Protocol Title: An Open-Label Phase 1a/1b Dose Escalation and Expansion Cohort Study of SL-172154 (SIRPα-Fc-CD40L) in Combination with Azacitidine or with Azacitidine and Venetoclax for the Treatment of Subjects with Higher-Risk Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML)

Short Title: Phase 1a/1b Study of SL-172154 in Subjects with Higher-Risk Myelodysplastic Syndrome or Acute Myeloid Leukemia

Protocol Identifying Number: SL03-OHD-104
Version Number: **v5.0**
Study Phase: 1a/1b

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

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LIST OF ABBREVIATIONS

Ab	Antibody
ADA	Anti-drug antibodies
ADCC	Antibody dependent cell-mediated cytotoxicity
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANA	Antinuclear antibody
aPTT	Activated partial thromboplastin time
APC	Antigen presenting cell
APL	Acute promyelocytic leukemia
AR	Adverse reaction
ARC	Agonist redirected checkpoint
AST	Aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	Area under the serum concentration-time curve
AUC0-last	Area under the serum concentration-time curve from time 0 to the last quantifiable concentration
AUC0-inf	Area under the serum concentration-time curve from time 0 extrapolated to infinity
AUC0-t	Area under the serum concentration-time curve from time 0 to time = t
%AUCext	Percentage of AUC0-inf due to extrapolation from Tlast to infinity
AUCtau	The area under the serum concentration-time curve, over the dosing interval
AV	atrioventricular
β-hCG	Beta- human chorionic gonadotropin
BP	Blood pressure
°C	Degrees Celsius
C1D1	Cycle 1, Day 1
CD	Cluster of differentiation
CD40L	Cluster of differentiation 40 ligand
CFR	Code of Federal Regulations
cGAS	Cyclic guanine monophosphate-adenosine monophosphate synthase
CHF	Congestive heart failure
CI	Confidence interval
CL	Clearance
cm	Centimeters
Cmax	Maximum observed concentration
Cmin	Minimum observed concentration
CML	Chronic myeloid leukemia
CMML	Chronic myelomonocytic leukemia
CMP	Clinical monitoring plan
CNS	Central nervous system
CO_2	Carbon dioxide
COVID-19	Coronavirus disease 2019
CR	Complete remission
CRh	Complete remission with partial hematologic recovery
CRi	Complete remission with incomplete hematologic recovery
CR_{MRD-}	Complete remission without minimal residual disease
CrCl	Creatinine clearance
CRF	Case report form
CRO	Contract research organization
CRS	Cytokine release syndrome
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events

CTLA-4	Cytotoxic T cell lymphocyte-associated antigen 4
CYP450	Cytochrome P450
DAMP	Damage associated molecular pattern molecules
DAT	Direct antiglobulin test
DC	Dendritic cells
DL	Dose level
DLCO	Diffusing capacity of the lungs for carbon monoxide
DLT(s)	Dose-limiting toxicity(ies)
DOR	Duration of response
ECD	Extracellular domain
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EFS	Event free survival
ELN	European Leukemia Net
EOI	End of infusion
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
FEVI	Forced expiratory volume
FISH	Fluorescent *in situ* hybridization
FSH	Follicle stimulating hormone
Gal-9	Galectin-9
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVHD	Graft versus host disease
H1/H2	Histamine 1/ Histamine 2
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
β-hCG	beta-human chorionic gonadotropin
HCT	Hematopoietic cell transplantation
HCV	Hepatitis C virus
Hgb	Hemoglobin
HI	Hematologic improvement
HIV	Human immunodeficiency virus
hr (time)	Hour(s)
HR	Heart rate
HSR(s)	Hypersensitivity reaction(s)
Hu5F9-G4	5F9 (i.e., anti-CD47 monoclonal antibody, magrolimab)
IB	Investigator brochure
IBW	Ideal body weight
ICF	Informed consent
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFNγ	Interferon gamma
IL	Interleukin
IND	Investigational new drug
INR	International normalized ratio
IP	Investigational product
IPSS-R	Revised International Prognostic Scoring System
irAE	Immune-related adverse event
IRB	Institutional Review Board
IRR(s)	Infusion-related reaction(s)

IUD	Intrauterine devices
IV	Intravenous
IWG	International Working Group
JMML	Juvenile myelomonocytic leukemia
K_D	Receptor off-rate constant
kg	Kilogram
LAIPs	Leukemia-associated immunophenotypes
LDH	Lactate dehydrogenase
mAb(s)	Monoclonal antibody(ies)
MAD	Maximum administered dose
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MFC	Multiparameter flow cytometry
MLFS	Morphologic leukemia-free state
MMF	Mycophenolate mofetil
MPN	Myeloproliferative neoplasm
MRD	Minimal residual disease
MTD	Maximum tolerated dose
MUGA	Multigated acquisition
mTPI-2	Modified toxicity probability interval 2
NCI	National Cancer Institute
NGS	Next-generation sequencing
NHL	Non-Hodgkin's lymphoma
NHP	Non-human primate
NFκB	Nuclear factor kappa B
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PD-1	Programmed cell death protein 1
PD-L1 / PD-L2	Programmed cell death ligand 1 / Programmed cell death ligand 2
PFS	Progression free survival
PK	Pharmacokinetic
pM	Picomolar
PO	Oral administration
PR	Partial remission
PT	Prothrombin time
PTV	Post treatment visit
PVR	Poliovirus receptor
PVRL2	Poliovirus receptor-related 2
q	Every
QTc	Corrected QT interval
RANKL	Receptor activator of nuclear factor kappa B ligand
RBC	Red blood cell
RNA	Ribonucleic acid
RP2D	Recommended phase 2 dose
RR	Respiratory rate
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 agonist redirected checkpoint
SLM	Study Laboratory Manual
SMC	Safety Monitoring Committee
SmPC	Summary of Product Characteristics
SOA	Schedule of Assessments
SOI	Start of infusion
SPM	Study Pharmacy Manual
SQ	Subcutaneous administration
STING	Stimulator of interferon genes
SUSAR	Suspected, unexpected serious adverse reaction
T	Temperature
T4	Thyroxine 4
t½	terminal elimination half-life
TCR	T cell repertoire
TIGIT	T cell immunoreceptor with Ig and ITIM domains
Tlast	Time of last observed quantifiable concentration
TLS	Tumor lysis syndrome
Tmax	Time of maximum observed concentration
TNF	Tumor necrosis factor
TP53	Tumor protein 53
TRAF	TNF receptor-associated factor
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
USPI	United States Prescribing Information
VAF	Variant Allele Frequency
Vz	Volume of distribution
WBC	White blood cell
WHO	World Health Organization
Wk	Week
WNL	Within normal limits
λz	Terminal elimination rate constant

Trademark Information

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Agonist Redirected Checkpoint (ARC™)	FluroTec®
	VIDAZA®
	VENCLEXTA®

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 participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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

Principal Investigator:

