10^9/L. Resume PLD at previous dose.
Grade 3	• Delay PLD until toxicity resolves to ANC 1.5 x 10^9/L, platelets 75 x 10^9/L. Resume PLD at previous dose. For prolonged or recurrent grade 3 toxicity, follow institutional standard practices.
Grade 4	• Delay PLD until toxicity resolves to ANC 1.5 x 10^9/L, platelets 75 x 10^9/L. Resume PLD at one reduced dose level and consider prophylactic granulocyte growth factor support.

Abbreviation: ANC = absolute neutrophil count

3.7.2.2 Management of Infusion-Related Reaction [PLD Cohort]

Serious and sometimes life-threatening IRRs can occur with PLD. The majority of the infusion-related events occur during the first infusion. Ensure that medications to treat IRRs, and cardiopulmonary resuscitation equipment are available for immediate use prior to initiation of PLD. Administer first dose of PLD on study (C1D1) as 1 mg/min IV infusion; after Cycle 1, if tolerated, PLD can be delivered as a 1-hour infusion. Management guidelines for PLD associated IRRs are noted below.

Infusion-Related Reaction	Toxicity Management
Grade 1 or Grade 2	• Temporarily stop PLD until resolution then resume at a reduced infusion rate per local practice. • Following Grade 1 or Grade 2 infusion reactions to PLD, PLD should be administered per institutional guidelines. • If there is no institutional guideline, the following is recommended: 5% of the total dose should be infused slowly over the first 15 minutes. If tolerated without reaction, the infusion rate may then be doubled for the next 15 minutes. If tolerated, the infusion rate may then be completed over the next hour for a total infusion time of 90 minutes.
Grade 3 or Grade 4	• Permanently discontinue PLD

3.7.2.3 Management of Mucocutaneous Toxicity [PLD Cohort]

The following are PLD dose modification recommendations for the management of mucocutaneous toxicity, including stomatitis and palmar-plantar erythrodyesthesia (hand foot syndrome).

Severity	PLD Dose Modification
Grade 1	• If no previous Grade 3 or 4 mucocutaneous AE: Continue PLD as planned. • If previous Grade 3 or 4 AE: delay PLD dose up to 2 weeks, then resume PLD at decreased dose level
Grade 2	• Delay PLD dosing up to 2 weeks or until resolved to Grade 1. • If no resolution to ≤ Grade 1 within 2 weeks, discontinue PLD. • If resolved to ≤ Grade 1 within 2 weeks, and no previous Grade 3 or 4 mucocutaneous AE: continue PLD treatment at previous dose. • If resolved to ≤ Grade 1 within 2 weeks but previous Grade 3 or 4 mucocutaneous AE: resume PLD treatment at decreased dose level
Grade 3	• Delay PLD dosing up to 2 weeks or until resolved to ≤ Grade 1. Then resume PLD treatment at decreased dose level. • Discontinue PLD if there is no resolution after 2 weeks.
Grade 4	• Delay PLD dosing up to 2 weeks or until resolved to ≤ Grade 1. Then resume PLD treatment at decreased dose level. • Discontinue PLD if there is no resolution after 2 weeks.

3.7.2.4 Management of Left Ventricular Ejection Fraction Decreased [PLD Cohort]

If a subject's left ventricular ejection fraction (LVEF) drops below institutional limit of normal or by at least 15% (absolute percentage points) from baseline value, study treatment (SL-172154, PLD or combination) should be discontinued. LVEF should be re-assessed within 45 days and every three months until full recovery. Upon full recovery, defined as LVEF increase to within 5% (absolute percentage points) of baseline within 45 days from LVEF nadir, study treatment (SL-172154, PLD or combination) can be resumed at investigator's discretion. Continuation of treatment should be followed by additional LVEF evaluation within 2 weeks.

3.7.3 Toxicity Management Guidelines for MIRV

The toxicity management guidelines provided in this section represent general guidance for AEs that are considered by the investigator to be possibly related or related to treatment with MIRV.

3.7.3.1 MIRV Treatment Criteria

In the absence of an AE that requires dose modification (as specified in the management guidance for a particular toxicity), a subject must meet the following criteria to receive MIRV at any cycle:

- Absolute neutrophil count (ANC) must be $\geq 1.5 \times 10^9$/L (1,500/µL)
- Platelet count must be $\geq 100 \times 10^9$/L (100,000/µL)
- All non-hematologic toxicities for which a causal association to MIRV cannot be ruled out, must be ≤ Grade 2 or returned to baseline; the exceptions to this rule being:
    - Treatment-emergent ocular disorders, which must have recovered to Grade < 1 or baseline
    - Treatment emergent pneumonitis which must have recovered to Grade ≤ 1

Dose reductions to be used for AEs that are considered by the investigator to be possibly related or related to treatment with MIRV are described in Table 6.

Table 6 MIRV Dose Reduction Dose Levels

If the subject was receiving MIRV at:	Dose should be reduced to:
6.0 mg/kg AIBW	5.0 mg/kg AIBW
5.0 mg/kg AIBW	4.0 mg/kg AIBW
4.0 mg/kg AIBW	Permanently discontinue
Reduction of MIRV below 4.0 mg/kg will not be permitted. Dose re-escalation is not permitted.	

Abbreviations: AIBW = adjusted ideal body weight; MIRV = mirvetuximab soravtansine

3.7.3.2 Dose Modifications for MIRV-Related Adverse Events

Table 7 Dose Modifications for MIRV-Related Adverse Events

Severity Grade (CTCAE v5.0)	Dose Modifications for MIRV[a]
HEMATOLOGICAL	
Neutropenia	
Grade 2 and Grade 3	• Hold drug until ANC is ≥ 1.5 x10⁹/L (1500/µL) and resume at the same dose level
Grade 4	• Hold drug until ANC is ≥ 1.5 x109/L (1500/µL) and then resume at one lower dose level
Febrile neutropenia Grade 3 or 4 (with single temperature reading ≥ 38.3°C or a sustained temperature of > 38°C for > 1 hour)	• Hold drug until ANC is ≥ 1.5 x109/L (1500/µL) and then resume at one lower dose level

Severity Grade (CTCAE v5.0)	Dose Modifications for MIRV[a]
Thrombocytopenia	
Grade 2 Grade 3 Grade 3 associated with clinically significant bleeding that requires transfusion therapy Grade 4	• Hold drug until PLT count is ≥ 100 x 109/L (100,000/µL) and dose reduce one dose level
Recurrence of Grade 4	• Permanently discontinue
NON-HEMATOLOGICAL	
Nausea and Vomiting	
Grade 3 (despite use of optimal antiemetics)	Hold drug until resolved to Grade ≤ 1, then resume at one lower level
Grade 4	Permanently discontinue
Diarrhea	
Grade 3 (despite use of optimal antidiarrheal treatment)	Hold drug until resolved to Grade ≤ 1, then resume at one lower level
Grade 4	Permanently discontinue
Ocular Disorders	Refer to Section 3.7.3.5
Noninfectious Pneumonitis	Refer to Section 3.7.3.6
Infusion-Related Reactions (IRR)	Refer to Section 3.7.3.8
ALL OTHER NON-HEMATOLOGICAL TOXICITIES (except AEs related to underlying disease, Grade 3 fatigue, isolated symptomatic Grade 3 biochemistry laboratory abnormalities that last for < 7 days including electrolyte abnormalities that respond to medical intervention)	
Grade 3	Hold drug until resolved to Grade ≤ 1, then resume at one lower level. For any Grade 3 hepatic toxicity that does not resolve to baseline within 7 days, an abdominal CT scan must be performed to assess whether it is related to progressive disease. Grade 3 ALT/AST increase: Hold MIRV until resolved to Grade ≤1. • If resolution to Grade ≤1 within 7 days, resume at the same dose level. • If resolution to Grade ≤1 takes more than 7 days, resume MIRV at one dose level lower starting at the next cycle.
≥ Grade 3 cardiac events (excluding Grade 3 hypertension)	Permanently discontinue
Grade 4	Permanently discontinue

Abbreviations: AE = adverse event; ANC = absolute neutrophil count; CT = computed tomography; CTCAE = common terminology criteria for adverse events; MIRV = mirvetuximab soravtansine; PLT = platelets.

a. Failure to meet retreatment criteria within 1 cycle (21 days) after the missed dose due to insufficient recovery from a treatment-related toxicity will result in treatment discontinuation unless otherwise specified in the management guidance for a particular toxicity.

3.7.3.3 Monitoring and Management of Nausea and Vomiting [MIRV Cohort]

MIRV-related nausea (46% all grades; 1% Grade ≥ 3) and vomiting (16% all grades; 1% Grade ≥ 3) have been reported in patients treated with MIRV, despite premedication with dexamethasone. Therefore, it is recommended that an antiemetic (e.g., 5-HT3 serotonin receptor antagonists such as palonosetron, granisetron, or ondansetron) medication is provided before each MIRV dose (Section 3.6). Additional antiemetics may be used at any time at the discretion of the investigator, according to institutional or other practice guidelines, ASCO, European Society for Medical Oncology (ESMO), and NCCN. Subjects should be advised to contact their treating physician at the first sign of vomiting or worsening nausea.

3.7.3.4 Monitoring and Management of Diarrhea [MIRV Cohort]

Mild to moderate diarrhea has been reported in subjects treated with MIRV. Subjects should be advised to contact the investigator at the first sign of diarrhea. Subjects may then be treated according to standard institutional practice. One suggested regimen would be the administration of loperamide 2 mg at the first sign of loose stool, with repeat dosing every two hours until symptoms resolve [Wadler, 1998].

3.7.3.5 Ocular Disorders [MIRV Cohort]

Changes in visual acuity resulting from reversible keratopathy have been reported in other studies of DM4-containing immunoconjugates that use the SPDB linker [Younes, 2012]. Subjects receiving MIRV in the Phase 1 and 3 trials (IMGN853-0401, IMGN853-0403) reported ocular AEs consistent with reversible keratopathy/corneal epitheliopathy. At the 6.0 mg/kg AIBW Q3W dose level, MIRV-related dry eye (26% all grades; 1% Grade ≥ 3), keratopathy (33% all grades; 1% Grade ≥ 3), blurred vision (42% all grades; 2% Grade ≥ 3), eye pain (13% all grades; 1% Grade ≥ 3), and photophobia (12% all grades; 1% Grade ≥ 3) were reported in Phase 3 study IMGN853-0403.

3.7.3.5.1 Monitoring and Preventive Measures [MIRV Cohort]

In early dose escalation there was a relationship observed between MIRV plasma exposure and likelihood of an ocular event as well as with response. Exposure-response modeling suggested that a dose of 6.0 mg/kg AIBW provided adequate exposure for response while also maintaining overall exposure within a range that decreased the potential for ocular AEs. Due to the observation of ocular disorders consistent with reversible keratopathy/corneal epitheliopathy in subjects treated with MIRV, ocular function will be carefully monitored. Ocular symptom assessments will be performed at baseline and at Day 1 of every cycle thereafter (Section 6.2).

A complete ophthalmic examination will be performed in all subjects receiving MIRV by an ophthalmologist, optometrist, physician assistant, or equivalent eye care professional and will include the following at a minimum: manifest refraction, best distance corrected visual acuity (BCVA), intra-ocular pressure (IOP) assessment, fundoscopy, and slit lamp examination to assess the cornea for keratopathy and other corneal abnormalities. The visual acuity assessment should be performed with refraction, rather than corrected or via pin hole. Fundoscopy is required at baseline and post-treatment visit (PTV) only.

- A complete ophthalmic examination will be performed in all subjects receiving MIRV at baseline (within 21 days before C1D1), prior to Day 1 dosing in Cycles 3, 5, and 7 and at

the PTV (± 2 weeks) including subjects who are asymptomatic or have ≤ Grade 1 ocular AEs. Abnormal corneal findings in asymptomatic subjects will be managed as per Table 8.

- Subjects receiving MIRV who experience CTCAE > Grade 1 ocular AEs while on study will have a complete ophthalmologic examination performed at the emergence of symptoms and at every other cycle thereafter until resolved to baseline or deemed irreversible in the opinion of the eye care professional. Subjects requiring an ophthalmological examination due to symptoms prior to Cycle 2 or 4 will then proceed to every other cycle (approximately 6 weeks) exams as indicated by findings and do not require the routine, asymptomatic exams at Cycle 3, 5, and 7.

Subjects are advised to avoid using contact lenses while on MIRV except when benefit outweighs risk per an eye care professional. Eyelid hygiene should be performed as per direction of an eye care professional. Please refer to Section 5.3.2.2 for details on the use of lubricating artificial tears and recommendations for prophylactic steroid eye drops in subjects with ocular symptoms. The use of UVA/UVB sunglasses in full daylight is recommended during the study. If subjects report signs or symptoms of ocular AEs, including but not limited to blurred vision or eye irritation, the management and dose modification guidelines outlined in Table 8 and Table 9 should be followed.

3.7.3.5.2 Management and Dose Modifications Guidelines [MIRV Cohort]

If a subject develops new CTCAE > Grade 1 ocular symptoms, MIRV will be held until the subject undergoes a complete examination by an eye care professional. If a subject is found to have confluent superficial keratitis, a cornea epithelial defect, or a 3-line or more loss in BCVA, MIRV dosing must be interrupted until findings improve to nonconfluent keratitis, prior baseline, or complete resolution. Uveitis must improve to Grade 1 or better or prior baseline. Treatment with MIRV may resume if the ocular event improves as above within 28 days of the next scheduled MIRV dose (refer to Table 8 and Table 9 for details). Corneal AEs of any severity should be followed to complete resolution, pretreatment baseline, or are deemed to be irreversible according to the eye care professional. For 2 or more overlapping ocular adverse events (ocular disorders/corneal adverse reactions), dose modification should be based on the ocular adverse event of greater severity. Any other ocular AEs not specifically noted in Table 8 or Table 9 will be managed at the discretion of the treating physician in consultation with their eye care professional.

Subsequent eye examinations will be scheduled to occur in every other cycle going forward from the time that the corneal AE was initially reported until resolution of the corneal toxicity to subject's prior baseline or complete resolution or until it is deemed irreversible even if the results of the subject's ocular symptom assessment show no obvious clinical findings. For subjects with ongoing keratitis/keratopathy, a cornea epithelial defect, or a 3-line or more loss in BCVA at the PTV, an ophthalmic examination should be done every 30 days until complete resolution, stabilization without likelihood of improvement in the opinion of the eye care professional, or return to pretreatment baseline. Ocular symptoms (e.g., blurred vision) should also be assessed at this time. The visual acuity assessment should be performed with refraction, rather than corrected or via pin hole. Refraction is crucial for cases where subjects report blurred vision or other ocular AEs.

Management of ocular AEs with inflammatory characteristics or other non-corneal/visual acuity ocular AEs should include measures as indicated by an eye care professional.

Recommended dosage modifications for corneal AEs should be based on both corneal examination findings using the system outlined in Table 8 and changes in BCVA. Dose modifications for non-corneal ocular AEs are at the discretion of the treating physician, in collaboration with an eye care professional.

Note: Table 8 describes the management of corneal adverse reactions with regard to MIRV dosing. See Table 15 and Table 16 in Appendix Section 16.6 for grading of ocular AEs.

Table 8 Management of Corneal Adverse Reactions (Keratitis/Keratopathy)

Ocular Exam Finding[a]	Management	Guidelines for MIRV Dose Modification
Nonconfluent superficial keratitis or nonconfluent keratopathy[b]	Complete eye examination as outlined in SOA (Section 6.2). Subjects should have frequent symptomatic ocular assessments and repeat eye examinations at least every 6 weeks until resolved to pretreatment baseline or nonconfluent superficial keratitis or better or are deemed to be irreversible by the investigator, even after treatment discontinuation, if needed	Monitor with scheduled ocular exam to complete resolution or return to pretreatment baseline. Continue MIRV dosing.
Confluent superficial keratitis or confluent keratopathy[b], cornea epithelial defect (+NaFl staining), or ≥ 3-line loss in BCVA	Complete eye examination as outlined in SOA (Section 6.2). Subjects should have weekly symptomatic ocular assessments and repeat eye examinations at least every 6 weeks until resolved to pretreatment baseline or are deemed to be irreversible by the investigator, even after treatment discontinuation, if needed.	Hold MIRV dosing until AE has resolved to pretreatment baseline or nonconfluent superficial keratitis or better. Subjects with corneal adverse reactions lasting < 14 days may be allowed to resume MIRV at the same dose level. Recurrence of toxicity on subsequent cycles despite best supportive care will require a dose reduction to one lower dose level. Subjects with corneal adverse reactions lasting ≥ 14 days but no more than 28 days may resume MIRV at one lower dose level. If findings persist >28 days, continuation at reduced dose level is at the discretion of the investigator in consultation with the Sponsor.
Corneal ulcer or clinically significant stromal opacity or BCVA 20/200 or worse	Complete eye examination as outlined in SOA (Section 6.2). Subjects should have weekly symptomatic ocular assessments and repeat eye examinations at least	Hold MIRV dosing. Subjects may be allowed to resume MIRV at one lower dose level after AE has resolved to

Ocular Exam Finding[a]	Management	Guidelines for MIRV Dose Modification
	every 6 weeks until resolved to baseline or are deemed to be irreversible by the investigator, even after treatment discontinuation, if needed.	nonconfluent keratitis or better or to pretreatment baseline within 28 days. If findings persist >28 days, continuation at reduced dose level is at the discretion of the investigator in consultation with the Sponsor.
Corneal perforation	Complete eye examination as outlined in SOA (Section 6.2). Subjects should have weekly symptomatic ocular assessments and repeat eye examinations at least every 6 weeks until resolved to baseline or are deemed to be irreversible by the investigator, even after treatment discontinuation, if needed.	Permanently discontinue MIRV dosing.

[a] Normal = clear cornea, no epithelial defects.

[b] Nonconfluent microcystic epithelial change, punctate epithelial keratopathy, subepithelial inclusion cyst and/or nonconfluent superficial keratitis, superficial punctate keratitis, epithelial erosion

Table 9 Management of Ocular Disorders

Refer to Table 8 for Corneal Adverse Reactions.

Severity Grade (CTCAE v5.0)	Management	Guidelines for MIRV Dose Modifications
Grade 1	Follow SOA (Section 6.2) Monitor for worsening symptoms	Continue MIRV dosing
Grade 2	Complete eye exam as outlined in SOA (Section 6.2) Repeat complete exam as clinically indicated. Subjects should have weekly symptomatic ocular assessments by the investigator until the symptoms resolve to Grade ≤ 1 or are deemed to be irreversible by the investigator.	Hold MIRV dosing until AE has resolved to Grade 1 or better. Subjects with ocular symptoms lasting < 14 days may be allowed to resume MIRV at the same dose level. Subjects with ocular symptoms lasting ≥ 14 days but no more than 28 days may resume MIRV at one lower dose level. Recurrence of Grade 2 toxicity on subsequent cycles despite best supportive care will require a MIRV dose reduction of one dose level.
Grade 3	Complete eye exam as outlined in SOA (Section 6.2). Repeat complete exam as clinically indicated. Subjects should have weekly symptomatic ocular assessments by the investigator until the symptoms resolve	Hold MIRV dosing. Subjects may be allowed to resume MIRV at a lower dose after AE has resolved to Grade 1 or better within 28 days. Recurrence of Grade 3 toxicity on subsequent cycles despite best supportive care will require a MIRV dose reduction of one dose level.

Severity Grade (CTCAE v5.0)	Management	Guidelines for MIRV Dose Modifications
	to Grade ≤ 1 or are deemed to be irreversible by the investigator.	
Grade 4	Complete eye exam as outlined in SOA (Section 6.2). Repeat complete exam as clinically indicated. Subjects should have weekly symptomatic ocular assessments by the investigator until the symptoms resolve to Grade ≤ 1 or are deemed irreversible by the investigator.	Permanently discontinue MIRV.

3.7.3.6 Monitoring of Noninfectious Pneumonitis [MIRV Cohort]

Noninfectious pneumonitis has been observed after the administration of MIRV. Noninfectious pneumonitis may result in fatigue, shortness of breath, cough, or respiratory distress. Drug-induced pneumonitis may be immediately life threatening. If a subject presents with signs or symptoms consistent with pneumonitis and/or other clinically meaningful signs or symptoms of pulmonary toxicity, the subject should be immediately evaluated. Subjects are advised to notify their treating physician immediately if they experience new or worsening shortness of breath, cough, or respiratory distress. Subjects who are asymptomatic may continue dosing of MIRV with close monitoring.

The management and treatment guidelines outlined in Table 10 should be followed.

Table 10 Management of Noninfectious Pneumonitis

CTCAE v5.0 Grade	CTCAE v5.0 Definition	Medical Management of Pneumonitis	Guidelines for Dose Modifications[a]
Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	• Radiologic assessments (CT scan and/or chest x-ray) should be performed as clinically indicated. • Monitor for pulmonary symptoms.	• Continue dosing in asymptomatic subjects and monitor closely.
Grade 2	Symptomatic; medical intervention indicated; limiting instrumental ADL	• Radiologic assessments (CT scan and/or chest x-ray) should be performed as clinically indicated. • Subject must be evaluated by a pulmonary specialist. • Treatment with corticosteroids may be indicated as recommended by a pulmonary specialist and/or institutional guidelines.	• Hold dosing until symptoms resolve to Grade ≤ 1. • MIRV may be resumed at same dose level or one dose level lower after discussion with the Sponsor.
Grade 3	Severe symptoms; limiting self-care		• Permanently discontinue MIRV.