_____ _____

Print/Type Name Signature

Date: _____

KEY TRIAL CONTACTS

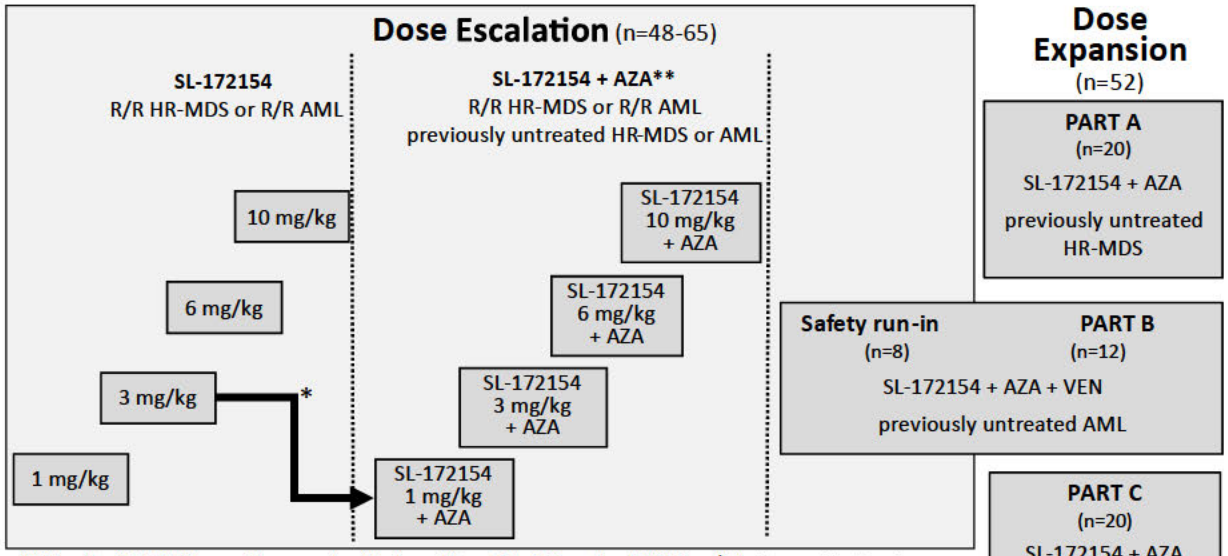
Medical Monitor Name and Contact Information is provided in the Study Contact List.

Sponsor Signatory:

3/14/2024

Date

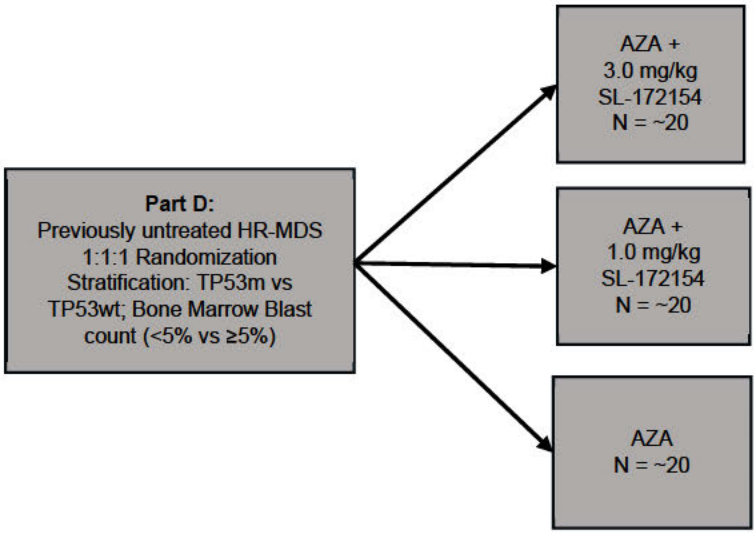
STUDY SCHEMA 1



*When the SL-172154 monotherapy cohort is cleared for safety in Dose Level 2 (3.0 mg/kg), the combination dose escalation cohort (1.0 mg/kg of SL-172154 with azacitidine) will open and can enroll subjects in parallel.
**To escalate the dose of SL-172154 in combination with azacitidine, the monotherapy dose level for SL-172154 should have been cleared for safety.
R/R: relapsed or refractory; HR-MDS: higher-risk MDS; AML: Acute Myeloid Leukemia; AZA: azacitidine; VEN: venetoclax; TP53m includes disease with tumor protein (TP) 53 gene mutation/deletion

* When the SL-172154 monotherapy cohort completes the DLT evaluation period in Dose Level 2 (3.0 mg/kg), the combination dose escalation cohort (1.0 mg/kg of SL-172154 with azacitidine) will open and can enroll subjects in parallel with continued monotherapy dose escalation of SL-172154.
**To dose escalate SL-172154 in combination with azacitidine, the corresponding monotherapy dose level for SL-172154 will have been cleared for safety.
Abbreviations: R/R = relapsed or refractory; HR-MDS = higher-risk myelodysplastic syndrome; AML = acute myeloid leukemia; AZA = azacitidine; VEN = venetoclax; TP53m includes disease with tumor protein (TP) 53 gene mutation/deletion.

STUDY SCHEMA 2



Abbreviations: HR-MDS = higher-risk myelodysplastic syndrome; AZA = azacitidine; TP53m includes disease with tumor protein (TP) 53 gene mutation/deletion; TP53wt=Wild-type tumor protein (TP) 53.

PROTOCOL SYNOPSIS

Sponsor	Shattuck Labs
Product Name	SL-172154
Other Names	SIRPα-Fc-CD40L recombinant fusion glycoprotein
Protocol Title	An Open-Label Phase 1a/1b Dose Escalation and Expansion Cohort Study of SL-172154 (SIRPα-Fc-CD40L) in Combination with Azacitidine or with Azacitidine and Venetoclax for the Treatment of Subjects with Higher-Risk Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML)
Protocol Number	SL03-OHD-104
Clinical Phase	Phase 1a/1b
Planned Sample Size	Approximately 160-177 subjects
Planned Number of Sites	Approximately 35 sites
Recruitment Duration	approximately 38 months
Study Duration	approximately 50 months

Background and Rationale

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

The combination of SIRPα-Fc-CD40L with hypomethylating agent, azacitidine, enhanced *in vitro* phagocytosis of AML and chronic myeloid leukemia (CML) tumor cell lines (Kasumi-3 and K562, respectively). A similar effect was observed with the combination of SL-172154 with a BCL-2-inhibitor, venetoclax. Upregulation of CD47, the target for SIRPα and induction of the prophagocytic protein, calreticulin was observed with azacitidine.

A multi-prong approach to overcoming immune evasion may be essential in MDS and AML. Stimulation of phagocytosis by induction of prophagocytic proteins (damage associated molecular pattern molecules or DAMPs) and inhibition of the checkpoint CD47/SIRPα along with augmentation of antigen presentation by antigen presenting cells (APC) to T cells may be achieved by combining SL-172154 with azacitidine or venetoclax. Azacitidine and venetoclax upregulate surface pro-phagocytic signals such as calreticulin, ultimately enhancing cancer cell phagocytosis by macrophages. To assess the activity of SL-172154, subjects in this study will either be treatment-naïve or have received no more than 4 prior lines of therapy for their disease as more heavily treated patients with relapsed/refractory disease are more likely to have an unfavorable immune microenvironment with exhausted and terminally differentiated T cells that are less likely to respond to immunotherapies.

SL03-OHD-104 is designed as a Phase 1a/1b open label, trial to evaluate the safety, pharmacokinetics (PK), pharmacodynamic (PD), and preliminary efficacy of SL-172154 monotherapy as well as in combination with azacitidine or in combination with azacitidine and venetoclax. Azacitidine and venetoclax are commonly used in

clinical practice and the safety, PK and PD profiles of each agent is well known in these patient populations. Each component is anticipated to have activity on distinct targets, and these agents combined with SL-172154 have the potential to further bridge innate and adaptive immunity, thus potentially improving treatment outcomes without increasing toxicity. No overlapping toxicities, other than fatigue, are anticipated with SL-172154. Hematologic toxicities (e.g., hemolysis, interference with crossmatch) have not been observed with SL-172154 in ongoing clinical trials.

Approximately 5 subjects with relapsed or refractory disease (AML or higher-risk MDS) will initially be enrolled to monotherapy dose escalation cohort at the starting dose of 1.0 mg/kg SL-172154. Subjects will be enrolled in cohorts of approximately 5 subjects each into sequential dose levels of SL-172154 and assessed for dose-limiting toxicity (DLT) during the first cycle (28 days) of treatment utilizing the mTPI-2 method. When the SL-172154 monotherapy cohort completes the DLT evaluation period in Dose Level 2 (3.0 mg/kg), enrollment may begin in parallel to the dose escalation cohorts investigating SL-172154 administered with azacitidine using a starting dose of 1.0 mg/kg SL-172154. To escalate the dose of SL-172154 in combination with azacitidine, the corresponding monotherapy dose level for SL-172154 will have been cleared for safety. Subjects with relapsed/refractory AML or higher-risk MDS will be enrolled in the dose escalation cohort; previously untreated subjects with AML and known adverse cytogenetics (e.g., European Leukemia Net [ELN] adverse risk group) as well as previously untreated subjects with MDS with at least one TP53 gene mutation/deletion may also be considered for enrollment in this cohort. Once the selected dose of SL-172154 administered with azacitidine is identified in dose escalation, enrollment to a safety run-in cohort (n=8) of SL-172154 administered with azacitidine and venetoclax will commence using the same SL-172154 dose. Treatment-naïve subjects with AML will be enrolled.

Upon identification of selected dose for the SL-172154 and azacitidine combination regimen, dose expansion cohorts will enroll additional subjects to further evaluate the safety and efficacy of the combination regimen. In the dose expansion part of the study, approximately 20 treatment naïve subjects with higher-risk MDS will be enrolled to receive SL-172154 at the selected dose with azacitidine (Part A). In addition, approximately 20 treatment naïve AML subjects with at least one known TP53 gene mutation or deletion will be enrolled to receive SL-172154 at the selected dose with azacitidine (Part C). Once the SL-172154 dose in combination with azacitidine and venetoclax is confirmed during the safety run-in, approximately 20 treatment naïve subjects with AML (including safety run-in cohort and dose expansion) will be enrolled to receive SL-172154 with azacitidine and venetoclax (Part B).

Part D: Safety and efficacy will be further explored in Part D. Approximately 60 subjects with previously untreated higher-risk MDS will be randomized equally into 3 groups: 3.0 mg/kg SL-172154+azacitidine, 1.0 mg/kg SL-172154+azacitidine and azacitidine monotherapy. Patients will be stratified based on the TP53 mutation status (TP53m vs TP53wt) and bone marrow blast count at study entry (<5% vs ≥5%).

Study Objectives

Primary Objectives	Outcome Measures
To evaluate the safety and tolerability of SL-172154 administered alone or with azacitidine OR azacitidine + venetoclax in subjects with higher-risk MDS or AML	• 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 safety laboratory values per NCI-CTCAE, version 5.0 • AEs leading to treatment discontinuation, AEs leading to dose reduction of SL-172154 • Maximum tolerated dose (MTD) of SL-172154 in monotherapy and each combination regimen based on the rate of DLTs, or the maximum administered dose (MAD; the highest dose administered).

To select the recommended Phase 2 dose (RP2D) for SL-172154 administered alone or with azacitidine OR azacitidine + venetoclax in subjects with higher-risk MDS or AML	• Number and occurrence of DLTs as defined in the protocol • Available pharmacokinetic (PK) parameters • Available pharmacodynamic (PD) effects • Safety • Anti-tumor efficacy
Part D: • To evaluate safety and anti-tumor activity of SL-172154 at 1.0 mg/kg and 3.0 mg/kg administered with azacitidine vs azacitidine monotherapy in higher-risk MDS subjects • To evaluate safety and anti-tumor activity of SL-172154 at 1.0 mg/kg vs 3.0 mg/kg administered with azacitidine in higher-risk MDS subjects	• Safety endpoints as listed above • Complete remission (CR) based on Investigator assessed disease response according to International Working Group (IWG) 2006 criteria
Secondary Objectives	**Outcome Measures**
To assess preliminary evidence of anti-tumor efficacy of SL-172154 administered alone or with azacitidine OR azacitidine + venetoclax in subjects with higher-risk MDS or AML Part D: To assess preliminary evidence of anti-tumor efficacy of SL-172154 administered with azacitidine compared to azacitidine monotherapy in subjects with higher-risk MDS	• Investigator assessed disease response according to International Working Group (IWG) 2006 criteria (MDS) or ELN 2017 criteria (AML) ○ Complete remission (CR) ○ Objective response rate (ORR) defined as CR, partial remission (PR), marrow CR, or hematologic improvement (HI) for MDS, or CR, CR with incomplete hematologic improvement (CRi), PR or morphologic leukemia-free state (MLFS) for AML ○ Composite CR rate (CR and CRi) for AML ○ CR/CR with partial hematological recovery (CRh) for AML • Time to response • Duration of response (DOR) • Progression free survival (PFS) • Event free survival (EFS) • Overall survival (OS) • Minimal residual disease (MRD)-negative response rate • Proportion of subjects with MDS with hematologic improvement
To evaluate immunogenicity to SL-172154 during and after treatment of SL-172154 administered alone or with azacitidine OR azacitidine + venetoclax in subjects with higher-risk MDS or AML	• Number/proportion of subjects with positive or negative anti-drug antibody (ADA) titer • ADA duration • Transient vs. persistent ADA
To assess the pharmacokinetic profile of SL-172154 when administered alone or with azacitidine OR azacitidine + venetoclax in subjects with higher-risk MDS or AML	• Maximum observed concentration (Cmax), time at which the maximum concentration is observed (Tmax), and minimum observed concentration (Cmin) following single and multiple doses of SL-172154 • Area under the serum concentration-time curve (AUC) • Terminal elimination half-life (t½), Clearance (CL) and Volume of Distribution (Vz)
Exploratory Objectives	**Outcome Measures**