CTCAE v5.0 Grade	CTCAE v5.0 Definition	Medical Management of Pneumonitis	Guidelines for Dose Modifications[a]
	ADL; oxygen indicated	• Radiologic assessments (CT scan and/or chest x-ray) should be performed as clinically indicated. • Subject must be evaluated by a pulmonary specialist. • Treatment with corticosteroids until resolution of symptoms may be indicated as recommended by a pulmonary specialist and/or institutional guidelines. • Bronchoscopy with lavage and/or biopsy when clinically feasible should be performed. • The pneumonitis event must be followed until resolution.	
Grade 4	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)		

Abbreviations: ADL = activities of daily living; AE = adverse event; CT = computed tomography; MIRV = mirvetuximab soravtansine.

a. Failure to meet retreatment criteria within 1 cycle (21 days) after the missed dose due to insufficient recovery from a treatment-related toxicity will result in treatment discontinuation unless otherwise specified in the management guidance for a particular toxicity

3.7.3.7 Management of Electrolyte Imbalance [MIRV Cohort]

Prompt attention should be given to the correction of potential electrolytes imbalance, especially hypokalemia and hypomagnesemia.

3.7.3.8 Potential Infusion-Related Reactions [MIRV Cohort]

Some subjects treated with IV infusions of therapeutic drugs have experienced concurrent IRR (see CTCAE version 5.0). The signs and symptoms may vary and include, for example, headache, fever, facial flushing, pruritus, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, lightheadedness, hypotension, palpitations, and somnolence. Anaphylaxis might occur at any time during an infusion. Before any infusion is started, appropriate medical personnel, medication (e.g., epinephrine, inhaled beta agonists, antihistamines, and corticosteroids), and other required resources to treat anaphylaxis must be readily available. In general, investigators should manage acute allergic or HSRs according to Institutional practices. General guidelines for the management of acute IRRs and for subsequent retreatment are provided in Table 11. Delayed IRRs may occur; therefore, subjects should be advised to seek immediate medical treatment if symptoms newly develop and/or recur after discharge from clinic.

Table 11 Management Guidelines for Potential Infusion-Related Reaction [MIRV Cohort]

Infusion Reaction CTCAE v5.0 Severity Grade	Management
Grade 1: Mild, transient reaction	• Maintain infusion rate unless progression of symptoms to Grade ≥ 2; if symptoms worsen, refer to guidelines below. • Promethazine (or equivalent) 150 mg PO per day (Q4h) PRN for nausea • Diphenhydramine (or equivalent) 25 to 50 mg PO or IV PRN • Methylprednisolone (or equivalent) 125 mg IV PRN
Grade 2: Moderate	• Interrupt infusion and disconnect infusion tubing from subject • Promethazine (or equivalent) 150 mg PO per day (Q4h) PRN for nausea • Diphenhydramine (or equivalent) 25 to 50 mg PO or IV PRN • Acetaminophen (or equivalent) 650 mg PO PRN • Methylprednisolone (or equivalent) 125 mg IV PRN • After recovery from symptoms, resume the infusion at 50% of the previous rate and if no further symptoms appear, gradually increase rate until infusion is completed. • For subsequent dosing in future cycles, subjects should be premedicated with dexamethasone (or equivalent) 8 mg PO BID the day before drug administration and acetaminophen (or equivalent) 650 mg PO, diphenhydramine (or equivalent) 25 to 50 mg PO, and dexamethasone 10 mg IV 30 to 60 min before dosing.
Grade 3: Severe, prolonged reaction not rapidly responsive to symptomatic medication and/or brief interruption of infusion; recurrence of symptoms after initial improvement; hospitalization indicated for clinical sequelae OR Grade 4: Life-threatening consequences, urgent intervention indicated	• Immediately stop infusion and disconnect infusion tubing from subject. • Administer diphenhydramine (25 to 50 mg) IV (or equivalent) • Administer IV steroids (methylprednisolone (or equivalent) up to 0.5 mg/kg Q 6h) to treat ongoing reaction and prevent recurrence • Administer bronchodilators (nebulized albuterol/salbutamol, 2.5 to 5 mg in 3 mL of saline or equivalent) as medically indicated • Administer normal saline as medically indicated • Administer epinephrine (0.2 to 0.5 mL of a 1:1000 dilution (0.2 to 0.5 mg) SQ or IM) as medically indicated. Epinephrine should only be used if all other treatment methods fail to manage the IRR. • Advise subject to seek emergency treatment and notify investigator/clinic if the infusion-related symptoms recur after discharge from clinic. • Report as an SAE (see Section 7.4). • Permanently discontinue study medication treatment

Abbreviations: BID = twice a day; CTCAE = common terminology criteria for adverse events; IM = intramuscular; IRR = infusion-related reaction; IV = intravenously; PO = orally; PRN = as needed; SAE = serious adverse event; SQ = subcutaneous

3.8 Subject Withdrawal of Consent

- A subject may withdraw from the study at any time at her own request; or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. The latter is expected to be uncommon. The subject may withdraw consent from further treatment on the study and continue in the survival follow-up (SFU) portion of the study or may withdraw consent from further

participation in the study (e.g., permanently discontinue study treatment, any follow-up study procedures, no longer be contacted for survival).

- At the time of study medication discontinuation, a PTV should be conducted, as shown in the SOA in Section 6.1 and Section 6.2. See SOA for data to be collected at the time of study discontinuation of study treatment and for any further evaluations that need to be completed. Every effort must be made to continue follow-up of subjects for protocol-specified safety follow-up procedures to capture AEs, SAEs, and unanticipated problems.
- If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data or biological samples collected before such a withdrawal of consent.
- If a subject withdraws from the study, she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

3.9 Lost to Follow-Up

- A subject 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 subject fails to return to the clinic for a required study visit:
    - The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.
    - Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter sent to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
    - Should the subject continue to be unreachable, she will be considered as lost to follow-up and withdrawn from the study.

3.10 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 country regulatory authorities as required. If the study is prematurely terminated or suspended, the investigator will promptly inform the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and will provide the reason(s) for the termination or suspension. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected or destroyed and a study-site closure visit has been performed.

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or Good Clinical Practice (GCP) guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further development of SL-172154
- Determination of unexpected, significant, or unacceptable risk to subjects

3.11 Study Treatment Discontinuation Criteria

A subject will receive the assigned study treatment (e.g., SL-172154 and PLD or SL-172154 and MIRV) until any of the following events occur during the study:

- Documented disease progression (radiological or clinical)
- A subject suffers an AE that, in the judgement of the investigator, Sponsor, or Medical Monitor, presents an unacceptable risk to the subject
- General or specific changes in the subject's condition (e.g., a significant intercurrent illness or complication) that, in the judgement of the investigator, are unacceptable for further administration of study treatment
- Subject decides to discontinue further study treatment
- Occurrence of pregnancy
- Significant non-compliance with protocol requirements
- Death
- Termination of the study by Sponsor

If one agent in the assigned regimen is permanently discontinued for any reason, at the investigator's discretion, the subject may continue to receive the other agent in the assigned regimen as monotherapy until meeting one of study treatment discontinuation criteria.

In the event of permanent discontinuation of all study treatment, subjects should be strongly encouraged to complete all scheduled assessments at the PTV and the SFU contacts.

3.12 Duration of Follow-Up

Subjects who are withdrawn from study treatment for unacceptable AE(s) should be followed until the event(s) are resolved, the subject is lost to follow-up, the AE is otherwise explained, or further recovery is not deemed to be feasible. Data on these events should be collected on the AE electronic case report form (eCRF).

Subjects who permanently discontinue study treatment for reasons other than progression will continue with disease assessments until progression or start of another anti-cancer therapy.

Subjects who discontinue study treatment for any reason other than withdrawal of consent will be followed for survival and will be contacted approximately every 3 months from PTV until death or the end of the study, whichever occurs first. During Survival Follow-up, the start date of the first anticancer therapy will be collected and entered in the electronic data capture (EDC) system.

3.13 End-of-Study Definition

The end of study is defined as the point of final data capture (e.g., the point at which all required data has been collected to answer the research questions in the protocol) or date the study is closed by the Sponsor, whichever occurs first.

After the end-of-study, subjects who are still in survival follow-up part of the study should receive standard of care treatment as determined by their health care provider after completion of the study.

4. STUDY POPULATION

Patients 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 Inclusion Criteria

Subjects must meet <u>all</u> the following criteria:

1. Subject has voluntarily agreed to participate by giving written informed consent in accordance with ICH/GCP guidelines and applicable local regulations.
2. Age ≥ 18 years.
3. **[PLD Cohort]** Subject has a histologically confirmed diagnosis of high grade EOC (including primary peritoneal cancer or fallopian tube cancer).

   NOTE: Non-epithelial tumors and ovarian tumors with low malignant potential are excluded.
4. **[PLD Cohort]** Subject must have platinum-resistant disease, defined as disease progression within 180 days (6 months) following the last administered dose of platinum therapy.

   NOTE: Progression should be calculated from the date of the last administered dose of platinum therapy to the date of the radiographic imaging showing progression.
   NOTE: Subjects who are primary platinum refractory, defined by progressing during or within 1 month of upfront platinum therapy, are excluded.
5. **[PLD Cohort]** Subjects may have received any number of prior lines of therapy for EOC; however, they may not have received more than 1 prior line of systemic anticancer therapy for platinum-resistant disease.

   Lines of therapy are defined in this study as:

   - Adjuvant ± neoadjuvant is considered 1 line of therapy.
   - Maintenance therapy (e.g., bevacizumab, PARP inhibitors) will be considered part of the preceding line of therapy (i.e., not counted independently).
   - Therapy changed due to toxicity in the absence of progression will be considered part of the same line (i.e., not counted independently).
   - Hormonal therapy will be counted as a separate line of therapy unless it was given as maintenance.

6. **[MIRV Cohort]** Subject has a histologically confirmed diagnosis of high grade serous EOC (including primary peritoneal cancer or fallopian tube cancer).

   NOTE: non-epithelial tumors and ovarian tumors with low malignant potential are excluded.

7. **[MIRV Cohort]** Subject must have platinum-resistant disease as defined by:

   - Subjects who have only had 1 line of platinum-based therapy must have received at least 4 cycles of platinum, must have had a response (complete response/remission [CR] or partial response/remission [PR]) and then progressed between > 3 months and ≤ 6 months after the date of the last dose of platinum.
   - Subjects who have received 2 or 3 lines of platinum therapy must have progressed on or within 6 months after the date of the last dose of platinum.

   NOTE: Progression should be calculated from the date of the last administered dose of platinum therapy to the date of the radiographic imaging showing progression.

   NOTE: Subjects who are platinum refractory during front-line treatment are excluded [primary platinum-refractory disease, defined as disease that did not respond to (CR or PR) or has progressed within ≤ 3 months of the last dose of first-line platinum-containing chemotherapy].

8. **[MIRV Cohort]** Subjects must have received at least 1 but no more than 3 prior systemic lines of anticancer therapy.

   Lines of therapy are defined in this study as:

   - Adjuvant ± neoadjuvant is considered 1 line of therapy.
   - Maintenance therapy (e.g., bevacizumab, PARP inhibitors) will be considered part of the preceding line of therapy (i.e., not counted independently).
   - Therapy changed due to toxicity in the absence of progression will be considered part of the same line (i.e., not counted independently).
   - Hormonal therapy will be counted as a separate line of therapy unless it was given as maintenance.

9. **[MIRV Cohort]** Willing to provide an archival tumor tissue block or slides or undergo new biopsy using a low-risk, medically routine procedure for IHC confirmation of FRα positivity.

10. **[MIRV Cohort]** Subject's tumor must be positive for FRα expression defined as PS2+ ≥ 25% by the Ventana FOLR1 Assay.

11. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.

12. Measurable disease by RECIST v1.1 using radiologic assessment.

13. Laboratory values must meet the following criteria.

Laboratory parameter	Threshold value
Absolute neutrophil count (ANC)	≥ 1.5 x 10^9/L without GCSF in prior 10 days or long-acting WBC growth factors in prior 20 days
Platelet count	≥ 100 x 10^9/L without platelet transfusion in prior 10 days
Hemoglobin (Hgb)	> 9.0 g/dL without packed RBC transfusion in the prior 7 days
Creatinine clearance (CrCl)	≥ 30 mL/min (using modified Cockcroft-Gault formula; Appendix Section 16.3)
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
Serum albumin **[MIRV cohort only]**	≥ 2 g/dL
Left ventricular ejection fraction (LVEF) **[PLD Cohort only]**	> 50% by ECHO/MUGA

14. Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test within 4 days of the first dose of study treatment. FCBP must use 2 highly effective methods of contraception starting at least 14 days prior to the first dose of study treatment, throughout the study, and for at least 6 months (or for the duration required by local regulatory guidance) after the last dose of PLD or at least 3 months after the last dose of SL-172154 or MIRV, whichever is longer. See Appendix Section 16.2 for further details regarding effective methods of contraception.
15. Subjects must have stabilized or recovered (Grade 1 or baseline) from all prior anti-cancer therapy-related toxicities. NOTE: Grade 2 alopecia is acceptable for either cohort; Grade 2 sensory neuropathy **[PLD Cohort only]** or Grade 1 sensory neuropathy **[MIRV Cohort only]** is acceptable.
16. **[MIRV Cohort only, Dose Expansion only]** Willing to consent to 1 mandatory pretreatment and 1 on-treatment tumor biopsy, unless there is excessive risk from the procedure as determined by the investigator.

4.2 Exclusion Criteria

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

1. Prior treatment with a SIRPα targeting agent, anti-CD47 agent or CD40 agonist.
2. **[PLD Cohort]** Prior treatment with doxorubicin or PLD.
3. **[MIRV Cohort]** Prior treatment with MIRV or another FRα-targeting agent.

4. Any anti-cancer therapy within the time intervals noted below prior to first dose (Day 1) of study treatment:

Therapy	Washout period
Chemotherapy	4 weeks or 5 half-lives, whichever is shorter
Hormonal therapy	4 weeks or 5 half-lives, whichever is shorter
PD-1/L1 inhibitor and other immunotherapies not otherwise specified	4 weeks or 5 half-lives, whichever is shorter
Tumor vaccine	4 weeks
Cell-based therapy	8 weeks
Other mAbs or biologic therapies	4 weeks or 5 half-lives, whichever is shorter
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

5. Concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment is prohibited. Concurrent use of hormones for non-cancer-related conditions is acceptable.
6. Receipt of live attenuated vaccine (including live attenuated vaccines for COVID-19) within 28 days of the first dose of study treatment.
7. Current or prior use of systemic immunosuppressive medication within 7 days prior to first dose of study treatment. The following are exceptions to this exclusion criterion:
    - Intranasal, inhaled, topical, injected (e.g., intra-articular injection) or local steroid or immunosuppressive medication.
    - Steroids as premedication for HSRs (e.g., CT scan premedication).
8. **[MIRV Cohort]** Requires use of folate-containing supplements (e.g., folate deficiency).
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, history of multiple sclerosis (MS) or other demyelinating disease and/or Lambert-Eaton syndrome (paraneoplastic syndrome). Exceptions include controlled Type I diabetes, vitiligo, alopecia areata or hypo/hyperthyroidism.
10. Ongoing or active infection (e.g., no systemic antimicrobial therapy for treatment of infection within 5 days of D1 of study treatment).
11. Known severe hypersensitivity to the active drug substance or to any of the excipients for the agents to be administered or subjects with known hypersensitivity to Chinese hamster ovary cell products. Prior severe hypersensitivity to monoclonal antibodies **[MIRV Cohort only]** or liposomal preparations **[PLD Cohort only]**.
12. Severe gastrointestinal conditions such as clinical or radiological evidence of bowel obstruction within 4 weeks prior to study entry.
13. Clinically significant or uncontrolled cardiovascular disease including any of the following:

- Myocarditis
- Unstable angina within 6 months from first dose of study treatment
- Acute myocardial infarction within 6 months from first dose of study treatment
- 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 block without a pacemaker, circulatory collapse requiring vasopressor or inotropic support, or arrhythmia requiring therapy)
- History of hemorrhagic or ischemic stroke within 6 months prior to enrollment
- Prior anthracycline-related cardiotoxicity or prior anthracycline exposure approaching the lifetime limit **[PLD cohort only]**

14. **[MIRV Cohort]** History of cirrhotic liver disease (Child-Pugh Class B or C).
15. **[MIRV Cohort]** Active or chronic corneal disorders, history of corneal transplantation, or active ocular conditions requiring ongoing treatment/monitoring, such as uncontrolled glaucoma, wet age-related macular degeneration requiring intravitreal injections, active diabetic retinopathy with macular edema, macular degeneration, presence of papilledema, and/or monocular vision.
16. Previous clinical diagnosis of noninfectious interstitial lung disease (ILD), including noninfectious pneumonia.
17. 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 first dose of study treatment and no longer require steroids.
18. Women who are pregnant or breast feeding, or who plan to become pregnant or breast feed while receiving study treatment.
19. 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.
20. 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 the study treatment.
21. Has undergone allogeneic stem cell transplantation or organ transplantation.
22. Known history or positive test for human immunodeficiency virus (HIV), 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 RNA).

    NOTE: *Hepatitis B virus (HBV)*: Subjects who are hepatitis B core antibody [HbcAb] positive, but HbsAg negative are eligible for enrollment. *HCV*: Subjects who are HCV Ab positive, but HCV RNA negative are eligible for enrollment.

4.3 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently treated in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reason, eligibility criteria, and any SAEs related to study procedure(s).

5. PHARMACEUTICAL PRODUCT INFORMATION

5.1 SL-172154

5.1.1 Investigational Product Description

Investigational Product Name:	**SL-172154**
Formulation description:	Solution containing SL-172154 10 mg/mL. Refer to the Study Pharmacy Manual (SPM) for further description of the drug product.
Dosage form:	Supplied as frozen liquid solution in a glass vial.
Unit dose strength(s)/Dose Level(s):	SL-172154 10 mg/mL (Refer to Section 3.2 for dose levels)
Physical Description:	SL-172154 solution, 10 mg/mL in a glass vial closed with a FluroTec® rubber stopper and sealed with a flip-off aluminium seal. See the SPM for additional details.
Route/ Administration/ Duration:	• Delivered as IV solution via a syringe pump or IV infusion pump. See the SPM for additional details. • Duration of infusion depends on the dose. See the SPM for additional details. Infusion rate may change based on final drug volume needed for administration, safety, and tolerability of the infusion for the subject and/or observed safety findings during the study. o For the 3.0 mg/kg dose the duration of infusion is 120 minutes (±15 min). o For the 6.0 mg/kg dose the duration of infusion is 180 minutes (±15 min). o For the 1.0 mg/kg dose the duration of infusion is 60 minutes (±10 minutes). • Premedication for IRR prophylaxis is to be administered at least 30 minutes prior to each SL-172154 administration, premedications are as follows: dexamethasone (8 mg IV), acetaminophen (650 to 1000mg PO), diphenhydramine (25 to 50mg, or equivalent, PO or IV), and famotidine (20 mg, or equivalent, IV or PO). If famotidine is used, IV administration is the preferred route for premedication. If IV formulation of famotidine is not available at the study site,

Investigational Product Name:	SL-172154
	oral famotidine may be used instead and should be administered approximately 60 min prior to SL-172154. • Additional premedication with dexamethasone (8 mg IV) one day prior to SL-172154 administration is not required but can be optionally given. • The dose and administration method of prophylactic premedication can be modified at the Investigator's discretion.
Dosing instructions:	Determine the number of vials needed based on the assigned dose level (in mg/kg) and the subject's weight (in kg). See the SPM for instructions on dose preparation and information on compatible administration materials. Doses of SL-172154 are to be administered as an IV infusion via an infusion or syringe pump that can ensure precision to at least 0.1 mL/min.
Secondary Packaging/Quantity/Label type	This is an open-label study. Each vial of SL-172154 will be supplied in a single vial carton. See SPM for details.
Manufacturer/ Source of Procurement:	Manufactured for Shattuck Labs by Lyophilization Services of New England, Bedford, NH, USA

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

5.1.2 Preparation, Handling, Administration, and Storage of SL-172154

5.1.2.1 Preparation

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

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

5.1.2.2 Handling

Under normal conditions of handling and administration, SL-172154 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 SL-172154.

5.1.2.3 Administration

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

administration of SL-172154. Refer to the SL-172154 SPM for further details regarding administration.

Infusion rate: The duration of infusion stipulated for each dose is outlined in Table 1 (Section 3.2.1; PLD Cohort) and Table 2 (Section 3.2.2; MIRV Cohort).