To assess the rate and duration of red blood cell (RBC) and platelet transfusion independence in subjects with higher-risk MDS or AML receiving SL-172154 alone or with azacitidine OR azacitidine + venetoclax Part D: To assess the rate and duration of red blood cell (RBC) and platelet transfusion independence in subjects with higher-risk MDS administered SL-172154 with azacitidine compared to azacitidine monotherapy	• Proportion of participants who have a 56-day or longer period with no RBC transfusions • Duration of RBC transfusion independence • Proportion of participants who have a 56-day or longer period with no platelet transfusions • Duration of platelet transfusion independence
To assess MRD in subjects with higher-risk MDS or AML receiving SL-172154 alone or with azacitidine OR azacitidine + venetoclax Part D: To assess MRD in subjects with higher-risk MDS administered SL-172154 with azacitidine compared to azacitidine monotherapy	• MRD assessed in bone marrow aspirate by next-generation sequencing (NGS) and/or flow cytometry
To assess pharmacodynamic biomarkers in peripheral blood and bone marrow aspirate prior to, on-treatment and following treatment with SL-172154 administered alone or with azacitidine OR azacitidine + venetoclax in subjects with higher-risk MDS or AML	Pharmacodynamic biomarkers in peripheral blood and bone marrow aspirate may include: • Changes in T cells subsets, B cells, macrophages, and dendritic cells (DCs) • Evidence of SL-172154 localization (CD47 or CD40 receptor occupancy) on hematopoietic cells and/or malignant cells in the bone marrow and peripheral blood

Treatment Schedules

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, or the subject meets other criteria for discontinuation (whichever occurs first).

SL-172154

The starting dose of SL-172154 is 1.0 mg/kg in the monotherapy dose escalation cohort. SL-172154 will be administered intravenously once weekly on Days 1, 8, 15 and 22 during the first 2 cycles (28 days per cycle), and on Day 1 and 15 during Cycle 3 and thereafter in the monotherapy cohort, and once weekly on Days 2, 9, 16 and 23 during the first 2 cycles (28 days per cycle) and on Day 2 and 16 during Cycle 3 and thereafter in the combination cohorts. For a dose 0.3 mg/kg, the duration of infusion is 30 minutes (± 10 minutes); for a dose of 1.0 mg/kg the duration of infusion is 60 minutes (± 10 minutes); for doses of 3.0 mg/kg, the duration of infusion is 180 minutes (± 15 minutes); for doses of 6.0 and 10.0 mg/kg, the duration of infusion is 180 minutes (± 15 minutes). On days when both SL-172154 and azacitidine are administered, the azacitidine administration should be completed at least 30 minutes prior to the start of the SL-172154 infusion.

Prophylactic premedication for infusion-related reactions (IRR) with an antipyretic and antihistamines [e.g., acetaminophen 650 to 1000 mg PO; diphenhydramine 25 to 50 mg (or equivalent) PO or IV; famotidine 20 mg PO or IV (or equivalent)] and dexamethasone (8 mg IV) should be administered at least 30 minutes prior to each SL-172154 administration.

The infusion rate of SL-172154 may change based on the final drug volume needed for administration, safety, and the subject's tolerability of the infusion and/or observed safety findings during the study.

Azacitidine

Azacitidine 75 mg/m^2 will be administered either IV (10- to 40-minute infusion) or subcutaneously once daily for 7 days (Days 1 to 7 or alternative 5-2-2 schedule) in 28-day cycles. Azacitidine is to be administered beginning on Day 1 of each cycle for all subjects, regardless of combination regimen cohort assignment. When SL-172154 is to be administered on the same day as azacitidine, the azacitidine administration should be completed at least 30 minutes prior to the start of the SL-172154 infusion.

Venetoclax

Venetoclax 400 mg will be administered orally, once daily, with food. A 3-day ramp-up dosing during Cycle 1 will be performed, with the dose of venetoclax 100 mg on Day 1 and 200 mg on Day 2; on Day 3, the target dose of 400 mg will be administered and continued until Day 28. In all subsequent 28-day cycles, the dose of venetoclax will be 400 mg daily. Subjects will self-administer venetoclax by mouth once daily. Tablets must be swallowed whole and must not be broken, chewed, or crushed.

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 28 days of treatment (i.e., Cycle 1). All toxicities except for cytokine release syndrome (CRS) will be graded as per NCI CTCAE v5; CRS will be graded per the ASTCT Consensus Grading Criteria for CRS. AEs clearly related to disease progression, intercurrent illness, or concomitant medications are not considered DLTs. Infection, bleeding, or other expected direct complications of cytopenias due to active underlying MDS or AML will not be considered a DLT. A DLT is defined as an event considered related or possibly related to SL-172154 and meets one of the following criteria:

- SL-172154 monotherapy cohort: Grade 4 neutropenia or thrombocytopenia lasting ≥ 14 days from start of the cycle in the absence of evidence of active AML or MDS.
- SL-172154 in combination with azacitidine or azacitidine and venetoclax: Grade 4 neutropenia or thrombocytopenia lasting ≥ 28 days from the start of the cycle in the absence of active AML or MDS.
- Any death not clearly related to underlying disease or intercurrent illness.
- Any Grade 3 elevations in aspartate aminotransferase (AST) alanine aminotransferase (ALT), or total bilirubin.
  - Evidence of Hy's Law (AST or ALT ≥3 x upper limit of normal (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 or greater non-hematologic AE that requires permanent discontinuation of SL-172154.
- Any Grade 3 or greater non-hematologic AE except for those listed below:
  - Grade 3 fatigue lasting ≤ 7 days.
  - 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.
  - Vitiligo or alopecia of any grade.

Other toxicities may be considered a DLT (e.g., a clinically significant Grade 2 AE) as determined by the Investigator in conjunction with the Safety Monitoring Committee (SMC).

Eligibility Criteria

Inclusion Criteria

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

1. Subject has voluntarily agreed to participate by giving written informed consent in accordance with ICH/GCP guidelines and applicable local regulations.
2. Age ≥ 18 years.
3. For subjects with AML, confirmation of AML diagnosis by 2016 WHO criteria [Arber, 2016] (World Health Organization [WHO] classification, excluding acute promyelocytic leukemia [APL]).
4. Subjects with MDS must have:

a. morphologically confirmed diagnosis of MDS by 2016 WHO criteria [Arber, 2016] with <20% blasts in bone marrow per bone marrow biopsy/aspirate or peripheral blood.
b. confirmation of intermediate, high or very high risk category by Revised International Prognostic Scoring System (IPSS-R).

Subjects with a diagnosis of any of the following are excluded: Atypical CML, juvenile myelomonocytic leukemia (JMML), chronic myelomonocytic leukemia (CMML), and unclassifiable MDS/ myeloproliferative neoplasm (MPN).