***NOTE**: A physician must be immediately available to respond to emergencies during all administrations of SL-172154. A fully functional resuscitation facility must be available. SL-172154 must not be administered via IV push or bolus but as an IV infusion using an infusion or syringe pump.*

5.1.2.4 Storage

SL-172154 must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of SL-172154 drug product will be limited to the investigator and authorized site staff. SL-172154 must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

SL-172154 drug product vials are to be stored frozen at a temperature -75°C ± 10°C. Please see SPM for guidance on temperature excursions outside of this range. 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 Dosing and Change in Weight

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

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

5.1.4 Monitoring Dose Administration

SL-172154 must be administered in an outpatient oncology treatment center or inpatient unit to enable close monitoring of subjects and proactive management of AEs. The risks associated with administration of SL-172154 include infusion reactions and CRS as described in Section 1.7.1. 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. In case an event of CRS should occur, ensure that at least 2 doses of tocilizumab are available prior to each infusion of SL-172154 (see Section 3.7.1.2 for toxicity management recommendations). When tocilizumab is not available, consider using drug with similar mechanism of actions such as anti-IL-6 receptor monoclonal antibodies (e.g., sarilumab) or anti-IL-6 mAbs (e.g., siltuximab).

Subjects will be monitored prior to, during, and after the completion of each SL-172154 infusion. Vital signs will be measured as outlined in the SOA in Section 6.1 and Section 6.2; vital signs may also be measured at other timepoints as clinically indicated.

5.1.5 SL-172154 Accountability and Treatment Compliance

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

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

Refer to the SL-172154 SPM for further instructions on handling and disposal requirements.

5.1.6 Treatment of SL-172154 Overdose

An overdose of SL-172154 is defined as the administration of a dose (> 10% of the intended dose) and/or schedule greater than the dose and/or schedule that had been studied to date. If an overdose is suspected, the investigator should contact the Sponsor to confirm the highest dose and schedule tested to date. In the event of an overdose of SL-172154, the investigator should:

- Closely monitor the subject for AEs/SAEs and laboratory abnormalities for at least 2 weeks following the infusion. No information on treatment of overdose of SL-172154 is currently available. General supportive measures should be used as appropriate. The appropriate AE management guideline should be followed (Section 3.7.1) where applicable. Pharmacologic effect could persist even after SL-172154 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.
- Overdose itself is not typically considered an AE or SAE. However, if the overdose results in an AE, the AE must also be recorded on the AE eCRF. Overdose does not automatically make an AE serious, but if the consequences of the overdose meet the definition of a serious event, for example death or hospitalization, the event is serious and must be reported as an SAE (Section 7.4).

- 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 planned and actual dose in the eCRF.

Decisions regarding dose interruptions for overdose of SL-172154 will be made by the investigator in consultation with the Sponsor Medical Monitor based on the clinical evaluation of the subject.

5.2 Pegylated Liposomal Doxorubicin (PLD)

PLD (40 mg/m^2) will be administered IV on Day 1 of each 28-day cycle. The first dose of PLD (Cycle 1 Day 1) should be administered as 1 mg/min IV infusion; after Cycle 1, if tolerated, subsequent doses of PLD can be delivered as a 1-hour infusion. Refer to the PLD local prescribing information for details regarding preparation, handling, administration, storage, instructions, and precautions. An accurate and current accounting of PLD administered to each subject must be maintained on an ongoing basis by a member of the study site staff throughout the course of the study.

The dose amount required to prepare the PLD infusion solution will be based on the subject's body surface area (m^2). All subjects should be weighed within 3 days prior to dosing for every cycle to ensure they did not experience either a weight loss or gain > 10% from the weight used for the last dose calculation. For weight change less than 10% the decision to recalculate the PLD dose can be in accordance with institutional practice. If the subject experienced either a weight loss or gain > 10% compared to the weight used for the last dose calculation, the amount of PLD must be recalculated. Dose capping should not be performed.

In order to mitigate IRRs, a premedication regimen may be administered as per local practice, which may include diphenhydramine 25 to 50 mg IV or oral equivalent, and/or acetaminophen/paracetamol 650 mg IV or oral equivalent. Primary prophylactic use of steroids for nausea/vomiting is not permitted.

Discontinue PLD for burning or stinging sensation or other evidence indicating perivenous infiltration or extravasation. Manage confirmed or suspected extravasation as per institutional practice.

5.3 Mirvetuximab Soravtansine (MIRV)

5.3.1 MIRV Product and Packaging Description

The investigational product, MIRV, will be provided by the Sponsor, at a protein concentration of 5.0 mg/mL in an aqueous pH 5.0 buffered solution. See the MIRV IB for complete list of excipients.

MIRV will be provided in a 20 mL glass, single-use Type I vial. The container closure for the Type I glass vials will consist of a 20 mm ethylene tetrafluoroethylene (ETFE)-coated serum stopper (FluroTec®) with a 20 mm aluminum TruEdge® seal with blue Flip-off® top.

Refer to the SPM for labeling and storage information.

5.3.2 Preparation and Administration of MIRV

5.3.2.1 Premedication for MIRV Treatment

All subjects must receive 325 to 650 mg of acetaminophen/paracetamol (orally [PO] or IV), 10 mg IV dexamethasone, and 25 to 50 mg diphenhydramine (IV or PO) (equivalent drugs of similar drug classes is also acceptable) at least 30 min before each infusion of MIRV. If individual subjects require more intensive treatment to prevent IRRs, investigators may modify the regimen accordingly. An antiemetic medication (e.g., 5-HT3 serotonin receptor antagonists such as palonosetron, granisetron or ondansetron or appropriate alternatives) is recommended before each MIRV dose and may be used at any time at the discretion of the treating physician.

5.3.2.2 Prophylactic Use of Eye Drops

5.3.2.2.1 Corticosteroid Eye Drops

All subjects assigned to receive MIRV will be mandated to use corticosteroid eye drops as prescribed by the treating physician unless the risk outweighs the benefit as per the ophthalmologist/physician. All subjects will be instructed to self-administer 1% prednisolone (Pred Forte® or generic equivalent) 6 times daily on Days -1 to 4 and 4 times daily on Days 5 to 8 of each cycle during the study. For individual subjects who cannot tolerate the preservative contained in 1% prednisolone, other corticosteroid eye drops may be substituted (e.g., difluprednate 0.05%; Durezol®) and administered on Days -1 to 8 of each cycle at a frequency prescribed by the eye care professional. If prednisolone eye drops cannot be obtained, alternate steroid eye drops are acceptable.

5.3.2.2.2 Lubricating Artificial Tears

Subjects assigned to receive MIRV will be mandated to use lubricating artificial tears on a daily basis (as directed by the product prescribing information or the treating physician). Preservative-free lubricating drops are recommended. Subjects should be advised to wait at least 15 minutes after corticosteroid eye drop administration before instilling lubricating eye drops.

5.3.2.3 Calculation for Adjusted Ideal Body Weight

The total dose of MIRV is calculated on each subject's AIBW using the formula provided in Appendix Section 16.4. The subject's weight will be collected each cycle. Dosing will be based off the weight at baseline prior to C1D1 unless current weight is >10% different. If required per institutional policy, it is acceptable to recalculate AIBW at each cycle using the subject's current weight. Sites must clearly document the weight used to calculate dose at each cycle. Dosing must be modified for significant (≥ 10%) changes in body weight (not influenced by weight gain or loss attributed to fluid retention).

5.3.2.4 Preparation of MIRV

MIRV is an anticancer drug, and, as with other potentially toxic compounds, caution should be exercised when handling this compound. It is recommended that gloves and protective garments be worn during preparation. The desired amount of drug should be withdrawn from the vial(s) and diluted using 5% dextrose to a final concentration as outlined in the SPM.

Note: MIRV is incompatible with saline (0.9% sodium chloride). Therefore, dilutions should be made using 5% dextrose. Infusion bags should be labeled with the protocol number, subject number, storage temperature, dose, and volume of MIRV filtered into the bag, or labeled according to institutional protocol. Once the solution is prepared, the infusion bag should be stored at room temperature protected from direct sunlight, and the infusion must be completed within eight hours of preparation. Please refer to the SPM for further details.

If necessary, MIRV from different drug lots may be mixed in a single-dose administration.

MIRV is administered at 6.0 mg/kg AIBW as an IV infusion following preparation as outlined in the SPM. Details on required and compatible infusion materials are also included in the SPM.

At C1D1 MIRV should be administered at a rate of 1 mg/min; after 30 min, the rate can be increased to 3.0 mg/min if well tolerated. If well tolerated after 30 min at 3.0 mg/min, the MIRV infusion rate may be increased to 5.0 mg/min. Subsequent infusions may be delivered at the tolerated rate. Therefore, the overall length of infusion will vary depending on dose and subject tolerability. After infusion, the IV line should be flushed with 5% dextrose as needed (PRN) to ensure delivery of the full dose.

Subjects will be carefully observed during each infusion and vital signs are taken as outlined in the SOA (Section 6.2). Subjects will remain in the clinic under observation for 2 hours after the first MIRV infusion, and for at least 1 hour after each subsequent MIRV infusion. While in the treatment area, subjects should be closely monitored for AEs.

5.3.3 MIRV Accountability

Specific details regarding storage and handling of MIRV can be found in the SPM.

Accountability and shipping documents for MIRV must be maintained by the investigator or designee (e.g., the study pharmacist). The investigator or designee must maintain an accurate record of all MIRV received, stored, dispensed, destroyed, and used in an Investigational Product Dispensing/Accountability Log or equivalent. These records must always be available for inspection, and a copy will be supplied to the Sponsor on request. Information recorded on the Accountability Log should include dates and quantities of drug received, dates and quantities of drug dispensed, subject number to whom drug is administered, lot number of drug administered, the recorder's initials, and dates and quantities of drug destroyed or returned. Upon receipt, vials should be visually inspected for vial integrity (i.e., cracks or leaks) and a record of any damaged or suspect drug should be kept on the Accountability Log.

Upon completion of the study, all MIRV dispatched to a site must be accounted for and unused supplies destroyed according to the site's standard operating procedures (SOPs) or returned to depot (refer to SPM). The original drug reconciliation records shall be maintained at the site and a copy collected and sent to the Sponsor or designee once a representative of the company has confirmed the drug accountability.

Drug accountability will be monitored.

5.3.4 MIRV Study Treatment Compliance

MIRV supplied for the study may not be used for any purpose other than the study or administered other than as described in this protocol.

If necessary, MIRV from different drug lots may be mixed in a single-dose administration.

Under no circumstances is the investigator allowed to release MIRV supplies to any physician not named in the Food and Drug Administration (FDA) Form 1572 (or equivalent) or to administer these supplies to a patient not enrolled in this study. If investigational supplies are to be dispensed from any facility other than that supervised directly by the investigator (i.e., hospital pharmacy, satellite pharmacy), it is the responsibility of the investigator to ensure that all MIRV is stored and administered as described (refer to the SPM for instructions).

5.3.5 MIRV Overdose and Medication Error

There is no known treatment/antidote available for MIRV. Supportive measures should be instituted if an instance arises in which a subject suffers an overdose of MIRV.

The Sponsor must be notified within 24 hours of any error leading to the administration of either 10% more or 10% less than the intended dose; in such cases, the event must be reported in the clinical trial database. If an error resulted in a SAE, a Serious Adverse Event form must be submitted within 24 hours of the event (see Section 7.4).

6. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SOA. Protocol waivers or exemptions are not allowed.
- 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 subject's routine clinical management (e.g., blood count) and obtained before signing of the informed consent form (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.
- Beginning with Cycle 2, if the start of a subsequent cycle (e.g., Day 1) is delayed, the current cycle length is extended [e.g., the cycle lasts longer than 28 days (PLD Cohort) or 21 days (MIRV Cohort)]. The SL-172154 doses in that cycle are not delayed (e.g., administered on Day 8, 15). In addition, the length of subsequent cycles will remain unchanged (i.e., 28 days for PLD Cohort or 21 days for MIRV Cohort).

6.1 Schedule of Assessments: SL-172154 + PLD Cohorts (Dose Escalation and Dose Expansion)

Cycle Length = 28 days		CYCLE 1 (C1)				CYCLE 2 (C2)			CYCLE 3 (C3) and Subsequent Cycles				
Assessment[b]	**Screening[a]**	**D1**	**D8**	**D9**	**D15**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**PTV[q]**	**SFU[r]**
Informed consent	X												
Eligibility criteria	X[c]	X											
Demographics	X												
Medical and disease history	X												
Cancer treatment history	X												
Type and screen (ABO/Rh), Blood phenotyping, DAT[d]	X												
TSH, free T4[j]	X												
Antiviral testing (HBV/HCV)[j]	X												
Record historical BRCA, HRD status (if known)	X												
12-lead ECG[e]	X												
ECHO/MUGA[f]	X								X[f]			X	
Physical examination[g]	X	X	X		X	X		X	X			X	
Vital signs[h]	X	X	X		X	X	X	X	X	X	X		
Pulse oximetry[h]	X	X	X		X	X	X	X	X	X	X		
Height (screening only) / weight	X	X				X			X				
ECOG performance status	X	X	X		X	X		X	X			X	
Pregnancy test[i] (serum or urine, FCBP only)	X								X[i]			X[i]	
Clinical chemistry[j]	X	X	X	X	X	X	X	X	X			X	
Hematology[j]	X	X	X	X	X	X	X	X	X			X	
Coagulation[j] (PT, aPTT, INR, d-dimer, fibrinogen)	X			X									
Ferritin	X			X									
C-reactive protein	X												
Haptoglobin	X			X									

Cycle Length = 28 days		CYCLE 1 (C1)				CYCLE 2 (C2)			CYCLE 3 (C3) and Subsequent Cycles				
Assessment[b]	**Screening[a]**	**D1**	**D8**	**D9**	**D15**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**PTV[q]**	**SFU[r]**
Blood sample for SL-172154 PK[k]			X	X	X		X						
Blood sample for SL-172154 ADA[k]			X		X		X			X[k1]		X[k]	X[k2]
Blood sample for cytokines[l]			X	X	X								
Blood sample for receptor occupancy[l]			X	X	X								
Scans for disease assessment[m]	X								X[m]			X[m]	
CA-125[m]	X								X[m]			X[m]	
SL-172154 administration[n]			X		X		X	X		X	X		
PLD administration[o]		X				X			X				
Concomitant medications	X	←---------- Continuous Monitoring During Treatment Phase of the Study ----------→										X	
Adverse events[p]	X	←---------- Continuous Monitoring During Treatment Phase of the Study ----------→										X	
Survival contact[r] (q3 months ± 14d)													X

Abbreviations: ADA = anti-drug antibodies; AE – adverse event; aPTT = activated partial thromboplastin time; C = cycle; CT = computed tomography; CTCAE = common terminology criteria for adverse event; D = day; DAT = direct antiglobulin test; DLT = dose limiting toxicity; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; FCBP = female of childbearing potential; HBV = hepatitis B virus; HCV = hepatitis C virus; HRD = homologous recombination deficiency; INR = international normalized ratio; IRR = infusion-related reaction; MUGA = multigated acquisition scan; NCI = National Cancer Institute; PK = pharmacokinetics; PLD = pegylated liposomal doxorubicin; PT = prothrombin time; PTV = post-treatment visit; q = every; SAE = serious adverse event; SFU = survival follow-up; RECIST = response evaluation criteria in solid tumors; TSH = thyroid stimulating hormone

a. **Screening**: Screening Period extends from Day -21 to Day -1 for routine clinical assessments unless otherwise specified; subjects may complete Screening and initiate dosing on the same day provided all Screening assessments are completed and confirmed to meet eligibility requirements prior to receipt of PLD or SL-172154. The following screening assessments do not need to be repeated on Cycle 1 Day 1 if performed within 72 hours of the first dose of study treatment: hematology, clinical chemistry, coagulation panel, ECOG status, and physical exam. Baseline CT or positron emission tomography (PET)/CT or Magnetic resonance imaging (MRI) tumor assessments are required for all subjects within 28 days prior to the first dose of study treatment.

b. **Assessment Window**: With the exception of Screening assessments and unless otherwise specified, assessments performed at ≤ 4-week intervals will have a ±3-day window and assessments performed at > 4-week intervals will have a ±1-week window. No assessment window is permitted during the DLT-evaluable period in the dose escalation cohorts.

c. **Eligibility Evaluation**: Subjects must meet eligibility criteria prior to first dose of study treatment.

d. **Blood Phenotyping (ABO/Rh) and DAT**: will be performed at local laboratories according to the laboratory's normal procedures. At screening the following tests will be performed: a) ABO and D group (ABO/Rh) type and antibody screen and antibody identification if required, b) DAT, and c) phenotype/genotype for, at a minimum, the minor antigens Rh C/c, E/e, K, Jk, Fy, and MNS. If assessment was performed within 21 days of first dose of study treatment and all requested information is available, this can be used for baseline assessment.

e. **ECG**: 12-lead electrocardiogram (ECG) must be performed at screening to serve as a baseline for comparison in the event of a cardiac AE/SAE during the study. ECG is to be performed within 30 days of the first dose of study treatment.

f. **ECHO/MUGA**: Echocardiograph (ECHO) or multigated acquisition scan (MUGA) is to be performed for all subjects within 30 days of the first dose of study treatment. ECHO/MUGA is to be performed every 8 weeks (e.g., C3D1, C5D1, etc.) ±7 days during study treatment and at the PTV. The same methodology should be used at each assessment.

g. **Physical Examination**: A full physical exam is required only at screening and PTV. Physical exams should be performed per standard of care during the on-treatment period.

h. **Vital Signs and Pulse Oximetry**: 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 on Day 1 of every Cycle at Predose (within 60 min of starting PLD infusion).
   2. Collect vital signs/pulse oximetry during Cycle 1 on Day 8 and Day 15: Predose (within 60 min of starting the SL-172154 infusion), at the end of infusion (EOI; ±5 min) and then 0.5 hour [hr] (±5 min), 2 hr (±10 min), and 4 hr (±10 min) after end of infusion (EOI) of SL-172154.
   3. Collect vital signs/pulse oximetry on Day 8 and 15 of Cycle 2 and in each subsequent cycle: Predose (within 60 min of starting the infusion) and at the end of infusion [EOI] (±5 min) of SL-172154.
   4. For subjects experiencing any grade IRR, refer to Section 3.7.1.1for schedule of vital signs that should be measured at time of the IRR event.

i. **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 4 days of the first dose of PLD on Cycle 1 Day 1. Repeat this test every 8 weeks during study treatment (i.e., C3D1, C5D1, C7D1, etc.) and at PTV. Contraception should be continued for at least 6 months (or for the duration required by local regulatory guidance) after the last dose of PLD or 3 months after the last dose of SL-172154, whichever is longer.

j. **Hematology/ Clinical Chemistry/ Coagulation/ TSH/ Free T4/ Antiviral Testing:** will be performed at local laboratories according to the laboratory's normal procedures. Laboratory tests required are provided in Section 6.5.9.

k. **Pharmacokinetic (PK) / Anti-Drug Antibody (ADA)**: Blood sample collection timings for SL-172154 PK/ADA measurement are outlined in Section 6.1.1. Blood volumes required will be provided in the Study Lab Manual (SLM). PK/ADA samples should not be collected from infusion port for drug delivery i.e., recommend having a separate line in the opposite arm for sample collection.
   1. If a subject discontinues SL-172154 due to IRR and continues on PLD monotherapy, to the extent feasible, an additional ad-hoc ADA sample should be collected at a subsequently scheduled visit.
   2. All subjects should have just one additional blood sample collected for SL-172154 ADA assessment within 45-90 days of last dose of SL-172154 study treatment.

l. **Cytokines and Receptor Occupancy**: Blood sample collection timing for cytokine and receptor occupancy assessments are outlined in Section 6.1.1. Blood volumes required will be provided in the SLM. Cytokine samples should not be collected from infusion port for drug delivery i.e., recommend having a separate line in the opposite arm for sample collection.

m. **Scans for Disease Assessment and CA-125**: Baseline tumor assessments are required for all subjects within 28 days prior to the first dose of study treatment. CA-125 should also be obtained at screening within 28 days of first dose of study treatment. Baseline and on-treatment tumor assessments for all tumor types by RECIST v1.1 should include CT with contrast of chest, abdomen, and pelvis and other known sites of disease at each time point. Bone scan, PET/CT, and/or MRI should be performed only if clinically indicated. Tumor assessments must be performed at screening and at the following intervals until radiologic disease progression: during the last week (Days 22 to predose on Day 29) of every 2 cycles/8 weeks±1 week through Cycle 6, every 3 cycles/ 12 weeks±1 week thereafter up to year 2, and then every 6 cycles/ 24 weeks±1 week up to conclusion of the study. Subjects who discontinue study treatment for reasons other than disease progression (e.g., AE or withdrawal of consent) will be monitored for radiologic response until start of another anti-cancer therapy, disease progression, withdrawal of consent, or death. CA-125 should be measured to coincide with each scheduled radiographic tumor assessment as outlined above with the last required assessment for CA-125 performed at the PTV which occurs 30 days (±7 days) after the last dose of study treatment. If there is more than one week delay in any cycle, please perform all the subsequent disease assessments per schedule in weeks.

n. **SL-172154 Administration**: Subjects will be monitored prior to and during each SL-172154 infusion. SL-172154 should be administered according to the prescribed dosing schedule in Cycle 1 to align with the safety DLT assessment and sample (PK, ADA, etc.) collection schedules. Beginning on Cycle 2 Day 8, a window of ±2 days is allowed for scheduled dosing days for drug administration (NOTE: each dose must be administered at least 5 days apart from the previous dose). If the start of a subsequent cycle (e.g., Day 1) is delayed, the current cycle length is extended (e.g., the cycle lasts longer than 28 days). The doses of SL-172154 in that cycle are not delayed (e.g., administered on Day 8, 15).

o. **PLD Administration:** PLD will be administered according to the dosing schedule provided. If the start of a subsequent cycle (e.g., Day 1) is delayed, the current cycle length is extended (e.g., the cycle lasts longer than 28 days). In addition, length of subsequent cycles will remain unchanged (i.e., 28 days for PLD Cohort).

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

q. **Post-Treatment Visit (PTV)**: visit should occur 30 days (±7 days) after the last dose of study treatment. If the subject is going to start a new anticancer therapy before the PTV due date, PTV should be conducted prior to starting the new therapy.

r. **Survival Follow-Up (SFU)**: All subjects will be contacted after discontinuing study treatment to collect survival status. Subjects should be contacted every 3 months (±14 days) from the PTV until death, withdrawal of consent, lost to follow-up or end of study. Contact may include clinic visit, telephone contact, email or mail, chart review, or obituary notice to document survival status. Initiation of any subsequent anti-cancer therapy should also be reported.

6.1.1 PK, ADA, Cytokines and Receptor Occupancy (SL-172154 + PLD Dose Escalation and Dose Expansion Cohorts)

CYCLE 1	C1D1		C1D8								C1D9	C1D15						
	Predose [1]	2h post EOI	Predose[1]	EOI	0.5h post EOI	1h post EOI	1.5h post EOI	2h post EOI	4h post EOI	6h post EOI	24h post EOI	Predose[1]	EOI	0.5h post EOI	1h post EOI	1.5h post EOI	2h post EOI	4h post EOI
Blood sample for SL-172154 PK[2,3,4,5,6]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for SL-172154 ADA[6]			X									X						
Blood sample for cytokines[3,5]			X					X			X	X					X	
Blood sample for Receptor Occupancy [3,5]			X			X					X	X			X			

CYCLE 2	C2D8								C3D8 and onwards in every cycle[7]
	Predose[1]	EOI	0.5h post EOI	1h post EOI	1.5h post EOI	2h post EOI	4h post EOI	6h post EOI	Predose[1]
Blood sample for SL-172154 PK[2,3,4,6]	X	X	X	X	X	X	X	X	
Blood sample for SL-172154 ADA[6]	X								X

Abbreviations: ADA = anti-drug antibodies; C = cycle; D = day; EOI = end of SL-172154 infusion; IRR = infusion-related reaction; PK = pharmacokinetics; PLD = pegylated liposomal doxorubicin

Note: Please refer to Table 1 for infusion duration for the assigned SL-172154 dose.

1. Predose samples should be collected within 60 minutes prior to the start of the SL-172154 infusion.
2. EOI samples should be collected ±5 min from the end of the SL-172154 infusion.
3. Any sample collected 1h to less than 4h post-EOI of SL-172154 will have ±10 min window.
4. Any sample collected 4h to 6h post-EOI of SL-172154 will have ±30 min window.
5. 24h post-EOI sample will have ±2h window.
6. Samples for SL-172154 ADA will also be collected at the PTV. All subjects should have just oneadditional blood sample collected for SL-172154 ADA assessment within 45-90 days of the last dose of SL-172154 study treatment.

6.2 Schedule of Assessments: SL-172154 + MIRV Cohorts (Dose Escalation and Dose Expansion)

Cycle Length = 21 days			CYCLE 1 (C1)					CYCLE 2 (C2)			CYCLE 3 (C3) and Subsequent Cycles				
Assessment[b]	**PreScrn**	**Scrn[a]**	**D1**	**D8**	**D9**	**D15**	**D16-22**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**PTV[u]**	**SFU[v]**
Informed consent	X	X													
Eligibility criteria		X[c]	X												
Demographics		X													
FFPE archival tumor tissue and/or new biopsy for FRα[p]	X														
Medical and disease history		X													
Cancer treatment history		X													
Type and screen (ABO/Rh), Blood phenotyping, DAT[d]		X													
TSH, free T4[l]		X													
Antiviral testing[l] (HBV/HCV)		X													
Record historical BRCA, HRD status (if known)		X													
12-lead ECG[e]		X													
ECHO/MUGA[f]		X													
Ophthalmic exam[g]		X									←prior to C3, C5, C7→			X	
Physical examination[h]		X	X	X		X		X		X	X			X	
Vital signs[i]		X	X	X		X		X	X	X	X	X	X		
Pulse oximetry[i]		X	X	X		X		X	X	X	X	X	X		
Height (screening only) / weight		X	X					X			X				
ECOG performance status		X	X	X		X		X		X	X			X	
Ocular symptom assessment[j]		X	X					X			X			X	
Pregnancy test[k] (serum or urine, FCBP only)		X									X[k]			X	
Clinical chemistry[l]		X	X	X	X	X		X	X	X	X			X	
Hematology[l]		X	X	X	X	X		X	X	X	X			X	
Coagulation[l] (PT, aPTT, INR, d-dimer, fibrinogen)		X			X										

Cycle Length = 21 days			CYCLE 1 (C1)					CYCLE 2 (C2)			CYCLE 3 (C3) and Subsequent Cycles				
Assessment[b]	**PreScrn**	**Scrn[a]**	**D1**	**D8**	**D9**	**D15**	**D16-22**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**PTV[u]**	**SFU[v]**
Ferritin		X			X										
C-reactive protein		X													
Haptoglobin		X			X										
Blood sample for SL-172154 PK[m]				X	X	X			X						
Blood sample for SL-172154 ADA[m]				X		X			X			X[m1]		X[m2]	X[m2]
Blood sample for cytokines[n]				X	X	X									
Blood sample for receptor occupancy[n]				X	X	X									
Blood sample for MIRV PK[m]			X					X			X			X	
Blood sample for MIRV ADA[m]			X					X			X			X	
Scans for disease assessment[o]		X									X[o]			X[o]	
CA-125[o]		X									X[o]			X[o]	
Tumor biopsy[q]		X					X[q]								
SL-172154 administration[r]				X		X			X	X		X	X		
MIRV administration[s]			X					X			X				
Concomitant medications		X	←---------- Continuous Monitoring During Treatment Phase of the Study ----------→											X	
Adverse events[t]	X	X	←---------- Continuous Monitoring During Treatment Phase of the Study ----------→											X	
Survival contact[v] (q3 months ± 14d)															X

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; aPTT = activated partial thromboplastin time; BCVA = best corrected visual acuity; C = cycle; CT = computed tomography; CTCAE = Common terminology criteria for adverse event; D=day; DAT = direct antiglobulin test; DLT = dose limiting toxicity; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; FCBP = female of childbearing potential; FFPE = formalin fixed paraffin embedded; FRα = folate receptor alpha; HBV = hepatitis B virus; HCV = hepatitis C virus; HRD = homologous recombination deficiency; INR = international normalized ratio; IOP = intra-ocular pressure; IRR = infusion-related reaction; MIRV = mirvetuximab soravtansine; MUGA = multigated acquisition scan; NCI = National Cancer Institute; PD = pharmacodynamics; PK = pharmacokinetics; PreScrn = prescreening; PT = prothrombin time; PTV = post-treatment visit; q = every; SAE = serious adverse event; Scrn = screening; SFU = survival follow-up; TSH = thyroid stimulating hormone

a. **Screening**: Screening Period extends from Day -21 to Day -1 for routine clinical assessments unless otherwise specified; subjects may complete Screening and initiate dosing on the same day provided all Screening assessments are completed and confirmed to meet eligibility requirements prior to receipt of MIRV or SL-172154. The following screening assessments do not need to be repeated pm Cycle 1 Day 1 if performed within 72 hours of the first dose of study treatment: hematology, clinical chemistry, coagulation panel, ECOG status, and physical exam.

Baseline CT or positron emission tomography (PET)/CT or Magnetic resonance imaging (MRI) tumor assessments are required for all subjects within 28 days prior to the first dose of study treatment.

b. **Assessment Window**: With the exception of Screening assessments and unless otherwise specified, assessments performed at ≤ 4-week intervals will have a ±3-day window and assessments performed at > 4-week intervals will have a ±1-week window. No assessment window is permitted during the DLT-evaluable period in the dose escalation cohorts.
c. **Eligibility Evaluation**: Subjects must meet eligibility criteria prior to first dose of study treatment.
d. **Blood Phenotyping (ABO/Rh) and DAT**: will be performed at local laboratories according to the laboratory's normal procedures. At screening the following tests will be performed: a) ABO and D group (ABO/Rh) type and antibody screen and antibody identification if required, b) DAT, and c) phenotype/genotype for, at a minimum, the minor antigens Rh C/c, E/e, K, Jk, Fy, and MNS. If assessment was performed within 21 days of the first dose of study treatment and all requested information is available, this can be used for baseline assessment
e. **ECG**: 12-lead electrocardiogram (ECG) must be performed at screening to serve as a baseline for comparison in the event of a cardiac AE/SAE during the study. ECG is to be performed within 30 days of the first dose of study treatment.
f. **ECHO/MUGA**: ECHO or MUGA is to be performed at screening to serve as a baseline for comparison in the event of a cardiac AE/SAE during the study. ECHO/MUGA is to be performed within 30 days of the first dose of study treatment. The same methodology should be used at each assessment.
g. **Ophthalmic Exam**: Ophthalmic examinations will be performed in all subjects by an ophthalmologist, optometrist, or other qualified health care provider ("eye care professional") within 21 days before C1D1 (baseline) and at PTV (+/- 14 days) and will include the following: manifest refraction, BCVA, IOP assessment, fundoscopy baseline and PTV only), and slit lamp examination. If a subject receiving MIRV develops new ocular symptoms of CTCAE > Grade 1, that subject is required to have a complete examination conducted by an eye care professional prior to next MIRV administration. All subjects receiving MIRV, regardless of reporting symptoms, are required to have ophthalmological exams including BCVA, IOP, and slit lamp exam **prior** to Day 1 dosing in Cycle 3, 5, and 7. For subjects with ongoing keratitis/keratopathy, a cornea epithelial defect, or ≥ 3-line loss in BCVA after end of treatment with MIRV, an ophthalmic examination should be done every 30 days until resolution, stabilization, or return to baseline. Ocular symptoms (blurred vision, etc.) should also be assessed at this time. Subjects requiring an ophthalmological examination due to symptoms prior to Cycle 2 or 4 will then proceed to every other cycle (approximately 6 weeks) exams as indicated by findings and do not require the routine, asymptomatic exams at Cycle 3, 5, and 7.
h. **Physical Examination**: A full physical exam is required only at screening and PTV. Physical exams should be performed per standard of care during the on-treatment period.
i. **Vital Signs and Pulse Oximetry**: 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 on Day 1 of every Cycle at Predose (within 60 min of starting the MIRV infusion); postinfusion vital signs should be collected as clinically indicated for potential infusion-related reaction.
    2. Collect vital signs/pulse oximetry during Cycle 1 on Day 8 and Day 15: Predose (within 60 min of starting the SL-172154 infusion), at the end of infusion (EOI; ±5 min) and then 0.5 hour [hr] (±5 min), 2 hr (±10 min), and 4 hr (±10 min) after end of infusion (EOI) of SL-172154.
    3. Collect vital signs/pulse oximetry on Day 8 and Day 15 of Cycle 2 and in each subsequent cycle: Predose (within 60 min of starting the infusion) and at the end of infusion [EOI] (±5 min) of SL-172154.
    4. For subjects experiencing any grade IRR, refer to Section 3.7.1.1 for schedule of vital signs that should be measured at time of the IRR event.
j. **Ocular Symptom Assessment**: will be performed by the treating physician or other qualified individual before the start of each cycle for all subjects. For subjects receiving MIRV reporting new CTCAE > Grade 1 ocular symptoms, treatment will be held until the subject is evaluated by an eye care professional for a complete examination. Refer to Table 8 and Table 9 for additional details on management of ocular findings on study.
k. **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 4 days of the first dose of MIRV on Cycle 1 Day 1. Repeat this test every 6 weeks during study treatment (i.e., C3D1, C5D1, C7D1, etc.) and at PTV. Contraception should be continued for at least 3 months after the last dose of either SL-172154 or MIRV.
l. **Hematology/ Clinical Chemistry/ Coagulation/ TSH/ Free T4/ Antiviral Testing**: will be performed at local laboratories according to the laboratory's normal procedures. Required laboratory tests are provided in Section 6.5.9.

m. **Pharmacokinetic (PK) / Anti-Drug Antibody (ADA)**: Blood sample collection timings for SL-172154 PK/ADA and MIRV PK/ADA measurement are outlined in Section 6.2.1. Blood volumes required will be provided in the Study Lab Manual (SLM). PK/ADA samples should not be collected from infusion port for drug delivery i.e., recommend having a separate line in the opposite arm for sample collection.
    1. If a subject discontinues SL-172154 due to IRR and continues on MIRV monotherapy, to the extent feasible, an additional ad-hoc ADA sample should be collected at a subsequently scheduled visit.
    2. All subjects should have just one additional blood sample collected for SL-172154 ADA assessment within 45-90 days of last dose of SL-172154 study treatment.

n. **Cytokines and receptor occupancy:** Blood sample collection timing for cytokine and receptor occupancy assessments are outlined in Section 6.2.1. Blood volumes required will be provided in the SLM. Cytokine samples should not be collected from infusion port for drug delivery, i.e., recommend having a separate line in the opposite arm for sample collection.

o. **Scans for Disease Assessment and CA-125**: Baseline tumor assessments are required for all subjects within 28 days prior to the first dose of study treatment. CA-125 should also be obtained at screening within 28 days of first dose of SL-172154. Baseline and on-treatment tumor assessments for all tumor types by RECIST v1.1 should include CT with contrast of chest, abdomen, and pelvis and other known sites of disease at each time point. Bone scan, positron emission tomography (PET)/CT, and/or MRI should be performed only if clinically indicated. Tumor assessments must be performed at screening and at the following intervals until radiologic disease progression: during the last week of every even cycle (Days 16 to Day 22) every 2 cycles/ 6 weeks±1 week through Cycle 18, every 3 cycles/ 9 weeks±1 week up to Cycle 27, and then every 4 cycles/ 12 weeks±1 week up to conclusion of the study. Subjects who discontinue study treatment for reasons other than disease progression (e.g., AE or withdrawal of consent) will be monitored for radiologic response until start of another anti-cancer therapy, disease progression, withdrawal of consent, or death. CA-125 should be measured to coincide with each scheduled radiographic tumor assessment as outlined above with the last required assessment of CA-125 performed at the PTV which occurs 30 days (±7 days) after the last dose of study treatment. If there is more than one week delay in any cycle, please perform all the subsequent disease assessments per schedule in weeks.

p. **FRα Expression Screening on Archival Tumor Tissue or Fresh**: Archival tissue will be collected from all subjects after signing the prescreening consent (if separate from the main study consent). The prescreening period is not time limited. Central testing for positive FRα expression is required for all subjects to determine eligibility. All subjects must submit archival tumor tissue block or fresh cut slides from available block (FFPE slides). Those who do not have archival tumor tissue to submit will be required to undergo procedure to obtain a new biopsy using low-risk, medically routine procedure during the Prescreening period to confirm eligibility. If the archival tumor tissue does not meet FRα criteria, a new biopsy tumor sample may be submitted and used to confirm this criterion.

q. **Tumor Biopsy**: Paired biopsies for exploratory PD analysis are required (pre- and on-treatment) to be obtained in subjects enrolled in the dose expansion cohort who have tumor accessible to core-needle biopsy and for whom there is an acceptable level of risk as per investigator assessment. Biopsies will be obtained at Screening (to evaluate the immune status of the tumor before SL-172154 treatment) and on or between Day 16 through Predose on Day 1 of Cycle 2.

r. **SL-172154 Administration**: Subjects will be monitored prior to and during each SL-172154 infusion. SL-172154 should be administered according to the prescribed dosing schedule in Cycle 1 to align with the safety DLT assessment and sample (PK, ADA, etc.) collection schedules. Beginning on Cycle 2 Day 8, a window of ±2 days is allowed for scheduled dosing days for drug administration (NOTE: each dose must be administered at least 5 days apart from the previous dose). If the start of a subsequent cycle (e.g., Day 1) is delayed, the current cycle length is extended (e.g., the cycle lasts longer than 21 days). The doses of SL-172154 in that cycle are not delayed (e.g., administered on Day 8, 15).

s. **MIRV Administration**: MIRV will be administered according to the dosing schedule provided. If the start of a subsequent cycle (e.g., Day 1) is delayed, the current cycle length is extended (e.g., the cycle lasts longer than 21 days). The length of subsequent cycles will remain unchanged (i.e., 21 days for MIRV Cohort).

t. **AE Monitoring**: Subjects will be followed continuously for AEs during the study and for 30 days after the last dose of study treatment. After a subject is discontinued from study treatment due to progressive disease or for other reasons, any ongoing AE should be followed until resolution (or return to baseline) and documented in the eCRF. If another anti-cancer agent is started within 30 days after the last dose of study treatment, only SAEs and AEs that occur prior to the start of the new anticancer therapy should be recorded. In the event of a continuing SAE, the subject should be asked to return for follow-up until the SAE 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

u. **Post-Treatment Visit (PTV)**: visit should occur 30 days (±7 days) after the last dose of study treatment. If the subject is going to start a new anticancer therapy before the PTV due date, PTV should be conducted prior to starting the new therapy.

v. **Survival Follow-Up (SFU)**: All subjects will be contacted after discontinuing study treatment to collect survival status. Subjects should be contacted every 3 months (±14 days) from the PTV until death, withdrawal of consent, lost to follow-up or end of study. Contact may include clinic visit, telephone contact, email or mail, chart review, or obituary notice to document survival status. Initiation of any subsequent anti-cancer therapy should also be reported.

6.2.1 PK, ADA, Cytokines and Receptor Occupancy (SL-172154 + MIRV Dose Escalation and Dose Expansion Cohorts)

CYCLE 1	C1D1			C1D8								C1D9	C1D15						
	Predose[1]	EOI[2]	2h post EOI	Pre-dose[1]	EOI[2]	0.5h post EOI	1h post EOI	1.5h post EOI	2h post EOI	4h post EOI	6h post EOI	24h post EOI	Pre dose[1]	EOI[2]	0.5h post EOI	1h post EOI	1.5h post EOI	2h post EOI	4h post EOI
Blood sample for SL-172154 PK[3,4,5,6]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for SL-172154 ADA[6]				X									X						
Blood sample for MIRV PK [D1 of each cycle] [6]	X	X																	
Blood sample for MIRV ADA, neutralizing antibodies [D1 of each cycle][6]	X																		
Blood sample for cytokines[3,5] (during dose escalation and for approximately 25 subjects in dose expansion)				X					X			X	X					X	
Blood sample for Receptor Occupancy[3,5] (during dose escalation and for approximately 25 subjects in dose expansion)				X			X					X	X			X			

CYCLE 2	C2D8								C3D8 and onwards in every cycle[7]
	Predose[1]	EOI[2]	0.5h post EOI	1h post EOI	1.5h post EOI	2h post EOI	4h post EOI	6h post EOI	Predose[1]
Blood sample for SL-172154 PK[3,4,6]	X	X	X	X	X	X	X	X	
Blood sample for SL-172154 ADA[6]	X								X

Abbreviations: ADA = anti-drug antibodies; C = cycle; D = day; EOI = end of SL-172154 infusion; IRR = infusion-related reaction; MIRV= mirvetuximab soravtansine; PK = pharmacokinetics

Note: Please refer to Table 2 for infusion duration for the assigned SL-172154 dose

1. Predose samples should be collected within 60 minutes prior to the start of the MIRV infusion or the SL-172154 infusion.
2. EOI samples should be collected ±5 min from the end of the MIRV infusion or the SL-172154 infusion.
3. Any sample collected 1h to less than 4h post-EOI of SL-172154 will have ±10 min window.
4. Any sample collected 4h to 6h post-EOI of SL-172154 will have ±30 min window.
5. 24h post-EOI sample will have ±2h window.
6. Samples for MIRV PK, MIRV ADA, and SL-172154 ADA will also be collected at the PTV. All subjects should have just one additional blood sample collected for SL-172154 ADA assessment within 45-90 days of the last dose of SL-172154 study treatment.
7. If a subject discontinues SL-172154 due to IRR and continues on MIRV monotherapy, to the extent feasible, an additional ad-hoc ADA sample should be collected at a subsequently scheduled visit.

6.3 Demographics, Medical History and Screening Assessments

6.3.1 Informed Consent

All subjects must sign and date the latest approved version of the Informed Consent form before any trial specific procedures are performed and prior to starting study treatment. Refer to Section 13.3.

For the MIRV cohort, subjects will sign a prescreening ICF to allow for central testing of fresh or archival tumor tissue by the assay required for study inclusion. If subjects meet entry criteria for FRα positivity (PS2+ ≥ 25%) as defined by the Ventana FOLR1 Assay, they may sign the main study ICF and can then proceed with remaining screening procedures per the SOA to be considered for enrollment to the MIRV cohort. In some cases, the prescreening ICF and main study ICF may be merged into a single ICF based on site-specific guidelines or preference.