5. [*Dose Escalation Cohort – SL-172154 Monotherapy*] Subjects with AML must have relapsed/refractory disease (≥5% blasts by manual aspirate differential, flow cytometry, or immunohistochemistry) following at least 1 prior line of therapy but no more than 4 prior lines of therapy. Subjects with higher-risk MDS must have relapsed/refractory disease following at least 1 prior line but no more than 4 prior lines of therapy.
   a. Prior hydroxyurea or other supportive care in the form of transfusions or growth factors will not be considered prior therapy.
   b. Subjects who have undergone allogeneic-hematopoietic cell transplantation (HCT) are eligible if they are at least 6 months post-HCT, have relapsed AML or MDS as defined above, are not on treatment or prophylaxis for graft versus host disease (GVHD) for at least 6 weeks before administration of study treatment, and have no active GVHD.
   c. Subjects must not be eligible for rescue chemotherapy and allogeneic-HCT per local or institutional guidelines at the time of screening.
6. [*Dose Escalation Cohort – SL-172154 Administered with Azacitidine*] Subjects with relapsed/refractory AML and MDS (as defined in Inclusion criterion 5) following at least 1 prior line of therapy but no more than 4 prior lines of therapy.
   a. Treatment for MDS preceding secondary AML will not be considered as a prior line of therapy for secondary AML.
   b. Prior hydroxyurea or other supportive care in the form of transfusions or growth factors will not be considered prior therapy.
   c. Subjects who have undergone allogeneic-HCT are eligible if they are at least 6 months post-HCT, have relapsed AML or MDS as defined above, are not on treatment or prophylaxis for GVHD for at least 6 weeks before the first dose of study treatment, and have no active GVHD.
   d. Subjects must not be eligible for rescue chemotherapy and allogeneic-HCT per local or institutional guidelines at the time of screening.

   In addition, previously untreated subjects meeting either of the following criteria are eligible for this cohort:

   a. Previously untreated subjects with AML with known adverse cytogenetics who fall into the adverse ELN risk group and who are unlikely to benefit from standard intensive induction therapy or refuse intensive induction therapy at time of enrollment.
   b. Previously untreated subjects with MDS with documentation of at least one TP53 gene mutation or deletion based on a local test. Prior MDS therapy with lenalidomide or other supportive care in the form of transfusions or growth factors is allowed.
7. [*Dose Expansion Cohort Part A: SL-172154 Administered with Azacitidine*] Subjects diagnosed with MDS must be previously untreated. Prior MDS therapy with lenalidomide, luspatercept or supportive care in the form of transfusions or growth factors is allowed. Up to 1 cycle of prior therapy with a hypomethylating agent is permitted. Subjects with newly diagnosed treatment-related MDS are also eligible for enrollment.
8. [*Dose Escalation – Safety Run-in Cohort AND Dose Expansion Cohort Part B: SL-172154 Administered with Azacitidine and Venetoclax*] Subjects with AML must be previously untreated as defined by:
   a. Subject must be ineligible for induction therapy with a standard cytarabine and anthracycline induction regimen due to age or co-morbidities as defined by the following:
      - ≥ 75 years of age

- ≥ 60 to 74 years of age with at least one of the following co-morbidities:
  - Eastern Cooperative Oncology Group (ECOG) Performance Status of 2
  - History of congestive heart failure (CHF) requiring treatment
  - Ejection fraction ≤ 50%
  - Chronic stable angina
  - DLCO ≤ 65% or FEV1 ≤ 65%
  - Creatinine clearance ≥ 30 mL/min to < 45 mL/min
  - Documented contraindication to anthracycline or cytarabine based therapy

b. Subjects with AML with known adverse cytogenetics who fall into the adverse ELN risk group and who are unlikely to benefit from standard intensive induction therapy or refuse intensive induction therapy at time of enrollment are also eligible.

c. Subjects with newly diagnosed secondary AML and who are unlikely to benefit from standard intensive induction therapy or refuse intensive induction therapy at time of enrollment are eligible for enrollment. Subjects with secondary AML after MDS must not have received prior chemotherapy or no more than 2 cycles of prior hypomethylating agent for MDS.

9. [*Dose Expansion Cohort Part C: SL-172154 Administered Azacitidine*]: Subjects with previously untreated *de novo* AML or secondary AML with TP53 gene mutation or deletion who are unlikely to benefit from standard intensive induction therapy or refuse intensive induction therapy at time of enrollment are eligible. All subjects must have documentation of at least one TP53 gene mutation/deletion based on local test. Subjects with secondary AML after MDS must not have received prior chemotherapy or no more than 2 cycles of prior hypomethylating agent for MDS.
10. ECOG Performance Status of 0, 1, or 2.
11. Laboratory values must meet the following criteria:

Laboratory parameter	Threshold value
White blood cell count (WBC)	≤ 20 x 10^9/L (Hydroxyurea is permitted to meet this criterion)
Creatinine clearance (CrCl)	≥ 30 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

12. Willing to provide consent for bone marrow aspirate samples at baseline and on-treatment for exploratory research as described in the Schedule of Assessments.
13. For subjects with relapsed/refractory disease, recovery from prior anti-cancer treatments including surgery, radiotherapy, chemotherapy or any other anti-cancer therapy to baseline or ≤ Grade 1. (NOTE: Low-grade or controlled toxicities (e.g., alopecia) may be allowed upon agreement by the Medical Monitor)
14. Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test within 72 hours of the first dose of study treatment. NOTE: females are defined as being of childbearing potential unless they are surgically sterile (i.e., have undergone a complete hysterectomy, bilateral tubal ligation/occlusion, bilateral oophorectomy, or bilateral salpingectomy), have a congenital or acquired condition that prevents childbearing or are naturally post-menopausal for at least 12 consecutive months. Documentation of post-menopausal status must be provided. To avoid pregnancy, FCBP must start using a highly effective method of contraception (i.e., <1% failure rate) at least 14 days prior to initiation of study treatment and continue use during treatment and for 30 days (which exceeds 5 half-lives) after the last dose of SL-172154, or for the duration required by local prescribing information after the last dose of azacitidine (i.e., for sites in UK, at least 6 months after the last dose of azacitidine in either combination regimen).
15. Male subjects with female partners must have azoospermia from a prior vasectomy, an underlying medical condition, or agree to use a highly effective method of contraception (i.e., <1% failure rate) during treatment and for 30 days (which exceeds 5 half-lives) after the last dose of SL-172154, or for the duration

required by local prescribing information after the last dose of azacitidine (i.e., for sites in UK, at least 3 months; for sites in Canada, at least 6 months).

16. [*Dose Expansion Cohort Part D: SL-172154 with Azacitidine vs Azacitidine monotherapy*]*:* Subjects diagnosed with MDS must be previously untreated. Prior MDS therapy with lenalidomide, luspatercept or supportive care in the form of transfusions or growth factors is allowed. No prior therapy with a hypomethylating agent is permitted. Subjects with newly diagnosed treatment-related MDS are also eligible for enrollment. TP53 mutation status results based on local test must be available prior to randomization.

Exclusion Criteria

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

1. [*Monotherapy and Combination Regimen Dose Escalation Cohorts*] Prior treatment with:
   - CAR-T cell therapy within 3 months from the first dose of the study drug.
   - Prior treatment with anti-CD47 targeting agent or CD40 agonist within 28 days prior to the first dose of study treatment.
   - Prior treatment with signal-regulatory protein alpha (SIRPα)-targeting agent.
   - Other experimental therapies for AML or MDS within 14 days or at least 5 half-lives (whichever is shorter) prior to the first dose of study treatment.
2. Evidence of active CNS involvement with leukemia.
3. Subjects requiring agents other than hydroxyurea to control blast counts within 14 days prior to the first dose of study treatment.
4. Evidence of active bleeding or bleeding diathesis or major coagulopathy (including familial).
5. [*Only for Cohorts Including Venetoclax in the Regimen*] Subject has received strong and/or moderate CYP3A inducers within 7 days prior to the first dose of venetoclax.
6. Use of systemic corticosteroids (>10 mg daily of prednisone or equivalent) or other non-steroidal immunosuppressive medication, current or within 14 days of the first dose of study treatment with the following exceptions (i.e., the following are allowed within 14 days of first dose):
   - Topical, intranasal, inhaled, ocular, intraarticular corticosteroids
   - Physiological doses of replacement steroid (e.g., for adrenal insufficiency)
   - Steroid premedication for hypersensitivity reactions (e.g., reaction to IV contrast) or a brief course of treatment of non-autoimmune conditions (e.g., transfusion reactions, delayed-type hypersensitivity reaction caused by contact allergen).
7. Receipt of live attenuated vaccine within 30 days of first dose of SL-172154 treatment.
8. Subject has active, uncontrolled infection (e.g., viral, bacterial, or fungal). Subjects are eligible if infection is controlled with antibiotics, antivirals and/or antifungals.
9. [*Only for Cohorts Including Venetoclax in the Regimen*] Subject has a malabsorption syndrome or other condition that precludes the enteral route of administration.
10. Subjects with:
    - Symptomatic peptic ulcer disease or gastritis,
    - active diverticulitis,
    - other serious gastrointestinal disease associated with diarrhea within 6 months of first dose of study treatment.
11. Clinically significant or uncontrolled cardiac 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 (AV) block without a pacemaker, circulatory collapse requiring vasopressor or inotropic support, or arrhythmia not stabilized on therapy)

12. Subject has chronic respiratory disease that requires continuous oxygen, or significant history of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, hepatic, cardiovascular disease, or any other medical condition that in the opinion of the Investigator would adversely affect his/her participation in the study.
13. Subjects who have had any major surgical procedure within 14 days of first dose of study treatment.
14. Subject is a woman who is pregnant or breast feeding or planning to become pregnant or breast feed while enrolled in this study.
15. 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.
16. Presence of another malignancy that requires active therapy and that in the opinion of the Investigator and Sponsor would interfere with the monitoring of disease assessments in this study.
17. Known hypersensitivity to any of the study medications including excipients of azacitidine.
18. Has undergone solid organ transplantation.
19. Known or active human immunodeficiency virus (HIV) infection
20. Known or active infection with hepatitis B (positive for hepatitis B surface antigen [HbsAg]) or hepatitis C virus ([HCV]; if HCV antibody (Ab) test is positive check for HCV ribonucleic acid [RNA]).
    NOTE: Hepatitis B virus (HBV): Subjects who are hepatitis B core antibody [HbcAb]-positive but HbsAg-negative are eligible for enrollment. HCV: Subjects who are HCV Ab-positive but HCV RNA-negative are eligible for enrollment.

Safety Oversight
During the study while subjects are receiving treatment with SL-172154, SMC meetings will be held to review relevant data with the Investigators or designees. These meetings will be held once a month (or more frequently if required) to review and discuss safety data and communicate results of ongoing analyses during dose escalation and dose expansion 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. All dose escalation or safety decisions made by the SMC will be documented in writing with copies maintained at each site and the Trial Master File at the Contract Research Organization.
Statistical Analyses
The safety evaluation will be based on the All-Treated Population defined as all subjects who received at least one dose of study treatment. Frequency tables by dose levels will be used to describe safety and tolerability parameters such as: AEs, serious adverse events (SAEs), fatal AEs, AEs leading to dose reduction of SL-172154, and AEs leading to discontinuation of SL-172154, azacitidine and venetoclax. 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 will be graded according to the NCI CTCTAE v5.0. CRS will be graded per the ASTCT Consensus Grading Criteria for CRS. The DLT evaluation will be based on the DLT-evaluable population [defined as all subjects enrolled in the dose escalation cohorts (SL-172154 monotherapy or SL-172154/azacitidine combination) or safety run-in cohort (SL-172154, azacitidine and venetoclax combination) who receive at least 2 of 4 scheduled doses of SL-172154 and at least 50% of the scheduled doses of the combination agent (azacitidine or venetoclax) and complete the safety follow-up through the DLT evaluation period or experience any DLT during the DLT evaluation period]. DLTs

will be summarized by dose level for monotherapy dose escalation cohorts, combination dose escalation cohorts, and the safety run-in cohort. The MTD will be estimated using isotonic regression.

For dose escalation and Part A, B and C of dose expansion, anti-tumor efficacy data will be summarized by dose level and overall for MDS and AML, 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). For Part D of dose expansion, efficacy analysis will be based on Intent-to-treat (all randomized subjects regardless of whether or not treatment was administered), All Treated and response evaluable population. All efficacy data will be summarized by the treatment arm. The CR rate and 95% CI in each arm will be calculated and CR rate will be compared between SL-172154 1.0 m/g/kg or 3.0 mg/kg in combination with azacitidine and azacitidine monotherapy using Fisher's exact test, 95% CIs for the difference in CR rate will be calculated.

The primary analysis is based on Investigator-assessed response per 2006 IWG criteria for subjects with MDS or per 2017 ELN criteria for subjects with AML. The ORR, CR, composite CR, CR/CRh, RBC and platelet transfusion independence rate and MRD-negative response rate will be estimated along with a 95% confidence interval using the exact probability method. DOR and time to response will be evaluated, using the Kaplan-Meier method, for the subgroup of subjects with CR, composite CR, CR/CRh, or ORR. Duration of RBC and platelet transfusion independence will be evaluated, using the Kaplan-Meier method, for the subgroup of subjects with transfusion independence. The Kaplan-Meier method will be used to estimate the PFS/EFS/OS curve and PFS/EFS/OS rate at timepoint 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 outcome measures may be explored, as data permit, using appropriate graphical and statistical methods. PD biomarkers values will be summarized descriptively by dose level and visit. The effect of ADA on PK, PD, safety and efficacy will be explored, as data permit, using appropriate graphical and statistical methods.