Any subject, regardless of whether or not his/her tumor meets the FRα positivity threshold, can, at the investigator's discretion, consent to participate in the PLD cohort provided that she meets all other eligibility criteria.

6.3.2 Eligibility Criteria

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

6.3.3 Subject Demographics

The age, year of birth, sex, race, and ethnicity (as permitted by local regulation) of each subject will be recorded during Screening.

6.3.4 Medical History

A complete medical history will be taken during the Screening period. The history will include the background and progress of the subject's malignancy and a description of prior therapies received to treat the disease under study and the response to these therapies. Breast cancer gene (BRCA) and homologous recombination deficiency (HRD) status will be recorded if known.

6.3.5 Concomitant Medications and Procedures

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

6.4 Evaluation of FRα Expression in Tumor Tissue [MIRV Cohort]

FRα expression varies with tumor histology, as reported in the literature and demonstrated in preclinical studies (MIRV IB). FRα expression in tumor samples will be analyzed using the Ventana FOLR1 Assay, an immunohistochemical assay developed to detect FRα in cut slide specimens of formalin-fixed paraffin-embedded (FFPE) epithelial ovarian cancer tissue stained on the BenchMark ULTRA automated staining instrument using the Ventana OptiView DAB IHC Detection Kit. This assay will be conducted at a central laboratory. All subjects being considered for enrollment in the SL-172154 + MIRV cohort must submit tumor tissue block or

fresh cut slides from available block (FFPE slides) for analysis of FRα expression prior to enrollment.

PS2+ is the terminology used to reference a scoring method based on membrane stain intensity level of 2 or greater. The PS2+ scoring method requires the pathologist (at the central laboratory) to assess the percentage of tumor cells with moderate (2) and/or strong (3) membrane staining compared to the total number of viable tumor cells. To be considered positive for FRα expression and eligibility for the study, ≥ 25% of viable tumor cells must exhibit level 2 and/or 3 membrane staining intensity (see Ventana Assay details within the MIRV IB).

Only subjects with the required FRα expression levels by Ventana FOLR1 Assay are eligible to enroll in the SL-172154 + MIRV Cohort. If a subject wishes to enroll and does not have archival material available for analysis, she must undergo a biopsy to assess FRα expression. Subjects for whom the only sites of disease would require biopsy procedures considered to be of significant risk must not be enrolled to receive MIRV in this study. These procedures include (but are not limited to) biopsies of the brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach, or bowel.

Instructions regarding processing and shipment of all samples for FRα testing are detailed in the applicable Study Lab Manual (SLM).

6.5 Safety Evaluations

6.5.1 Physical Examination

A complete physical examination should be performed by a qualified physician or their designee per the schedule described in Section 6.1 and Section 6.2. A full physical exam is only required at screening and PTV. The exam should include, at a minimum, assessments of the head and neck, eyes, ears, nose throat, skin, thyroid, cardiovascular, respiratory, gastrointestinal and neurological systems, lymph nodes and extremities. Height (at screening only) 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.

6.5.2 ECOG Performance Status

Subject's performance status will be assessed using the ECOG performance status tool (see Appendix Section 16.1).

6.5.3 Pulse Oximetry

Oxygen saturation will be measured with a pulse oximeter at room air without supplementation. Refer to the SOA table for details on when to collect pulse oximetry (Section 6.1 and Section 6.2).

6.5.4 Vital Signs

Vital signs should 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 subject in a quiet setting

without distractions. Refer to the SOA table for details on when to collect vital signs (Section 6.1 and Section 6.2).

6.5.5 Electrocardiogram - ECG

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

6.5.6 Echocardiogram (ECHO)/Multigated Acquisition Scan (MUGA)

An ECHO or MUGA will be obtained at Screening for all subjects as outlined in the SOA (Section 6.1 and Section 6.2) to assess LVEF. The same methodology should be used at each assessment. For subjects enrolled to receive PLD in either dose escalation or dose expansion, an ECHO/MUGA will also be obtained every 8 weeks ± 7 days during the study treatment part of the study and also at the PTV. ECHO/MUGAs may also be performed as clinically indicated at any time during the conduct of the study. Any treatment emergent abnormalities of clinical consequence should be reported as AEs.

6.5.7 Ocular Symptom Assessment [MIRV Cohort Only]

Ocular symptom assessment will be performed at the screening visit and before the start of each cycle by the treating physician or other qualified individual. For subjects reporting CTCAE > Grade 1 ocular symptoms, study drug will be held until the subject is evaluated by an eye care professional. The ocular symptom assessment will also be performed at the PTV (Section 6.2). All ocular SAEs, and those ocular AEs assessed by the investigator as at least possibly related to MIRV, should continue to be followed until they resolve or stabilize, whichever comes first.

6.5.8 Ophthalmic Examination [MIRV Cohort Only]

An ophthalmic examination will be performed at the screening visit by an eye care professional and will include the following: manifest refraction, BCVA, IOP, fundoscopy, and slit lamp examination. Subjects who experience ocular AEs while on study will have a complete ophthalmologic examination performed at the emergence of the symptoms and at every other cycle thereafter until resolved to baseline or as specified in Table 8 and Table 9. All subjects in the MIRV cohort, regardless of the reporting of ocular symptoms and events during treatment, will have an ophthalmologic examination including BCVA, IOP, and slit lamp examination performed prior to Cycle 3, 5, and 7. All subjects will have an ophthalmologic exam at the PTV which will include manifest refraction, BCVA, fundoscopy, IOP, and slit lamp examination. The visual acuity assessment should be performed with refraction, rather than corrected or via pin hole. Refraction is crucial for cases where subjects report blurred vision or other ocular AEs.

For subjects with ongoing keratitis/keratopathy, a cornea epithelial defect, or ≥ 3-line loss in BCVA after end of treatment with MIRV, an ophthalmic examination should be done every 30 days until resolution, stabilization, or return to baseline. Ocular symptoms (blurred vision, etc.) should also be assessed at this time. Subjects requiring an ophthalmological examination due to symptoms prior to Cycle 2 or 4 will then proceed to every other cycle (approximately 6 weeks) exams as indicated by findings and do not require the routine, asymptomatic exams at Cycle 3, 5, and 7.

6.5.9 Local and Central Clinical Laboratory Assessments

Refer to the SOA (Section 6.1 and Section 6.2) for the timing and frequency of local laboratory tests performed.

<table>
<tr><th colspan="4">Local Clinical Labs</th></tr>
<tr><th>Hematology</th><th colspan="3">Clinical Chemistry</th></tr>
<tr><td>Hemoglobin
Hematocrit
Platelet Count
Red Blood Cell Count
White Blood Cell Count
Mean Corpuscular Volume</td><td colspan="3">Blood urea nitrogen or Urea
Creatinine
Glucose
Sodium
Potassium
Calcium
Aspartate aminotransferase
Alkaline phosphatase
Magnesium
Phosphorus
Total Protein
Albumin
Lactate dehydrogenase
Bicarbonate or CO2
Total and direct bilirubin*
Alanine aminotransferase</td></tr>
<tr><th>Automated WBC Differential</th><th colspan="2">Antiviral Testing</th><th>Thyroid</th></tr>
<tr><td>Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td><td colspan="2">Hepatitis B: HbsAg / HBV core Ab
Hepatitis C: HCV Ab / HCV RNA viral load</td><td>Thyroid stimulating hormone (TSH)
Free thyroxine 4</td></tr>
<tr><th colspan="2">Coagulation</th><th colspan="2">Serum/Urine Pregnancy Test</th></tr>
<tr><td colspan="2">Prothrombin time and International- normalized ratio
Activated partial thromboplastin time
Fibrinogen
D-Dimer</td><td colspan="2">β-human chorionic gonadotropin</td></tr>
<tr><th colspan="4">Other</th></tr>
<tr><td colspan="4">Ferritin and haptoglobin (Screening and Cycle 1 Day 9)
C-reactive protein (Screening)</td></tr>
<tr><td colspan="4">Blood Type and Screen (Screening)</td></tr>
<tr><td>ABO/Rh
D, C, E</td><td>Kell, Kidd
Direct antiglobulin test (DAT)</td><td colspan="2">Duffy, MNS
Antibody Screen</td></tr>
</table>

* Both total and direct bilirubin assessments should be performed, but if required per the standard practices, direct bilirubin can be omitted when total bilirubin is normal.

Refer to the SOA (Section 6.1, Section 6.2, Section 6.1.1 and Section 6.2.1) for the timing and frequency of central laboratory tests performed. A separate SLM detailing the preparation, storage, and shipping requirements for these samples collected during the study will be provided.

Central Laboratory Tests	
Peripheral Blood	
Pharmacokinetics	SL-172154 serum concentration (all subjects) MIRV serum concentration **[MIRV cohort only]**
Immunogenicity	Anti-drug antibodies (ADA) to SL-172154 MIRV ADA **[MIRV cohort only]**

Protein analysis (serum)	Assessment of potential immune regulators such as cytokines
Receptor occupancy	Flow cytometry-based measurement for receptor occupancy of SL-172154 on CD47 and CD40 in select subsets of peripheral blood mononuclear cells
Tumor Tissue	
Ventana FOLR1 Assay	Confirmation of FRα positivity to meet eligibility criterion **[MIRV Cohort only]**
IHC on paired tumor biopsies	IHC/IF to assess changes in immune cell population, expression of targets and PD-L1. NGS based analysis of changes in target-associated regulatory networks**. [MIRV Cohort only]**

6.5.9.1 Ad Hoc Labs for IRR or CRS AEs

Ad hoc labs should be collected as noted if IRR or CRS events occur. The samples to be collected are provided below.

Ad Hoc Lab[a,b]	
Local Clinical Labs	**Central Labs**
Complete blood count with differential Chemistry Panel D-Dimer Coagulation panel Ferritin Haptoglobin C-Reactive Protein	Pharmacokinetics (SL-172154 serum concentration) Anti-drug antibodies (SL-172154)[c] Cytokines Receptor occupancy

ADA = anti-drug antibody; CRS = cytokine release syndrome; IRR = infusion-related reaction; MIRV = mirvetuximab soravtansine; PK = pharmacokinetic(s); PLD = pegylated liposomal doxorubicin

a) Refer to the Study Lab Manual for sample collection, handling, storage and shipment instructions. PK will be measured with each corresponding ADA sample.
b) Specific biomarker, PK, ADA, and clinical samples should be collected as soon as possible if an event of IRR or CRS.
c) If a subject discontinues SL-172154 due to IRR and continues on PLD or MIRV monotherapy, to the extent feasible, an additional ad-hoc ADA sample should be collected at a subsequently scheduled visit.

6.5.9.2 Pregnancy Testing

All FCBP subjects must have a negative pregnancy test (serum or urine) at Screening. A separate assessment is required if a negative Screening pregnancy test is obtained more than 72 hours before the first dose of SL-172154. Subjects with a positive pregnancy test must be excluded from the study. Subjects with a negative pregnancy test result must agree to use an effective contraception method as described in Appendix Section 16.2.

6.5.9.3 CA-125

Serum CA-125 assessments will be performed within 28 days prior to the first dose of PLD or MIRV, and at each radiologic tumor assessment (Section 6.1 and Section 6.2). CA-125 should be assessed by the same laboratory throughout the study.

6.5.9.4 Blood type and Screen (ABO/Rh) and DAT

SL-172154 does bind RBCs but has not been shown to cause hemolysis in non-human primates. However, treatment with SL-172154 may obscure the assessment of RBC phenotyping due to expected coating of SL-172154 on 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; and 3) phenotype/genotype for, at a minimum, the minor antigens Rh C/c E/e, K, Jk, Fy and MNS. If the subject has had transfusion within 21 days of Cycle 1 Day 1 (e.g., Screening period) and the type/screen/DAT information is known, this information can be reported in the EDC as baseline and the assessment does not need to be repeated. However, if the requested information is unknown to the investigator/site staff, then the assessment is to be performed during the Screening period.

6.6 Pharmacokinetics

The sampling schedule for PK assessment of SL-172154 was determined based on observed PK in the Phase 1 trial (SL03-OHD-101) of SL-172154 monotherapy administered to subjects with ovarian cancer. The sampling schedule for PK assessment of SL-172154 is outlined in Section 6.1.1 and Section 6.2.1.

The sampling schedule for PK assessment of MIRV is outlined in Section 6.2.1. If a dose delay occurs, then PK and PD assessments should be performed on the actual day of MIRV administration, and not on the original scheduled administration day.

6.7 Anti-Drug Antibody and Neutralizing Antibody Assessments

Presence of ADA for SL-172154 will be assessed in samples collected according to the SOA (Section 6.1.1 and Section 6.2.1). Samples will also be collected for assessing the neutralization capacity for confirmed positive ADA samples. All subjects should have an additional blood sample collected for ADA/neutralizing antibodies and PK assessment within 45 to 90 days of last dose of study treatment.

The immunogenic potential of MIRV (MIRV ADA, neutralizing antibodies) will also be assessed in samples collected according to the SOA (Section 6.2.1).

6.8 Cytokine Analysis

Levels of serum cytokines may provide context to AEs observed in subjects following infusion of SL-172154 and may act as PD markers of activity. Refer to Section 6.1 and Section 6.2 for the schedule of the sample collection for these analyses.

6.9 Receptor Occupancy Analysis

Receptor occupancy of SL-172154 on CD47 and CD40 in peripheral blood cells will be measured by flow cytometry. This analysis will provide evidence that SL-172154 is engaging the expected targets and allows receptor occupancy to be calculated and assessed across dose groups. Refer to Sections 6.1, 6.1.1, 6.2 and 6.2.1 for the schedule of the sample collection for these analyses.

6.10 Tumor Biopsy

6.10.1 Baseline and On-Treatment Fresh Tumor Biopsies [MIRV cohort only]

The efficacy of cancer immunotherapy is conditioned by the infiltration of tumors by activated tumor-specific T cells. The activity of these T cells will be affected by the immunosuppressive environment in the tumor (e.g., T-regulatory cells, and suppressive myeloid cells such as myeloid-derived suppressor cells and M2 macrophages). Therefore, the direct evaluation of the "immune landscape" inside the tumor is of great value for understanding the mechanism of action of SL-172154 and optimizing cancer immunotherapy. IHC analyses will be performed on the fresh tumor samples. The immune infiltrate of the tumor will be assessed by visualizing and assessing the phenotype of cells in the tumor micro-environment by IHC. Additionally, treatment-related changes in the spatial distribution 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. Changes in the immune profile of the tumor from baseline to on-treatment could also be used to predict clinical response or validate the mechanism of the immune response to SL-172154 in the context of cytotoxic agents. For each time point, three core needle biopsies should be obtained for research studies (see SLM for details).

Baseline and on-treatment biopsies for exploratory PD analysis (to evaluate the immune status of the tumor before and on treatment) are required for all subjects in the SL-172154 + MIRV dose expansion cohort for whom the biopsy has minimal risk. Biopsy must be obtained at the following timepoints (the expected time of an immune response to SL-172154 therapy):

- SL-172154 + MIRV Cohort: Screening/baseline and an on-treatment biopsy performed at Cycle 1 on or between Day 16 through predose on Day 1 of Cycle 2 in the MIRV cohort

It is recommended that the biopsies are obtained from non-target lesions. The same lesion should be biopsied pre- and post-treatment. Where possible lymph node biopsies should be avoided as reliable measure of tumor infiltrating lymphocytes (or their activation) in a background of non-tumor lymphoid tissue is challenging.

Biopsy Collection Safety Considerations and Procedure

For a given subject, 3 core needle biopsies of the selected tumor lesion should be obtained at the time points noted in the SOA (Section 6.2). Please refer to the SLM for further processing and shipping instructions.

Subjects who would require biopsy procedures considered to be of significant risk must not undergo paired tumor biopsy collection. These procedures include (but are not limited to) biopsies of the brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach, or bowel.

Contraindications to percutaneous biopsy:

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

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

The use of imaging to facilitate biopsies will be decided by members of the Interventional Radiology team at the clinical site and may include ultrasound, CT scan, or magnetic resonance imaging (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 subject as determined by the investigators and interventional radiologist.

6.11 Assessment of Anti-Tumor Activity

The primary analysis of anti-tumor activity will be assessed according to RECIST v1.1 for solid tumors using CT with contrast of chest, abdomen, and pelvis and other known sites of disease. Bone scan, positron emission tomography (PET)/CT, and/or MRI should be performed only if clinically indicated. Tumor assessments must be performed at screening and at the following intervals until radiologic disease progression:

- SL-172154 + PLD: during the last week (Day 22 to predose on Day 29) of every 2 cycles/ 8 weeks±1 week through Cycle 6, and every 3 cycles/ 12 weeks ±1 week thereafter up to year 2 and then every 6 cycles/ 24 weeks ±1 week up to study conclusion. If there is more than one week delay in any cycle, please perform all the subsequent disease assessments per schedule in weeks.
- SL-172154 + MIRV: during the last week (Day 16 to predose on Day 22) of every 2 cycles / 6 weeks±1 week through Cycle 18, and every 3 cycles/ 9 weeks±1 week thereafter through Cycle 27, and every 4 cycles/ 12 weeks±1 week until study conclusion. If there is more than one week delay in any cycle, please perform all the subsequent disease assessments per schedule in weeks.

Refer to Section 8 for additional details.

6.12 Unscheduled Visit

Additional visits can be performed as appropriate and at the discretion of the investigator. Assessments completed during unscheduled visits will be captured in the eCRF. 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

Safety surveillance reporting of AEs commences when a subject has signed the ICF, throughout the course of treatment, and up to 30 days after the last dose of investigational drug. If another anti-cancer agent is started within 30 days after the last dose of study medications, only SAEs and AEs that occur prior to starting the new anticancer therapy should be recorded. After signing of informed consent, but prior to initiation of study medications, only AEs (both serious or

nonserious) caused by a protocol-mandated procedure will be collected (e.g., AEs related to invasive procedures such as biopsies). All observed or volunteered AEs (serious or non-serious) and abnormal laboratory test findings, if applicable, whether suspected to have a causal relationship to study treatment or not will be recorded in the subject medical record and in the eCRF. 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, PLD, or MIRV. All AEs (both serious and nonserious) will be followed in accordance with good medical practice until resolution, return to baseline, subject is lost to follow-up, the AE is otherwise explained, or it is deemed that further recovery is unlikely. Following the PTV, subjects with ongoing drug-related AEs and SAEs should be followed until resolution to baseline or stabilization of these events, unless the subject withdraws from the study or starts another anti-cancer treatment. Follow-up will stop when the subject begins another anti-cancer treatment. Refer to Section 7.4 for documentation and reporting of AEs.

7.1 Definitions for Safety Parameters

Event	Definition
Adverse Event (AE)	The AE observation period starts at the time of signing informed consent and includes baseline or washout periods, even if no study treatment has been administered. An AE is defined as any untoward medical occurrence in a subject to whom the drug has been administered, regardless of whether the event is considered related to that product. An AE is also defined as an undesirable medical condition due to a study-related procedure.
Adverse Reaction (AR)	AR is an untoward and unintended response in a subject to IP. A causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	An AE or suspected AR that is considered "serious" if, in the view of either the investigator or Sponsor, it results in any of the following outcomes: • Death (Note: death is an outcome not an event) • A life-threatening AE (an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe) • Inpatient hospitalization or prolongation of existing hospitalization • A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions • A congenital anomaly/birth defect. • Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
Laboratory test(s) that meet definition of an AE or SAE:	• Any laboratory test result that meets the definition of an AE or SAE or requires holding or discontinuation of IP, or requires corrective therapy, must be documented appropriately. • Ad hoc labs should be collected as noted in Section 6.5.9.1 if an event of IRR or CRS occurs. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the subject's medical record and recorded in the AE section of the eCRF. The laboratory reports must be filed with the source

Event	Definition
	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 subject'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 results recorded in the eCRF. If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator (e.g., AE, SAE or dose interruption), then the results must be recorded in the eCRF.
Unexpected Adverse Reaction	An adverse reaction (causality related Adverse Event), the nature, severity, or outcome of which is not consistent with the reference safety information section of the SL-172154 IB, MIRV IB or the current PLD prescribing information. Product reference safety information is contained in the current Guidance for Investigators in the SL-172154 and MIRV IBs provided to the investigator by the Sponsor and the current PLD label prescribing information.
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

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 eCRF.
- Clear progression of disease under study should not be reported as an AE or SAE unless the investigator considers the progression of underlying neoplasia to be atypical in its nature, presentation, or severity from the normal course of the disease in a particular subject. Signs and symptoms that are clearly consistent with the expected progression of the underlying cancer should not be reported as an AE, and hospitalizations due to the progression of cancer do not necessarily qualify for an SAE. Deaths that are clearly determined to be due to disease progression should not be reported as AEs/SAEs.
- In the case where the medical condition is known when the subject enters the trial, only worsening (increased frequency or intensity of the episodes or attacks) will be documented as an AE. If the medical condition is detected during the trial, and if repeated

episodes enable diagnosis of a chronic disease, the episodes will be grouped together in the eCRF, 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

All measures required for AE management and the ultimate outcome of the event will be recorded in the source document and reported to the Sponsor.

7.2.1 Assessment of Severity

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

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

- Grade 1: mild
- Grade 2: moderate
- Grade 3: severe
- Grade 4: life-threatening
- Grade 5: death

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 study treatment 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 the administered treatment (SL-172154 and PLD or MIRV) assessed. In a clinical trial, the drug(s) being administered must always be suspect. Investigators should consider alternative causes such as natural history of the underlying disease, concomitant medications, comorbidities, and other risk factors when making an assessment.

To help assess causality, the following guidelines are used.

- **Related** – There is reasonable causal relationship between the IP(s) being administered and the AE. The event responds to interruption of study drug and recurs with re-challenge, when clinically feasible.

- **Possibly Related** - There is reasonable causal relationship between the IP(s) being administered and the AE. Information on whether the event responds to interruption of administered treatment and/or re-challenge is lacking or unclear.
- **Unlikely Related** - There is a temporal relationship to administration of the IP(s) in the study, but there is not a reasonable causal relationship between the IP(s) being administered and the AE (i.e., the AE is doubtfully related to SL-172154, PLD, or MIRV).
- **Not Related** – There is not a temporal relationship to administration of the IP(s) in the study (e.g., too early, too late, or SL-172154, PLD or MIRV not taken), or there is a reasonable causal relationship between another drug, concurrent disease, or circumstance and the AE.

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 in Guidance for Investigators of the current SL-172154 IB or MIRV IB and the current PLD prescribing information. "Unexpected," as used in this definition, also refers to AEs or ARs that are mentioned in the IB or prescribing information as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug not specifically mentioned as occurring with SL-172154, MIRV or PLD.
- **Expected** - AEs that are common and known to occur for SL-172154, MIRV or PLD. Expectedness refers to the awareness of AEs previously observed, not on what might be anticipated from the properties of SL-172154, MIRV and PLD.

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 (e.g., medical history) and not reported as an AE.

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 30 days after the last dose of SL-172154. After a subject is discontinued from SL-172154 due to progressive disease or for other reasons, any ongoing AE should be followed until resolution (or return to baseline) and documented in the eCRF, regardless of whether the event(s) is attributed to trial medication. If another anti-cancer agent is started within 30 days of the last dose of SL-172154, only AEs and SAEs 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

Event	Reporting Procedures
	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 study treatment. A subject may also voluntarily withdraw from study treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the subject must undergo an end of treatment assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.
Serious Adverse Event	The study clinician will complete a SAE Form within the following timelines: • All deaths and immediately life-threatening events meeting the SAE criteria (as outlined in Section 7.1), whether related or unrelated, will be recorded on the SAE Form and submitted to the study Sponsor or designee *within 24 hours of site awareness.* • Other SAEs regardless of relationship, will be submitted to the study Sponsor or designee *within 24 hours of site awareness*. All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the Sponsor and should be provided as soon as possible. The Sponsor will be responsible for notifying Regulatory Authorities of any unexpected fatal or life-threatening suspected adverse reaction (AR) as soon as possible but in no case later than 7 calendar days after the Sponsor's initial receipt of the information. The Sponsor will be responsible for notifying Regulatory Authorities of any other serious unexpected suspected adverse reaction as soon as possible but in no case later than 15 calendar days after the Sponsor's initial receipt of the information. **Sponsor Contact Information for SAE Reporting** [redacted]

7.5 Reporting of Pregnancy

Although not an AE in and of itself, pregnancy as well as its outcome must be documented via the Pregnancy Report Form provided by the Sponsor. Any pregnancy occurring in a subject or subject's partner from the time of consent to 30 days after the last dose of SL-172154 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.

FCBP must discontinue study treatment 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 and brought to the investigator's attention after the subject has discontinued study treatment must be promptly reported to the Sponsor.

7.6 Reporting of Events to Sponsor

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

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

7.7 Study Halting Rules

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

7.8 Safety Oversight

An SMC will be implemented in this study and will consist of investigators and Sponsor representatives. Study progress and safety data will be reviewed by the SMC throughout the conduct of the study. During the study while subjects are receiving treatment with SL-172154 +MIRV or PLD, SMC meetings will be held to review relevant data with the investigators or designees during both dose escalation and dose expansion. These meetings will be held once a month (or more frequently if required) during dose escalation to share safety data and communicate results of ongoing analyses 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 as well as the process for safety review and meeting frequency. As dose escalation proceeds, the SMC will take into account data from Study SL03-OHD-105 as well as other knowledge obtained for SL-172154, including the data from the monotherapy SL-172154 dose escalation in Study SL03-OHD-101. Safety and PK data from Study SL03-OHD-101 will be shared with the SMC for SL03-OHD-105. Doses explored in SL03-OHD-105 will not exceed the highest dose cleared for safety in SL03-OHD-101. All dose escalation or safety decisions made by the SMC will be documented in writing with copies maintained at each site and in the Trial Master File at the Contract Research Organization. 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 SL-172154 is to provide a possible therapeutic benefit, and thus the subject will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. For the purposes of this study, subjects should be evaluated for response as outlined in the SOA. All subjects who underwent the first post-baseline disease assessment at the 8-week (PLD Cohort) or

6-week (MIRV Cohort) time point or progress or die before the first post-baseline disease assessment will be considered evaluable for response.

Refer to the SOA (Section 6.1 and Section 6.2) and Section 6.11 for the schedule of disease assessments. More frequent disease assessments may be performed at the discretion of the investigator as clinically indicated. CA-125 levels should be measured concurrently with radiologic tumor assessments (Section 6.5.9.3) and reported in EDC however response determination will be solely based on radiologic assessment in this study.

8.1 Disease Assessment

Imaging studies, preferably by contrasted computed tomography scan, for disease assessment of chest, abdomen and pelvis and all other sites of known disease will be performed at baseline and at the following intervals until disease progression as described in Section 6.11.

PET-CT, MRI, and/or bone scan should be performed as clinically indicated. The same imaging modality used at baseline should be employed subsequently. All post-baseline assessments require imaging of disease sites identified by baseline scans. Confirmatory scans should be performed at least 4 weeks (> 28 days) after initial documentation of an objective response. Contrast enhanced imaging is required unless the subject is precluded from receiving contrast (e.g., hypersensitivity, renal impairment).

If study treatment is withdrawn for reasons other than disease progression, radiographic disease assessments should continue as per the SOA until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent or death.

8.1.1 Assessment of Response

Investigator-assessed response will be evaluated in this study using RECIST v1.1 [Eisenhauer, 2009]. The RECIST v1.1 guideline is included in this document (Appendix Section 16.5).

8.2 Criteria for Treatment Beyond Initial Progression

Subjects will be permitted to continue study treatment beyond initial progressive disease provided the subject does not have clinical symptoms of progression, is tolerating study treatment, 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 study treatment in the setting of progressive disease by signing a separate written informed consent.

The subject may continue to be treated beyond disease progression 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.
- Experiences rapid progressive disease with risk to vital organs or critical anatomical sites requiring urgent medical intervention.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSIS

9.1 Study Design and Sample Size Determinations

9.1.1 Dose Escalation

The SL-172154 dose escalation will utilize an mTPI-2 design [Guo, 2017] with a target DLT rate of 30% for the MTD.

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 subinterval 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 for each dose level are:

- 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%;

See Table 12 for dose escalation decision rules based on the total number of subjects evaluable for DLT and the number of DLTs observed.

Table 12 SL-172154 Dose Escalation Decision Rules for Each Dose Level Based on mTPI-2

Number of 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	S
4	.	DU	DU	DU	D	D	D	D	D	S

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 evaluable 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., two subjects experience DLT before the third subject enrolls.

9.1.2 Dose Expansion

For the SL-172154 + PLD dose expansion cohort, the goal is to enroll approximately 20 subjects treated at the potential RP2D in either dose expansion or dose escalation. The sample size of 20 is primarily chosen to obtain a preliminary assessment of the antitumor activity with a certain degree of precision. Table 13 provides the 90% confidence interval (CI) based on exact probability method for a range of possible responses out of 20 subjects. Approximately 14 of these subjects at the potential RP2D will be enrolled in the dose expansion cohort.

Table 13 Response Rate 90% CI Out of 20 Subjects

# Responses/20 Subjects	Response Rate	90% CI
2	10%	1.8%, 28.3%
4	20%	7.1%, 40.1%
6	30%	14.0%, 50.8%
8	40%	21.7%, 60.6%
10	50%	30.2%, 69.8%
12	60%	39.4%, 78.3%
14	70%	49.2%, 86.0%
16	80%	59.9%, 92.9%
18	90%	71.7%, 98.2%

For the SL-172154 + MIRV dose expansion cohort, the goal is to enroll approximately 20 subjects treated at the potential RP2D for each of the following three tumor FRα expression subgroups in either dose expansion or dose escalation: high (PS2+ ≥ 75%), medium (PS2+ ≥ 50% and < 75%), and low (PS2+ ≥ 25% and < 50%). The sample size of 20 is primarily chosen to obtain a preliminary assessment of the antitumor activity with a certain degree of precision (Table 13). Approximately 64 subjects treated at the potential RP2D will be enrolled in the dose expansion cohort.

9.1.3 Safety Monitoring During Dose Expansion

Each dose expansion cohort will allow further characterization of the safety profile of SL-172154 in combination with either PLD or MIRV, with particular emphasis on toxicities

leading to discontinuation of SL-172154 and the combination agents. Continuous toxicity monitoring based on Pocock-type stopping boundary [Ivanova, 2005] will be used within each dose expansion cohort. Accrual will be temporarily stopped if an excessive number of subjects discontinue SL-172154 and a combination agent due to toxicities.

9.1.3.1 Safety Monitoring in the SL-172154 + PLD Dose Expansion Cohort

In the JAVELIN Ovarian 200 study, the discontinuation rate in the PLD monotherapy group owing to AEs was 11% and treatment-related AEs leading to treatment discontinuation was 7% [Pujade-Lauraine, 2021], thus a 20% rate of AE leading to treatment discontinuation regardless of causality is selected as the Pocock-type stopping boundary for the SL-172154 + PLD dose expansion cohort. Enrollment to the SL-172154 + PLD dose expansion cohort will be temporarily stopped if an excessive number of subjects experience AEs leading to treatment discontinuation; that is, if the number of subjects with AEs leading to treatment discontinuation is equal to or more than b_n out of n subjects as described in the table below. The sequential stopping boundaries are selected to have at least 70% probability to temporarily stop when the underlying true rate of subjects with AEs leading to treatment discontinuation is 10% higher than 20%.

Number of subjects, *n*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	-	2	3	3	3	3	4	4	4	4	4	4	5	5	5	5	5	6	6	6

9.1.3.2 Safety Monitoring in the SL-172154 + MIRV Dose Expansion Cohort

In the IMGN853-0401 study, 15% of the subjects at 6.0 mg/kg MIRV monotherapy discontinued treatment due to AEs (MIRV IB), thus a 20% rate of AE leading to treatment discontinuation regardless of causality is selected as the Pocock-type stopping boundary for the SL-172154 + MIRV dose expansion cohort. Enrollment to the SL-172154 + MIRV dose expansion cohort will be temporarily stopped if an excessive number of subjects experience AEs leading to treatment discontinuation; that is, if the number of subjects with AEs leading to treatment discontinuation is equal to or more than b_n out of n subjects as described in the table below. The sequential stopping boundaries are selected to have at least 82% probability to stop when the true underlying rate of subjects with AEs leading to treatment discontinuation is 10% higher than 20%.

Number of subjects, *n*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Boundary, b_n	-	-	3	4	4	4	5	5	5	5	6	6	6	6	7	7	7
Number of subjects, *n*	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34
Boundary, b_n	7	8	8	8	8	9	9	9	9	10	10	10	10	11	11	11	11
Number of subjects, *n*	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51
Boundary, b_n	11	12	12	12	12	12	13	13	13	13	14	14	14	14	14	15	15
Number of subjects, *n*	52	53	54	55	56	57	58	59	60	61	62	63	64	65			

Boundary, b_n	15	15	15	16	16	16	16	16	17	17	17	17	17	18			

9.1.4 Sample Size Determination

The planned sample size is approximately 102 subjects, depending on the number of dose levels evaluated in dose escalation for each of the combinations. Approximately 24 subjects will be enrolled in dose escalation cohorts (12 subjects in PLD cohorts and 12 subjects in MIRV cohorts) and approximately 78 subjects will be enrolled in a dose expansion cohort (an additional 14 subjects at the selected dose in PLD cohort and an additional 64 subjects at the selected dose in MIRV cohort).

All subjects with tumors that are FRα-positive (PS2+ ≥ 25%) enrolled in the MIRV combination cohort will be retrospectively binned in expression subgroups (high, medium, low) for study analysis. The goal is to enroll approximately 20 subjects at the potential RP2D in either dose expansion or dose escalation for each of the following three tumor FRα expression subgroups: high (PS2+ ≥ 75%), medium (PS2+ ≥ 50% and < 75%), and low (PS2+ ≥ 25% and < 50%). This estimation is based on the anticipated frequency of subjects with high grade serous ovarian cancer who fall into each of these FRα expression subgroups. If this distribution is not achieved in any subgroup, approximately 10 additional subjects may be enrolled in this dose expansion cohort in order to achieve it.

NOTE: The planned sample sizes may be revised if additional dose levels are evaluated or if more subjects (i.e., subjects available for dosing beyond the number required in a cohort) are enrolled than anticipated. The actual number of subjects to be enrolled for each combination dose escalation will depend upon the number of dose levels evaluated and the number of DLT observed for each dose level and related dose escalation/stay/de-escalation decisions. The Sponsor, in consultation with the SMC, may also elect to add subjects to the dose escalation cohorts if additional data is needed to select the dose level for the dose expansion cohort.

9.2 Statistical Analysis

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.

When determining the RP2D, the totality of the safety, tolerability, PK, PD, and efficacy data collected during both dose escalation and dose expansion is taken into consideration.

9.2.1 Analysis Populations

The populations defined for analysis will include the following:

Population	Description
Screened	All subjects who have signed the main study ICF
Screen Failures	All subjects who have signed the main study ICF but have not received any study treatment.
All Treated	All subjects who receive at least one dose of SL-172154, PLD, or MIRV. Safety data will be evaluated based on this population.

Population	Description
DLT-Evaluable	All subjects enrolled in the dose escalation cohorts who receive at least 50% of the scheduled doses of SL-172154 and 1 dose of PLD or MIRV and complete the safety follow-up through the DLT evaluation period or 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 either had at least one post-baseline disease assessment or who have discontinued study treatment due to disease progression or death before any post-baseline disease assessment.
Pharmacokinetic	Subjects in All Treated Population from whom at least one post-baseline PK sample is obtained and analyzed
Pharmacodynamic	Subjects in the All Treated Population for whom a baseline and at least one on-treatment PD sample is obtained and analyzed.

9.2.2 Data Analysis During Dose Escalation

During the dose escalation, the number of subjects with DLTs will be determined after each cohort of approximately 3 subjects has been evaluated for DLT. The summary of DLTs will be based on the DLT-Evaluable Population; the number of subjects with DLTs will be summarized by dose level for each of the combination dose escalation cohorts. 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 each of the combination regimens. 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 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 for each combination regimen 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/regimen for combination dose escalation cohorts. Frequency tables by dose levels will be used to describe safety and tolerability parameters such as: AEs, SAEs, fatal AEs and AEs leading to discontinuation of SL-172154, PLD or MIRV. Changes in toxicity grade for safety assessments (e.g., laboratory parameters, etc.) will also be summarized. Figures may also be presented where appropriate. AEs will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ classification. Concomitant medications will be coded using the World Health Organization Drug Dictionary. All toxicities except CRS and ocular AEs will be graded according to the NCI CTCAE v5.0. CRS will be graded per the ASTCT Consensus Grading Criteria for CRS (described in

Section 3.7.1.2); ocular AEs for the MIRV cohort will be graded per the tables provided in Appendix Section 16.6.

Maximum Tolerated Dose:

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% among all dose with the isotonic estimate of DLT rate ≥ 25%. If two or more doses tie for the smallest difference, the following rules will be performed:

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

A Maximum Administered Dose (MAD) will be reported if the isotonic estimate of DLT rate is less than 25% for 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 all subjects for each combination regimen in the All Treated population and Response-Evaluable population. For the MIRV combination regimen, the anti-tumor activity will be summarized for each of the three tumor FRα expression subgroups: high (PS2+ ≥ 75%), medium (PS2+ ≥ 50% and < 75%), and low (PS2+ ≥ 25% and < 50%). The ORR and CBR based on investigator-assessed response per RECIST v1.1 will be estimated along with a 95% confidence interval using the exact probability method. Change from baseline sum of diameters for target lesions will be provided for each subject. DOR and 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/OS curve and PFS/OS rate at time point of interest.

9.2.6 Pharmacokinetic Analysis

Plasma concentrations for SL-172154 will be summarized using tabular and graphical format. SL-172154 PK parameters will be derived from the plasma concentration vs. time curve (using actual dose and collection times) using Phoenix WinNonlin version 6.3 or later (Pharsight Corp.), as data permits. SL-172154 PK parameters will be summarized and analyzed using appropriate statistical methods. The relationship between PK exposure parameters and ADA, safety, efficacy, and PD endpoints may be explored, as data permit, using appropriate graphical and statistical methods.

Plasma concentrations for MIRV will also be summarized. All concentration data will be determined using validated assays.

Table 14 Serum SL-172154 PK Parameters

Parameter	Description
C_{max}	Maximum observed concentration
T_{max}	Time of maximum observed concentration
AUC_{last}	The area under the serum concentration time curve, from time 0 to the last quantifiable concentration, calculated by a combination of linear and logarithmic trapezoidal methods (Linear up/log down method).
AUC_{0-t}	The area under the serum concentration time curve, from time 0 to time=t, calculated by a combination of linear and logarithmic trapezoidal methods (Linear up/log down method).
AUC_{0-inf}	Area under the serum concentration time curve from time 0 extrapolated to infinity, calculated as AUC_{last} + C_{last}/terminal elimination rate constant (λ_z). Reliability of AUC_{0-inf} values is contingent on the percent of the total area obtained by extrapolation: AUC_{0-inf} values with < 20% of the total area coming from C_{last}/λ_z are considered acceptable. Any exceptions to the above procedures will be clearly documented/justified in the PK report.
AUC_{tau}	The area under the serum concentration time curve, over the dosing interval following doses > first dose, calculated by a combination of linear and logarithmic trapezoidal methods (Linear up/log down method)
$\%AUC_{ext}$	Percentage of AUC_{0-inf} due to extrapolation from T_{last} to infinity
t½	Terminal elimination half-life, estimated using the equation [ln(2)/λ_z]
CL	Clearance; calculated as Dose/AUC_{0-inf}
V_z	Volume of distribution; calculated as Dose/(λ_z * AUC_{0-inf})
V_{ss}	Volume of distribution at steady state

PK parameters based on the elimination phase (e.g., AUC_{0-inf}, t½, CL, V_z) will be calculated and reported as data allow.

9.2.6.1 Immunogenicity Analysis

The immunogenic potential of SL-172154 will be assessed by summarizing the number/proportion of subjects with positive and negative postdose ADA titer by SL-172154 dose level. ADA titer, neutralization capacity, duration of ADA response and whether ADA are transient or persistent will be listed for each individual and summarized by SL-172154 dose level. As data permit, the effect of ADA on PK and PD parameters, safety and efficacy will be explored using appropriate graphical and statistical methods.

The immunogenic potential of MIRV will also be assessed.

9.2.7 Pharmacodynamics Analysis

The PD data analysis will be based on the PD population. PD biomarkers values will be summarized descriptively by SL-172154 dose level for each combination regimen.

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 summarized 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 subjects in this study. The clinical study site will permit access to such records to permit study-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. Subject 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 ICH E6 or in compliance with the Declaration of Helsinki, CIOMS, 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/Independent Ethics Committee

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

13.3 Informed Consent Process

13.3.1 Consent/Assent and Other Informational Documents Provided to Subjects

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

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

- Subjects must be re-consented to the most current version of the ICF(s) while receiving study treatment.
- A copy of the signed and dated ICF(s) must be provided to the subject or the subject's legally authorized representative.
- Subjects who are rescreened are required to sign a new ICF.

The ICF may contain a separate section or a separate ICF may be used for optional exploratory research. The investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be informed that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study period.

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 subjects. Consent forms will be IRB/IEC approved and the subject and/or the legally authorized representative will be asked to read and review the document. All subjects 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 subjects. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subject and/or the subject's legally authorized representative will sign and date the informed consent document prior to any procedures being done specifically for the study. The subject may withdraw consent at any time throughout the course of the trial. A copy of the signed and dated informed consent document will be given to the subject or the subject's legally authorized representative for their records. The rights and welfare of the subjects 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 Subject and Data Confidentiality

Subject 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 subjects. 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 subjects' 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 subjects, 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 subject will be referred to by the trial subject 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 subject 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 subject's contact or identifying information. Rather, individual subjects 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 PK and PD of SL-172154, PLD, and/or MIRV, as well as biomarkers associated with ovarian cancer and/or the mechanism of action of each study drug. Research may include the study of genomic alterations and changes in the TME which may correlate with drug safety or efficacy.