1. BACKGROUND AND STUDY RATIONALE

1.1 Bridging Innate and Adaptive Immunity

Cluster of differentiation (CD) 47 is expressed by many somatic and hematopoietic tissues and is an important protective mechanism to prevent red blood cell (RBC) and platelet destruction by macrophages and splenic CD4+ dendritic cells (DCs) [Oldenborg, 2000; Blazar, 2001; Yamao, 2002; Olsson, 2005; Yi, 2015]. The anti-phagocytic activity of CD47/SIRPα led to the description of this axis as the macrophage 'do not eat me' signal. The 'eat me' signal which ultimately leads to red blood cell (RBC) destruction by splenic 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 increases 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 hematogenous and solid 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 an important target of CD47/SIRPα inhibition in the context of tumor immunotherapy [Liu, 2015]. Specifically, inhibition of SIRPα signaling in CD8α+ DCs has been shown to enhance sensing of phagocytosed tumor mitochondrial 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 [Liu, 2015; Xu, 2018]. Increased antigen priming of CD8α+ DCs 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 (APC) to cross-present exogenous tumor antigens. Following phagocytosis, these tumor antigens gain entry to the DC cytosol and then are cross-presented to CD8+ T cells. CD40 ligation by CD40 ligand (CD40L), expressed by resting CD8α+ DCs (but not CD8α-), 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 [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 . 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 Myelodysplastic Syndrome

Myelodysplastic syndromes (MDS) is a heterogeneous group of clonal stem cell disorders characterized by ineffective hematopoiesis resulting in cytopenias in at least one hematologic lineage and a risk of evolution to acute myeloid leukemia (AML) [Cazzola, 2020]. Variable degrees of cytopenias result in a high symptom burden with a risk of death from complications and transformation to AML. The median age at diagnosis of MDS is ~ 70 years. Based on the SEER–Medicare database the incidence of MDS is estimated as high as 75 per 100,000 persons aged 65 years [Cogle, 2011]. With the current demographic trend, both incidence and prevalence is expected to grow.

The Revised International Prognostic Scoring System (IPSS-R) is used to estimate the risk of evolution to AML and expected survival. IPSS-R considers the number and degree of cytopenias, proportion of blasts in the marrow, and the risk of specific cytogenetic abnormalities. IPSS-R defines 5 major prognostic categories: very low, low, intermediate, high, and very high risk. In clinical practice, a cut-off IPSS-R score of 3.5 distinguishes patients between lower-risk ($\leq$ 3.5; median survival of 5.9 years) and higher-risk MDS (score > 3.5; median survival of 1.5 years). Lower-risk and higher-risk MDS accounts for approximately two-thirds and one-third, respectively, of all cases at onset of disease [Pfeilstocker, 2016].

Molecular profiling can improve risk stratification and substantially inform clinical decision making [Cazzola, 2020]. Mutations in SF3B1, TET2, SRSF2, ASXL1, DNMT3A, and RUNX1 occur in at least 10% of patients who have MDS, with a long list of additional genes that are mutated less frequently. TP53, NRAS, ASXL1, and EZH2 mutations are consistently associated with poor outcomes while SF3B1 mutations are associated with more favorable outcomes. Patients with therapy-related MDS frequently have TP53 mutations or PPM1D mutations and a complex karyotype. Biallelic defects in TP53 predicts a risk of leukemic transformation and death independent of IPSS-R score. The deletion on the long arm of chromosome 5 is the initiating driver mutation that leads to haploinsufficiency of multiple genes and, in turn, to clinical manifestations. Some patients with MDS have features of myeloproliferative diseases associated with an over-representation of mutations such as JAK2, SRSF2, SETBP1, CSF3R, and BCOR compared with those without these features.

Not all MDS patients need to be treated immediately upon diagnosis. When treatment is required, the main objective is to ameliorate cytopenias, primarily anemia, and improve the quality of life. For patients with higher-risk MDS, treatment is aimed not only at ameliorating cytopenias but also at preventing evolution to AML and thus prolonging survival. Allogeneic-hematopoietic cell transplantation (HCT), is the only potentially curative treatment. However, the morbidity and mortality associated with the allogeneic-HCT in older adults with comorbid diseases precludes this as a viable option for many. Several drugs can modulate myelodysplastic hematopoiesis, but available treatments fail to eradicate it, mainly because selective pressure leads to the emergence of resistant subclones. The use of a hypomethylating agent, azacitidine or decitabine, currently represents the initial treatment in patients with higher-risk MDS who are ineligible for

transplantation. About half the patients treated with azacitidine have a hematologic response, including some with a complete response. Treatment is associated with prolonged survival [Fenaux, 2009], although the survival benefit observed in real-life studies is on the order of a few months [Ozbalak, 2012].

1.3 Acute Myeloid Leukemia (AML)

AML is a heterogeneous disease characterized by acquired genetic alterations in hematopoietic progenitor cells. AML is defined by the World Health Organization (WHO) as a myeloid neoplasm with 20% or more blasts in the peripheral blood or bone marrow [Vardiman, 2002]. The pathogenesis involves an abnormal proliferation and differentiation of a clonal population of myeloid stem cells. The estimated number of new cases in the United States is 19,940 and the number estimates deaths is 11,180. Per SEER database (accessed 18 January 2021, https://seer.cancer.gov/statfacts/html/amyl.html), the median age of diagnosis is 68 years with approximately one-third of patients being diagnosed over the age of 75. More than 70% of patients 65 years or older will die of their disease within 1 year of diagnosis.

Prognostic risk is defined at diagnosis based on certain cytogenetic and molecular aberrations [Dohner, 2017]. Well characterized chromosomal translocations result in the formation of chimeric proteins which alter the normal maturation process of myeloid precursor cells. In addition to chromosomal translocations, genetic mutations (e.g., NPM1, CEBPA, RUNX1, FLT3, IDH1, IDH2, K/NRAS, TP53, ASXL1, c-KIT) are identified often in the absence of translocations. Alterations in genes involved in epigenetic regulation (DNMT3A, ASXL1, TET2) and less frequently in splicing factor genes (SF3B1, SRSF2), have emerged as another class of mutations with downstream effects on cellular differentiation and proliferation.

Although advances in the treatment of AML have led to significant improvements in outcome for younger patients, the prognosis in the elderly remains poor. Standard treatment for the medically fit, newly diagnosed AML patient consists of remission induction therapy with cytarabine combined with an anthracycline, usually daunorubicin or idarubicin (7 + 3). Induction therapy is followed by consolidation therapy. Allogeneic stem cell transplantation can be curative for some patients with AML. A therapeutic graft-versus-leukemia effect ensues in which donor-derived T cells recognize the minor histocompatibility antigens expressed on host leukemia cells. Unfortunately, only a minority of patients are candidates for stem cell transplantation, but the success of this procedure suggests that other immune strategies may be beneficial in AML. Higher proportion of unfavorable cytogenetics, higher frequency of antecedent hematologic disorders or prior therapy for previous malignancies, and more frequent expression of the multidrug resistance phenotype account for the poor outcomes associated with current therapy.