Storage: Access to stored samples will be limited to specified study personnel/vendor personnel. Samples will be identified by unique subject identification (ID) codes. Samples and data will be stored using subject ID assigned by the Sponsor and investigators. An individual subject may choose to withdraw their consent at any time; however, the Sponsor will retain all data previously analyzed and will retain and continue to use any data or biological samples collected prior to the consent withdrawal, unless the subject specifically requests disposal of their samples.

14. DATA HANDLING AND RECORD KEEPING

14.1 Communication and Data Dissemination Plan

During the study while subjects are receiving study treatment in dose escalation as well as dose expansion cohorts, SMC meetings will be held to review relevant data with the investigators or designees (see Section 7.8 for details). These meetings will be held once a month (or more frequently if required) during dose escalation, provided subjects have been enrolled and data are available to be reviewed, to share safety data and communicate results of ongoing analyses. All available safety, PK, PD, 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 as well as the process for safety review and meeting frequency.

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

14.2 Data Collection and Management Responsibilities

An eCRF will be used to record all subject data specified by this protocol. The eCRF must be completed by designated and trained study personnel. The eCRF will be electronically signed by the Principal Investigator or a Sub-investigator listed on the Form FDA 1572 (or equivalent). 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 these checks are to be resolved as quickly as possible with clarification from study sites.

14.3 Study Records Retention

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

US IND regulations (21 CFR 312.62c) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug(s) including eCRFs, consent forms, laboratory test results, and medication inventory records be kept on file by the Principal Investigator for 2 years following the date a marketing application is approved for the drug for the indication for which it is being studied. If no application is to be filed or if the application is not approved for such indication, these records must be kept until 2 years after the investigation has been discontinued and regulatory authorities (i.e., FDA, Health Canada, European Medicines Agency, etc.) have been notified. ICH guidelines indicate that study documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. If there is a country or institutional policy that specific records and documents be retained for a longer period than described above, the applicable sites must comply with those policies in addition to US and ICH policies.

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

14.4 Protocol Deviations

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

It is the responsibility of the site to use continuous vigilance to identify and report deviations to the Sponsor Medical Monitor or designee as soon as protocol deviation is identified. All documentation regarding protocol deviations will be maintained in the regulatory file. All deviations must be addressed in study source documents and reported to the 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 ECOG Performance Status Criteria

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease 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.

16.2 Contraception Requirements

Definition of Female of Childbearing Potential (FCBP)

A female subject who is not sterile due to surgery (i.e., from bilateral tubal ligation/occlusion, bilateral oophorectomy, bilateral salpingectomy, or complete hysterectomy) or who does not have a congenital or acquired condition that prevents childbearing or who is not naturally postmenopausal 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 postmenopausal if defined as amenorrheic for 12 consecutive months without an alternative medical cause. In women < 50 years of age and/or perimenopausal, 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.

Highly Effective Methods of Contraception (< 1% failure rate)

A highly effective method of contraception is defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. 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 (IUD)
    - vasectomy of a female subject's male partner
    - contraceptive rod implanted into the skin

- Combination methods
    - Female subjects: the following hormonal contraceptive methods (stable dose at least 3 months prior to first dose of study treatment) 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)
        - subcutaneous contraceptive injection
        - contraceptive skin patches
        - vaginal contraceptive rings
        - contraceptive implants into skin

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is: (1) consistently employed during the entire period of risk associated with the administered drugs; (2) consistent with the subject's preferred and usual lifestyle; and (3) considered acceptable by local regulatory agencies and IRBs/IECs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, postovulation 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 SL-172154, PLD, or MIRV 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) starting at least 14 days prior to the first dose of study treatment, during treatment, and through at least 6 months (or for the duration required by local regulatory guidance) after the last dose of PLD or at least 3 months after the last dose of MIRV or SL-172154, whichever is longer.

16.2.1 Pregnancy Status

In the rare event that beta-human chorionic gonadotropin (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.

16.3 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.

If a subject's actual body weight is less than his or her ideal body weight (IBW), then actual weight should be used. However, if the patient is obese, then a correction is used. If a subject's actual weight >30% his or her ideal body weight, then AIBW should be used in the Cockcroft-Gault equation. See Section 16.4 for calculation of AIBW and IBW.

Reference:

Winter M. Impact of Various Body Weights and Serum Creatinine Concentrations on the Bias and Accuracy of the Cockcroft-Gault Equation. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy.2012; 32:604-612.

16.4 Adjusted Ideal Body Weight Calculation

MIRV dose will be based on AIBW.

Adjusted Ideal Body Weight (AIBW)

$AIBW = IBW^1 + 0.4 (Actual\ weight - IBW^1)$

Ideal Body Weight (IBW)

$IBW^1\ (female) = 0.9H^1 - 92$

(^{1}H=height in cm; W=weight in kg)

16.5 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 subject, these are preferred for selection as target lesions.

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

After baseline, a value should be provided on the eCRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately

measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

16.5.1 Evaluation of Response

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

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

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

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

An **Overall Response** assessment will be reported with **each protocol-specified timepoint** for a disease assessment. The following table provides a summary of the overall response status at each timepoint for subjects who have measurable disease at baseline.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable

16.6 Grading of Ocular AEs [MIRV Cohort Only]

Table 15 Grading for Ocular Symptoms

Ocular AE	Grade 1	Grade 2	Grade 3	Grade 4
Blurred Vision *A disorder characterized by visual perception of unclear or fuzzy images*	Intervention not indicated	Symptomatic; limiting instrumental ADL[1]	Symptomatic; Limiting self-care ADL[2]	Blindness in the affected eye
Dry Eyes *A disorder characterized by dryness of the cornea and conjunctiva.*	Asymptomatic; clinical or diagnostic observations only; symptoms relieved by lubricants	Symptomatic	Symptomatic; limiting self-care ADL[2]	--
Eye Pain *A disorder characterized by a sensation of marked discomfort in the eye.*	Mild pain	Moderate pain; limiting instrumental ADL[1]	Severe pain; limiting self-care ADL[2]	--
Floaters *A disorder characterized by an individual seeing spots before their eyes. The spots are shadows of opaque cell fragments in the vitreous humor or lens.*	Symptomatic but not limiting ADL	Limiting instrumental ADL[1]	Limiting self-care ADL[2]	--
Photophobia *A disorder characterized by fear and avoidance of light.*	Symptomatic but not limiting ADL	Limiting instrumental ADL[1]	Limiting self-care ADL[2]	--

Abbreviations: ADL = activities of daily living

Table 16 Grading for Other Ocular Events

Ocular AE	Grade 1	Grade 2	Grade 3	Grade 4
Cataract *A disorder characterized by partial or complete opacity of the crystalline lens of one or both eyes. This results in a decrease in visual acuity and eventual blindness if untreated.*	Asymptomatic; clinical or diagnostic observation only; intervention not indicated	Symptomatic; glare symptoms affecting instrumental ADL1[1]	Symptomatic limiting self-care ADL[2]	Blindness in the affected eye
Conjunctivitis *A disorder characterized by inflammation, swelling and redness to the conjunctiva of the eye.*	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic	Symptomatic; limiting self-care ADL[2]	Blindness in the affected eye

Ocular AE	Grade 1	Grade 2	Grade 3	Grade 4
Decline in Best Corrected Visual Acuity (BCVA) (Vision Decreased) *A disorder characterized by a decrease in visual acuity from baseline*	--	Moderate decrease in visual acuity (BCVA 20/40 and better or 3 lines or less decreased vision from known baseline)	Marked decrease in visual acuity (BCVA worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200)	BCVA worse than 20/200 in the affected eye
Extraocular muscle paresis *A disorder characterized by incomplete paralysis of an extraocular muscle.*	Asymptomatic; clinical or diagnostic observations only	Unilateral paresis without double vision	Bilateral paresis or unilateral paresis causing double vision in peripheral gaze, but not in central gaze	Bilateral paresis requiring head turning to see beyond central 60 degrees or double vision in central gaze
Eyelid Function Disorder *A disorder characterized by impaired eyelid function.*	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; non-operative intervention indicated; limiting instrumental ADL[1]	Limiting self-care ADL[2]; operative intervention indicated	--
Flashing lights *A disorder characterized by a sudden or brief burst of light.*	Symptomatic but not limiting ADL	Limiting instrumental ADL[1]	Limiting self-care ADL[2]	--
Glaucoma *A disorder characterized by an increase in pressure in the eyeball due to obstruction of the aqueous humor outflow.*	Less than 8 mmHg of elevated intraocular pressure (EIOP); no visual field deficit	EIOP which can be reduced to 21 mmHg or under with topical medications and no visual field deficit	EIOP causing marked visual field deficits	Visual field deficit within the central 10 degrees of the visual field in the affected eye
Night blindness *A disorder characterized by an inability to see clearly in dim light.*	Symptomatic but not limiting ADL	Symptomatic; Limiting instrumental ADL[1]	Symptomatic; Limiting self-care ADL[2]	Blindness in the affected eye
Papilledema *A disorder characterized by swelling around the optic disc.*	Asymptomatic; no visual field deficit	Symptomatic[3]	Symptomatic[3]	Blindness in the affected eye
Periorbital edema *A disorder characterized by swelling due to an excessive accumulation of fluid around the orbits of the face.*	Soft or non-pitting	Indurated or pitting edema; topical intervention indicated	Edema associated with visual disturbance; increased intraocular pressure, glaucoma or retinal hemorrhage; optic neuritis; diuretics indicated; operative	--

Ocular AE	Grade 1	Grade 2	Grade 3	Grade 4
			intervention indicated	
Retinal detachment *A disorder characterized by fear and avoidance of light.*	--	--	Macular sparing rhegmatogenous detachment	Macula-off rhegmatogenous retinal detachment
Retinal tear *A disorder characterized by a small laceration of the retina, this occurs when the vitreous separates from the retina. Symptoms include flashes and floaters.*	No retinal detachment and treatment not indicated	No retinal detachment and treatment indicated	--	--
Retinal vascular disorder *A disorder characterized by pathological retinal blood vessels that adversely affects vision.*	--	Retinal vascular disorder without neovascularization	Retinal vascular disorder with neovascularization	--
Retinopathy *A disorder involving the retina.*	Asymptomatic; clinical or diagnostic observations only	Symptomatic; limiting instrumental ADL[1]	Symptomatic; disabling; limiting self-care ADL[2]	Blindness in the affected eye
Scleral disorder *A disorder characterized by involvement of the sclera of the eye.*	No change in vision from baseline	Symptomatic; limiting instrumental ADL[1]	Symptomatic; limiting self-care ADL[2]	Blindness in the affected eye
Uveitis *A disorder characterized by inflammation to the uvea of the eye.*	Anterior uveitis with trace cells	Anterior uveitis with 1+ or 2+ cells	Anterior uveitis with 3+ or greater cells; intermediate posterior or pan-uveitis	Blindness in the affected eye
Vitreous hemorrhage *A disorder characterized by bleeding into the vitreous humor.*	Intervention not indicated	Symptomatic; limiting instrumental ADL[1]	Symptomatic; limiting self-care ADL[2]; vitrectomy indicated	Blindness in the affected eye
Watering eyes *A disorder characterized by excessive tearing in the eyes; it can be caused by overproduction of tears or impaired drainage of the tear duct.*	Intervention not indicated	Symptomatic[3]	Symptomatic[3]	Blindness in the affected eye
Eye Disorders - Other, specify	Asymptomatic or mild symptoms; clinical or	Moderate; minimal, local or non-invasive	Severe or medically-significant but not immediately sight-	Sight-threatening consequences; urgent

Ocular AE	Grade 1	Grade 2	Grade 3	Grade 4
	diagnostic observations only; intervention not indicated; no change in vision	intervention indicated; limiting instrumental ADL[1]	threatening; limiting self-care ADL[1]	intervention indicated; Blindness in the affected eye

Abbreviations: ADL = activities of daily living; BCVA = best corrected vascular acuity; EIOP = elevated intraocular pressure

[1] Instrumental ADL: Ability to independently use a phone, do laundry, shop, prepare food, maintain housekeeping except occasional assistance, take own medications and manage finances.

[2] Self-Care ADL: Ability to independently bathe, dress, transfer, eat and perform personal toileting.

[3] Per clinical practice and assessment of ophthalmologist or designee.

16.7 Summary of Changes from Version 0.0 to 1.0

This amendment applies to all Investigator sites participating in this study. This amendment includes modifications to eligibility criteria, updated text for dose modification guidelines and updated ocular assessments for MIRV cohorts, and the collection of PD samples in the dose expansion cohorts. Minor editorial changes (including protocol version number, approval date, and the table of contents) as well as minor clarification edits to the text are incorporated in this amendment. A summary of the changes to this protocol from Version 0.0 (dated 13 May 2022) are described in the table below:

Section	Description/Rationale
Throughout	Replaced ranitidine with famotidine or other available histamine 2 receptor antagonist throughout. Premedication revised from "approximately" to "at least" 30 min prior to either SL-172154 or MIRV. Removed references to chemokines and chemokine assessments.
Study Schema	Revised for clarity and to match current protocol.
Synopsis	Revised to reflect changes in the protocol.
1.4.7 Summary of Clinical Data for SL-172154	Updated to reflect data provided in the SL-172154 IB Supplement with data cut-off date of 12 September 2022.
2 Exploratory objective and outcome measure	Revised and updated exploratory outcome measures to reflect current study.
3.1.1 Sample size	Revised description of sample size to clarify how many subjects would be treated with SL-172154 in each cohort (PLD or MIRV).
Table 1, and 2 and Section 5.1.1 and other places	Time of infusion for 6.0 mg/kg SL-172154 increased to 180 ± 15 min from 120 ± 15 min to mitigate the risk of IRR
3.5, 9.2.4	Updated grading of CRS to reflect use of the ASTCT Consensus Grading Criteria for CRS as described in Table 4.
3.5, 3.7, 9.2.4	Updated grading of ocular symptoms and events for MIRV cohort per the tables in Appendix 16.6 to align with Immunogen's post- FDA approval updates
3.7.1.1 and 3.7.1.2	Revised to describe collection of ad hoc labs during IRR events and during CRS events.
3.7.1.2	Revised dosing of tocilizumab to "per institutional guidelines and local prescribing information".
3.7.1.4	Revised guidance for hematologic toxicity for SL-172154 based on the hematology laboratory data from SL03-OHD-101 study which demonstrates transient decrease consistent with margination and not myelosuppression or destruction. Added a reminder that investigators can make more conservative dose modification if clinically indicated.
3.7.2.1	Revised guidance for hematologic toxicity for PLD to be consistent with the PLD prescribing information: removed the text requiring PLD discontinuation if PLD was delayed by 14 days as this is not in the label or standard of care). Added dose reduction for recurrent Grade 3 in accordance with institutional practice.

Section	Description/Rationale
3.7.3.2	Added dose reduction guidelines for Grade 2-4 thrombocytopenia associated with MIRV; added permanent discontinuation for recurrence of Grade 4 thrombocytopenia.
3.7.3.5.1 and 6.5. 8	Revised text describing procedures and timing of ophthalmic exam and eye care in subjects in MIRV Cohort based on updates from Immunogen
3.7.3.5.2 and Table 8 6.5.8	Revised text and table describing management, care and dosing modifications in the event of ocular symptoms in subjects in MIRV Cohort.
3.11 Discontinuation criteria	Clarification of conditions under which a subject may be removed by the Investigator.
4.1 Inclusion criterion 4	Clarification of calculation of days for disease progression.
4.1 Inclusion criterion 5	Removal of requirement for prior bevacizumab therapy in PLD cohort.
4.1 Inclusion criterion 8	Removal of requirement for prior bevacizumab therapy in MIRV cohort.
4.1 Inclusion criterion 10	Clarified that positive for FRα expression is defined as PS2+ ≥ 25% by the Ventana FOLR1 Assay.
4.1 Inclusion criterion 16	Removed mandatory pretreatment and on-treatment biopsies for PLD cohort (required for MIRV cohort only).
4.2 Exclusion criterion 7	Clarified exclusion due to immunosuppressive medication.
4.2 Exclusion criterion 9	Clarified exclusion due to autoimmune disease to add requiring treatment in past 2 years.
5.1.6	Defined overdose of SL-172154 as > 10% of intended dose.
5.3.2.3	Revised text describing calculation of adjusted ideal body weight per institutional policy for MIRV dosing.
Section 6	Revised text to ensure doses of SL-172154 are not delayed. Clarify that the length of subsequent cycles remains unchanged
6.1 Schedule SL-172154 + PLD	• Added eligibility evaluation at D1. • Removed assessment on C1D9 for Type and screen, blood phenotyping, DAT. • Allowing ECHO or MUGA to be used; same methodology to be used throughout. • Revised footnote “d” to reflect removal of C1D9 assessment. • Added footnote “g” clarifying that a full physical exam is required only at screening and PTV • Added vital sign collection and pulse oximetry assessment on D8 of C3 and subsequent cycles. • Revised footnote “k1” to reflect that all subjects have blood sample collection for ADA and PK within 45-90 days of last dose. • Added blood collection for receptor occupancy at D8, 9, 15 in Cycle 1. • Added hematology and clinical chemistry lab tests on C2D8. • Revised footnote “m” that CA-125 can be obtained within 28 days of first dose. • Added collection of ConMeds at Screening visit. • Added collection of AEs at Screening visit.

Section	Description/Rationale
	• Removed tumor biopsy assessment from table and footnote describing it. Removed "D16-22" column that contained this assessment.
6.1.1	• Added blood collection for receptor occupancy. Added cytokine samples to dose expansion cohort • Revised footnote designations to clarify collection windows. • Added to footnote 6 that collection of blood sample for SL-172154 PK and ADA should be within 45-90 days of last dose.
6.2 Schedule SL-172154 + MIRV	• Added eligibility evaluation at D1.Removed assessment at C1D9 for Type and screen, blood phenotyping, DAT. • Added collection of TSH, free T4 at Screening visit. • Allowing ECHO or MUGA to be used; same methodology to be used throughout. • Revised ophthalmic exam to clarify timing at screening visit, *prior* to C3, C5 and C7, and at PTV. • Revised footnote "d" to reflect removal of C1D9 assessment. • Revised text in footnote "g" to reflect updated ophthalmic examinations and timing. • Added footnote "h" clarifying that a full physical exam is required only at screening and PTV. • Added hematology and clinical chemistry lab tests on C2D8. • Added collection of vital signs and pulse oximetry assessment at D8 of C3 and subsequent cycles. • Revised text in footnote "j" to reflect updated ocular symptom assessment and timing. • Revised footnote "m1" to reflect that all subjects have blood sample collection for ADA and PK within 45-90 days of last dose. • Added blood collection for receptor occupancy at D8, 9, 15 in Cycle 1. • Revised collection of tumor biopsy from prescreen to screening visit. • Added collection of Concomitant Medicines at Screening visit. • Added collection of AEs at prescreen and screening visit. • Removed immunophenotyping from footnote "n". • Revised footnote "o" that CA-125 can be obtained within 28 days of first dose.
6.2.1	• Removal of cytokine sample taken at predose and 2h post-EOI. • Added blood collection for receptor occupancy. Added cytokine samples to dose expansion cohort • Revised footnote designations to clarify collection windows. • Added to footnote 6 for collection of blood sample for SL-172154 PK and ADA should be within 45-90 days of last dose.
6.5.9	• Rearranged tests in the local labs section for clarity. • Added receptor occupancy to central lab tests
6.5.9.1	Added receptor occupancy to Ad hoc Labs

Section	Description/Rationale
6.5.9.3	Revised to serum CA-125 can be obtained within 28 days of first dose (as noted for footnote “m” in 6.1 and footnote “o” in 6.2)
6.5.9.4	Removed assessment for blood type and screen, blood phenotyping, and DAT at Cycle 1 Day 9. Based on the data from SL03-OHD-101, a first-in-human Phase I study in platinum resistant ovarian cancer, there was no interference in RBC crossmatch and there was no interference in ABO/Rh typing.
6.7	Revised text to reflect collection of blood sample for ADA and PK within 45-90 days of last dose of study treatment.
6.9	Section on receptor occupancy analysis added.
6.10.1	Removed biopsy for SL-172154+ PLD cohort. Removed paragraph as archival tissue not acceptable for screening tumor biopsy.
6.11	Clarification that anti-tumor activity assessment occurs every 3 cycles up to year 2 and then every 6 cycles up to study conclusion in the PLD cohort.
7.4	Corrected e-mail address for SAE reporting
9.2.4	Changed safety analyses to include CRS and ocular grading systems
13.3.2	Clarified and simplified the Consent Procedures and Documentation paragraphs.
13.4.1	Revisions to description of intended use of samples and data collected. Clarification of retention and use of analyzed data and biological samples under conditions of subject withdrawal of consent.
Former 13.5	Removal of section describing storage and future use of specimens collected for this study.
16.3 Cockcroft- Gault Formula	Revised to describe use of adjusted ideal body weight (AIBW) for subjects with actual weight >30% of ideal body weight. Removed IBW calculations. Refer to section 16.4 for AIBW and IBW calculations. Devine reference removed and Winter reference added.
Appendix 16.6 Ocular Symptoms and Other Ocular Events	Table 15 and 16 added to describe grading of ocular AEs to align with Immunogen’s other MIRV protocols
Appendix 16.7	Summary of Changes added.

16.8 Summary of Changes from Version 1.0 to 2.0

This amendment applies to all Investigator sites participating in this study. This amendment includes dexamethasone premedication prior to SL-172154 dosing, with revised guidelines for management of IRR despite premedication, and the addition of dose modifications in the context of Grade 2/3 liver enzyme elevations (the subject of SL03-OHD-105 Protocol Safety Update Memo dated 23-Oct-2023); and clarification of the method visual acuity assessment (the subject of SL03-OHD-105 Protocol Clarification Memo No. 4 dated 05-Dec-2023). Other revisions include updates to collection of samples for SL-172154 PK and ADA, and addition of C-reactive protein assessments at screening and to ad-hoc labs collected in the event of CRS or IRR AEs.

A summary of the changes to this protocol from Version 1.0 (dated 20-Jun-2023) are described in the table below:

Section	Description/Rationale
Throughout the protocol	Based on data from ongoing studies with SL-172154, dexamethasone 8 mg IV is added to prophylactic premedication prior to each dose of SL-172154. Subject of SL03-OHD-105 Protocol Memo dated 23-Oct-2023.
Section 3.6.1 Prohibited Medications or Treatments	Adjustments on use of steroids for IRR made based on dexamethasone use for premedication.
Section 3.7.1.1 Management of IRR [SL-172154]	Provided guidelines for Grade 2, recurrent Grade 2, Grade 3, and recurrent Grade 3 IRR following SL-172154 dosing if it occurs despite premedication with dexamethasone. Subject of SL03-OHD-105 Protocol Memo dated 23-Oct-2023.
Section 3.7.1.3 Management of Hepatotoxicity	Modifications to the guidance table for dose of SL-172154 in the context of Grade 2 or 3 liver enzyme elevations, based on emerging data from this study. Subject of SL03-OHD-105 Protocol Memo dated 23-Oct-2023.
Section 3.7.1.4 Management of Hematologic AEs	Addition of consult with Medical Monitor for management of Grade 4 hematologic AE in event of transient decrease in hemoglobin.
Section 3.7.3.2 Dose Modifications for MIRV-Related AEs	Modifications to the guidance table for dose of MIRV in the context of Grade 3 liver enzyme elevations, based on emerging data from this study. Subject of SL03-OHD-105 Protocol Memo dated 23-Oct-2023.
Section 3.7.3.5.1 Monitoring and Preventive Measures [MIRV Cohort] Section 3.7.3.5.2 Management and Dose Modifications Guidelines [MIRV Cohort]; Section 6.5.8 Ophthalmic Examination [MIRV Cohort Only]	Added clarification that visual acuity assessment should be performed with refraction. Subject of SL03-OHD-105 Clarification Letter No. 4 dated 05-Dec-2023.
Section 6.1 Schedule of Assessment – PLD; Section 6.2 Schedule of Assessment – MIRV; Section 6.5.9 Local and Central Clinical Laboratory Assessments	Addition of C-reactive protein at screening as a baseline assessment and under ad hoc labs

Section	Description/Rationale
Section 6.1; 6.2 Schedules of assessments	Correction in the table re: C1D9 SL-172154 PK collection to match Section 6.1.1 and Section 6.2.1.
Sections 6.1, 6.1.1, 6.2, 6.2.1 Schedules of assessments Section 6.5.9 Local and Central Clinical Laboratory Assessments Section 6.5.9.1 Ad Hoc Labs for IRR or CRS AEs	• Based on emerging data, removal of SL-172154 PK sample collections from C3 onwards, PTV or SFU) and updates to corresponding footnotes. • Addition of footnote to describe collection of ad hoc SL-172154 ADA if subject discontinues SL-172154 due to IRR but continues on PLD or MIRV.
Section 6.11 Assessment of Anti-Tumor Activity	Removal of statement regarding scans during delay for toxicity management. to avoid confusion.
Section 7.1.1 Events not Qualifying as AEs/SAEs	Clarification that deaths due to disease progression should not be reported as AE/SAEs.
Section 7.2.2 Assessment of Causality	Clarification that underlying disease history should be considered in assessment of causality.
Section 9.2.1 Analysis Populations	Clarification of definition of response-evaluable population.

16.9 Summary of Changes from Version 2.0 to 2.1

This is a country specific amendment for Spain and applies to Investigator sites participating in this study in Spain. At the AEMPS request,16.8 Summary of Changes from Version 1.0 to 2.0 was revised to include detailed justification and reason for each of the changes. In addition, some of the text that was deleted due to an oversight in Section 3.7.1.1, Management of IRRs, was added back into Protocol Amendment version 2.1, and the text was revised as needed to reflect the updated IRR guidance.

A summary of the changes to this protocol from Version 2.0 (dated 29-Feb-2024) are described in the table below:

Section	Description/Rationale
Throughout the protocol	**Description of Change**: Based on data from ongoing studies with SL-172154, dexamethasone 8 mg IV is added to prophylactic premedication prior to each dose of SL-172154. Subject of SL03-OHD-105 Protocol Memo dated 23-Oct-2023. **Rationale/Justification**: Infusion-related reaction (IRR) is a common SL-172154-related treatment emergent AE. Addition of dexamethasone as primary prophylaxis to the standard premedication regimen of acetaminophen, H1 and H2 blockade was shown to be effective in reducing the incidence and severity of IRR symptoms in a parallel study (SL03-OHD-104). The data from SL03-OHD-104 study were shared with the safety monitoring committee for the SL03-OHD-105 study. The safety monitoring committee agreed to the addition of dexamethasone 8 mg IV to the premedication prior to each dose of SL-172154 in the current study.
Section 3.6.1 Prohibited Medications or Treatments	**Description of Change**: Adjustments on use of steroids for IRR made based on dexamethasone use for premedication. **Rationale/Justification:** Previous version of the protocol prohibited primary prophylactic use of steroids for the prevention of SL-172154 associated IRR. With the addition of dexamethasone to the premedication regimen prior to each SL-172154 infusion, the previous text was no longer applicable. Therefore, it was deleted, and clarification was added that steroid premedication prior to each SL-172154 administration for IRR prophylaxis is required.
Section 3.7.1.1 Management of IRR [SL-172154]	**Description of Change**: Provided guidelines for Grade 2, recurrent Grade 2, Grade 3, and recurrent Grade 3 IRR following SL-172154 dosing if it occurs despite premedication with dexamethasone. Subject of SL03-OHD-105 Protocol Memo dated 23-Oct-2023. **Rationale/Justification:** Previous version of the IRR management guidance was applicable for IRRs that occurred without dexamethasone prophylactic premedication. With the addition of dexamethasone premedication prior to each SL-172154 infusion, more conservative guidance for SL-172154 administration was necessary for managing Grade 2 and Grade 3 IRRs that may occur despite dexamethasone premedication. • The guidance for Grade 2 IRRs was revised to (1) allow for SL-172154 dose reduction (from 3 mg/kg to 1 mg/kg) based on severity of symptoms; (2) if the symptoms did not recur at the reduced dose (1 mg/kg) in subsequent administrations, the dose could be increased back to the original dose (3 mg/kg) at ≤50% of the rate specified in the protocol; (3) if tolerated at this rate with subsequent administrations, the rate could be

Section	Description/Rationale
	increased to the original rate stated in the protocol; and (4) recurrent Grade 2 IRR associated with significant signs or symptoms despite dose reduction, requires permanent discontinuation. • The guidance for Grade 3 IRR was revised to clarify a stepwise approach (1) if the reduced dose of SL-172154 (1 mg/kg) is tolerated at a reduced infusion rate (of ≤50%) during subsequent two infusions, the rate can be increased back to the original rate stated in the protocol; and (2) if the reduced dose of SL-172154 (1 mg/kg) is tolerated at the original rate stated in the protocol, then the dose may be re-escalated to the original dose (3 mg/kg). • Due to oversight, some of the original guidance for Grade 2 and Grade 3 IRR management was removed in amendment 2.0. This information is added back in the current version.
Section 3.7.1.3 Management of Hepatotoxicity	**Description of Change:** Modifications to the guidance table for dose of SL-172154 in the context of Grade 2 or 3 liver enzyme elevations, based on emerging data from this study. Subject of SL03-OHD-105 Protocol Memo dated 23-Oct-2023. **Rationale/Justification:** Both SL-172154 and MIRV can cause liver enzyme elevations, and the attribution to a specific agent may not always be clear. Additionally, the liver enzyme elevations are transient and recover without intervention (especially the use of steroids). Based on the emerging data from this study, the dose modifications recommended for SL-172154 (with MIRV or PLD) in the context of Grade 2 or 3 liver enzyme elevations were updated to take into account the transient nature of the elevations.
Section 3.7.1.4 Management of Hematologic AEs	**Description of Change:** Addition of consult with Medical Monitor for management of Grade 4 hematologic AE in event of transient decrease in hemoglobin. **Rationale/Justification:** Per the guidance for hematological toxicities in Section 3.7.1.4, permanent discontinuation of SL-172154 is required if no other etiology can be determined and SL-172154 is determined to be the cause of Grade 4 anemia. A transient decrease in hemoglobin (i.e., spontaneous recovery without intervention) associated with SL-172154 infusion may not necessarily require discontinuation of SL-172154. In the event of a transient decrease in hemoglobin consultation with the medical monitor was recommended. This clarification was added to the protocol.
Section 3.7.3.2 Dose Modifications for MIRV-Related AEs	**Description of Change**: Modifications to the guidance table for dose of MIRV in the context of Grade 3 liver enzyme elevations, based on emerging data from this study. Subject of SL03-OHD-105 Protocol Memo dated 23-Oct-2023. **Rationale/Justification**: Both SL-172154 and MIRV can cause liver enzyme elevations, and the attribution to a specific agent may not always be clear. The dose modifications for MIRV were clarified in Table 7. Grade 3 ALT/AST increase: Hold MIRV until resolved to Grade ≤1. • If resolution to Grade ≤1 within 7 days, resume at the same dose level. • If resolution to Grade ≤1 takes more than 7 days, resume MIRV at one dose level lower starting at the next cycle.

Section	Description/Rationale
Section 3.7.3.5.1 Monitoring and Preventive Measures [MIRV Cohort] Section 3.7.3.5.2 Management and Dose Modifications Guidelines [MIRV Cohort]; Section 6.5.8 Ophthalmic Examination [MIRV Cohort Only]	**Description of Change**: Added clarification that visual acuity assessment should be performed with refraction. Subject of SL03-OHD-105 Clarification Letter No. 4 dated 05-Dec-2023. **Rationale/Justification**: It is a common practice to correct for refraction during visual acuity assessments. However, for subjects on the MIRV arm undergoing visual acuity assessment, refraction is crucial to accurately identify ocular AEs. Therefore, corrections to refraction should not be made during the visual acuity assessments. This clarification was added to the protocol.
Section 6.1 Schedule of Assessment – PLD; Section 6.2 Schedule of Assessment – MIRV; Section 6.5.9 Local and Central Clinical Laboratory Assessments	**Description of Change**: Addition of C-reactive protein at screening as a baseline assessment and under ad hoc labs **Rationale/Justification**: Elevated C-reactive protein levels may be associated with cytokine release syndrome (CRS) or IRR AEs. It is helpful to know baseline (pretreatment) C-reactive protein levels as well as determine C-reactive protein levels when a CRS or IRR is suspected to accurately assess these AEs. Therefore, C-reactive protein assessment was added at baseline and as ad hoc assessments in cases of suspected CRS or IRR AEs.
Section 6.1; 6.2 Schedules of assessments	**Description of Change**: Correction in the table re: C1D9 SL-172154 PK collection to match Section 6.1.1 and Section 6.2.1. **Rationale/Justification**: 24hr PK sample is collected after Cycle1 Day 8 (C1D8) dosing and this sample falls on C1D9. Although explained in text and correctly shown in 6.1.1 and 6.2.1, the main schedule of assessment Tables 6.1 and 6.2 were missing the notation on C1D9. This error was corrected.
Sections 6.1, 6.1.1, 6.2, 6.2.1 Schedules of assessments Section 6.5.9 Local and Central Clinical Laboratory Assessments Section 6.5.9.1 Ad Hoc Labs for IRR or CRS AEs	**Description of Change**: • Based on emerging data, removal of SL-172154 PK sample collections from C3 onwards, PTV or SFU) and updates to corresponding footnotes. **Rationale/Justification:** Analysis of serum concentrations of SL-172154 in a completed Phase I study in ovarian cancer patients (SL03-OHD-101) showed that following single and multiple IV infusions of 0.1 to 10 mg/kg SL-172154, maximum mean serum SL-172154 concentrations were reached at the end of infusion followed by multi-phasic decline and rapid clearance. SL-172154 concentrations were only detectable (>10.0 ng/mL) post-EOI for up to 2 hours for ≤1.0mg/kg and up to 8 hours for 3.0 mg/kg. Based on these data, pre-dose SL-172154 infusion PK sample collection was removed from C3 onwards as concentrations should not be detectable this long after dosing. **Description of Change**: • Addition of footnote to describe collection of ad hoc SL-172154 ADA if subject discontinues SL-172154 due to IRR but continues on PLD or MIRV. **Rationale/Justification**: If an IRR leads to discontinuation of SL-172154, patients have the option to continue on PLD or MIRV monotherapy. To investigate for the presence of antidrug antibodies to SL-172154, text was added to ensure additional ADA sample would be collected at a subsequent visit, if feasible.
Section 6.11 Assessment of Anti-Tumor Activity	**Description of Change**: Removal of statement regarding scans during delay for toxicity management. to avoid confusion.

Section	Description/Rationale
	Rationale/Justification: There was a sentence about not having to repeat scans when subsequent cycles are delayed for toxicity management. This sentence was unclear, not relevant, and led to confusion. It was therefore removed.
Section 7.1.1 Events not Qualifying as AEs/SAEs	**Description of Change**: Clarification that deaths due to disease progression should not be reported as AE/SAEs. **Rationale/Justification**: For the purpose of clarification, a sentence was added to explain that deaths that are clearly determined to be due to disease progression should not be reported as AEs/SAEs.
Section 7.2.2 Assessment of Causality	**Description of Change**: Clarification that underlying disease history should be considered in assessment of causality. **Rationale/Justification:** A sentence was added to remind that Investigators should consider alternative causes such as natural history of the underlying disease, concomitant medications, comorbidities, and other risk factors when making an assessment of causality.
Section 9.2.1 Analysis Populations	**Description of Change:** Clarification of definition of response-evaluable population. **Rationale/Justification**: The definition of response-evaluable population was always intended to include subjects who discontinue study treatment due to disease progression or death before any post-baseline disease assessment. For clarity, “discontinued study treatment due to” was added to the protocol.

16.10 Summary of Changes from Version 2.0/2.1 to 3.0

This amendment applies to all Investigator sites participating in this study. In this amendment the protocol was updated to include information from two protocol memos: 1. Protocol safety memo No. 2 regarding guidelines for management of IRR (dated 21-Jun-2024) and Protocol clarification memo No. 5 (dated 18-Apr-2024) regarding disease assessment schedule. A summary of the changes from Protocol Version 2.0 are described in the table below:

<table>
<tr><th>Section</th><th>Description/Rationale</th></tr>
<tr><td>Section 3.7.1.1 Management of IRR [SL-172154] (changes previously included in version 2.1 for Spain)</td><td>Description of Change: Due to oversight, some of the relevant guidance that was in amendment 1.0 for Grade 2 and Grade 3 IRR management was removed in amendment 2.0. This correction was shared with the investigators in a memo dated 21-Jun-2024 and the deleted text was added back to the current version of the protocol, and minor edits were made to restructure the section. The updated sections are shown below; text that is added back is shown in italics and new text in regular font:
<table>
<tr><td>Grade 2</td><td>• Temporarily interrupt SL-172154.
• Vital signs should be measured after the onset of an IRR approximately every 15 minutes through the completion of the infusion followed by approximately every 15 minutes for one hour after completion of the SL-172154 infusion and then approximately every 30 minutes for the second hour after the completion of the SL-172154 infusion.
• Begin IV infusion of normal saline and treat symptoms as indicated and per institutional guidelines, e.g., with antipyretic and antihistamines; consider opioids (e.g., meperidine) for rigors, leukotriene inhibitor, bronchodilator therapy, or corticosteroids as appropriate.
• Monitor subjects with close observation in an outpatient or inpatient setting until recovery from symptoms. Consider if admission to hospital is necessary.
• Restart the infusion after resolution of symptoms. Based on the severity of symptoms, reduce the rate to ≤50% of the rate at which the reaction occurred.
• If symptoms recur, then no further SL-172154 will be administered at this visit.
• Subsequent Infusions:
o If the Grade 2 IRR signs and symptoms were not severe, the investigator may administer the next two infusions at the current dose but at ≤50% rate. If the symptoms do not recur, the infusion rate may be increased back to the original rate stated in the protocol.
o If the Grade 2 IRR signs and symptoms were severe, the investigator may reduce the SL-172154 dose for the next two infusions to 1 mg/kg. If the symptoms do not recur, SL-172154 dose may be increased back to 3 mg/kg at ≤50% of the original rate. If tolerated, the rate may be increased back to the original rate stated in the protocol.</td></tr>
<tr><td>Grade 3</td><td>• Immediately discontinue infusion of SL-172154
• Vital signs should be measured after the onset of an IRR approximately every 15 minutes for one hour after discontinuation of SL-172154 infusion and then approximately every 30 minutes for hours 2 and 3 after the discontinuation of the SL-172154 infusion.
• Begin IV infusion of normal saline and treat symptoms as indicated and per institutional guidelines e.g., epinephrine, bronchodilators, diphenhydramine, famotidine or other available H2 receptor antagonist, corticosteroids, consider opioids (e.g., meperidine) for rigors, oxygen, fluids, vasopressors, etc. 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 12 hours or until recovery from symptoms. Strongly consider admission to hospital.</td></tr>
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<table>
<tr><th>Section</th><th>Description/Rationale</th></tr>
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Rechallenge should not be attempted in cases of true anaphylaxis. In other cases, once the subject has completely recovered, carefully consider if it is safe for the subject to receive SL-172154 at the next scheduled dose with premedication and dose reduction.

Reduce the SL-172154 dose for the next two infusions to 1 mg/kg at ≤50% of the rate stated in the protocol. These two subsequent infusions of SL-172154 (after an event of Grade 3 IRR) must be administered in an inpatient or outpatient setting with prolonged observation for a minimum of 12 hours after the completion of the infusion.
If symptoms do not recur at 1 mg/kg SL-172154 dose, subsequent infusions may be administered at the original rate stated in the protocol. If no further symptoms, the SL-172154 dose may be re-escalated to 3 mg/kg but administered at ≤ 50% of the rate stated in the protocol.

</td></tr>
</table>

Rationale/Justification: IRR management guidance in amendment 1.0 was applicable for IRRs that occurred without dexamethasone prophylactic premedication. With the addition of dexamethasone premedication prior to each SL-172154 infusion, more conservative guidance for SL-172154 administration was necessary for managing Grade 2 and Grade 3 IRRs that may occur despite dexamethasone premedication. Updates were made in amendment 2.0 and the rationale is included below. However, while doing so, some of the relevant guidance from amendment 1.0 was accidentally deleted. This information is added back in the current version.

The guidance for Grade 2 IRRs was revised to (1) allow for SL-172154 dose reduction (from 3 mg/kg to 1 mg/kg) based on severity of symptoms; (2) if the symptoms did not recur at the reduced dose (1 mg/kg) in subsequent administrations, the dose could be increased back to the original dose (3 mg/kg) at ≤50% of the rate specified in the protocol; (3) if tolerated at this rate with subsequent administrations, the rate could be increased to the original rate stated in the protocol; and (4) recurrent Grade 2 IRR associated with significant signs or symptoms despite dose reduction, requires permanent discontinuation.
The guidance for Grade 3 IRR was revised to clarify a stepwise approach (1) if the reduced dose of SL-172154 (1 mg/kg) is tolerated at a reduced infusion rate (of ≤50%) during subsequent two infusions, the rate can be increased back to the original rate stated in the protocol; and (2) if the reduced dose of SL-172154 (1 mg/kg) is tolerated at the original rate stated in the protocol, then the dose may be re-escalated to the original dose (3 mg/kg).

</td></tr>
<tr><td>Section 6.1; 6.2 Schedules of assessments; Section 6.11 Assessment of Anti-Tumor Activity (changes applicable from version 2.0 and 2.1 to version 3.0)</td><td>Description of Change:
Text was revised to allow disease assessments to be performed per schedule in Weeks instead of treatment Cycles
Rationale/Justification:
Per the protocol, disease assessment scans should be performed at screening and during the last week of scheduled Cycle (Cycle 2, 4 etc.) until radiologic disease progression. However, delays in treatment Cycles due to adverse events have resulted in scan delays for several subjects. To avoid this issue, if there is more than one week delay in any Cycle, all the subsequent disease assessments can be performed per schedule in Weeks. This information was also communicated to the Investigators in a clarification memo dated 18-Apr-2024.</td></tr>
</table>