AML in elderly patients is a biologically and clinically distinct disease. The presence and severity of comorbid conditions, compromised end organ function that enhance the toxicity of induction chemotherapy, and limitations in functional capacity all decrease the ability for the elderly patient to tolerate induction chemotherapy and survive life-threatening infections often associated with AML therapy. While some elderly patients are able to receive standard induction or intensive chemotherapy, the majority are treated with less intensive therapies such as hypomethylating agents or low dose cytarabine. In a recent clinical trial, overall survival (OS) was longer and the

incidence of remission was higher among AML patients who received azacitidine plus venetoclax compared to those who received azacitidine alone [DiNardo, 2020b]. This regimen is being adopted as the new standard of care in previously untreated patients who are ineligible for intensive chemotherapy.

Nonetheless, the benefit of improved median OS from the combination of azacitidine and venetoclax has not been observed in TP53-mutated AML patients. No benefit in OS was observed in this poor prognostic subgroup although an increase in objective response rate (ORR) was observed (55% vs. 0% in patients treated by the combination of azacitidine and venetoclax vs. the combination of azacitidine and placebo, respectively) [DiNardo, 2020b; Cluzeau, 2021]. This is in line with other retrospective cohorts of TP53-mutant AML patients treated with decitabine, another hypomethylating agent, and venetoclax. Despite use of extended decitabine courses, these cohorts demonstrated a median OS of approximately 6 months regardless of venetoclax receipt [Maiti, 2019; DiNardo, 2020b; Venugopal, 2021]. These clinical findings are supported by recent mechanistic observations identifying TP53 mutation to be a direct driver of venetoclax resistance [Nechiporuk, 2019; DiNardo, 2020c]. In total, these data demonstrate that the addition of venetoclax to azacitidine has not provided a significant improvement for AML patients with TP53 mutation, and thus the investigation of novel agents in combination with azacitidine is warranted.

1.4 CD47 and CD40 Targeting in MDS/AML

CD47 is upregulated in hematopoietic stem cells and leukemia cells [Jaiswal, 2009]. Increased expression of CD47 is observed on CD34+CD38–CD90–Lin–leukemia stem cells compared to normal CD34+CD38–CD90+Lin– hematopoietic stem cell counterparts. The expression of CD47 increases from low- to high-risk MDS and to AML and may represent a key event in the transformation from preleukemic to leukemic state [Pang, 2013]. In AML, high CD47 expression at diagnosis is associated with a significantly worse event-free and OS [Majeti, 2009].

Immune evasion is a barrier to effective immunotherapy in AML. Acute myeloid leukemia activates immune regulatory mechanisms to avoid immune mediated elimination. These mechanisms include the expression of checkpoint ligands, such as CD47, programmed cell death ligand-1 (PD-L1), and galectin 9 (Gal-9), poliovirus receptor and poliovirus receptor-related 2 (PVR/PVRL2), T cell immunoreceptor with Ig and ITIM domains (TIGIT) on AML cells, and expansion of regulatory T cells and myeloid-derived suppressor cells [Vadakekolathu, 2017; Lamble, 2020; Vadakekolathu, 2020]. Immune-infiltrated and immune-depleted profiles in the Immune landscape of AML may also predict chemotherapy resistance and immunotherapy response [Vadakekolathu, 2020]. Additionally, TP53 mutated AML correlates with an immune-infiltrated tumor microenvironment and high levels of actionable immune checkpoints [Sallman, 2020b; Vadakekolathu, 2020].

A number of leukemia-associated antigens have been identified in AML. These antigens, however, are typically expressed in other tissues including the thymus. T cells capable of recognizing these antigens are most likely deleted via mechanisms of central tolerance thus leaving behind low-affinity T cells which elicit an ineffective immune response. AML also has a low mutational burden thus resulting in a paucity of neoantigens for presentation to T cells [Beyar-Katz, 2018].

In an AML animal model, leukemia specific CD8 T cells undergo abortive proliferation, leaving a small number of partially dysfunctional antigen-specific T cells [Zhang, 2013]. Deletional T cell tolerance in AML-bearing hosts appears to be regulated by host APCs especially CD8α DCs as it can be reversed *in vivo* following the administration of agonistic anti-CD40 antibody (Ab), which results in enhanced anti-leukemia T cell immunity and prolonged survival [Kline, 2013]. This body of data suggest that activation of innate immunity by enhancing phagocytosis of AML cells and inducing antigen presentation to CD8 T cells could overcome tolerance and promote clinically meaningful immunity against AML.

Chemotherapeutic agents such as azacitidine, venetoclax, and anthracyclines, used in the treatment of AML and MDS, are known to induce endoplasmic reticulum stress and promote translocation of the chaperone protein, calreticulin, to the surface of cancer cells. Calreticulin stimulates phagocytosis by macrophages and DCs via their expression of CD91 (low-density lipoprotein-receptor related protein). Calreticulin expression has also been observed on viable malignant cells–including leukemia blasts. Induction of calreticulin alone is not sufficient for stimulating macrophage phagocytosis. Calreticulin-mediated phagocytosis of cancer cells can be inhibited by increased expression of CD47, a mechanism co-opted by leukemic cells to promote survival through evasion of phagocytosis [Chao, 2010]. Additionally, it has been shown that AML cells engineered to express high-levels of calreticulin promoted enhanced anti-leukemia T cell responses and prolonged survival in mice, an effect that did not occur in Rag2-/- mice, or following *in vivo* T cell depletion [Chen, 2017]. This demonstrates the dependence on adaptive immunity.

CD47 over-expression on leukemia cells is targetable through receptor blockade. Limited clinical response was reported in patients with AML receiving magrolimab (Hu5F9-G4), a CD47 targeting antibody as monotherapy [Vyas, 2018; Sallman, 2019b]. In contrast, promising clinical activity has recently been reported in patients with MDS and AML receiving magrolimab in combination with azacitidine. Objective responses were reported in 91% (in 31/33 patients: 42% (complete remission [CR], 24% marrow CR, 3% partial remission [PR], 21% hematologic improvement (HI) alone, 9% stable disease [SD]) of untreated patients with MDS [Sallman, 2019b]. Similarly, in treatment-naïve AML patients unfit for intensive chemotherapy, objective responses were reported in 63% (27/43) of the patients, including 42% CR, 12% marrow CR, 2% PR, and 7% morphologic leukemia-free state (MLFS) [Sallman, 2020a]. Common treatment-related adverse events (AEs) included anemia (38%), fatigue (21%), neutropenia (19%), thrombocytopenia (18%) and infusion reactions (16%). In transfusion-dependent patients, 58% of MDS and 64% of AML patients became transfusion-independent.

Dysregulation of the apoptotic pathway has been well described in AML, including overexpression of BCL-2, which is an important anti-apoptotic protein. This has supported the development of BCL-2 inhibitors to promote the induction of apoptosis in AML cells, as evidenced in a Phase 3 study of venetoclax administered with azacitidine in treatment-naïve AML patients [DiNardo, 2020b]. Composite CR was achieved in 66.4% of treatment-naïve AML patients receiving venetoclax and azacitidine compared to 28.3% of those receiving azacitidine monotherapy. An improvement in median OS was also reported (14.7 months for the venetoclax-azacitidine group compared to 9.6 months in the azacitidine control group). Venetoclax is a potent and selective

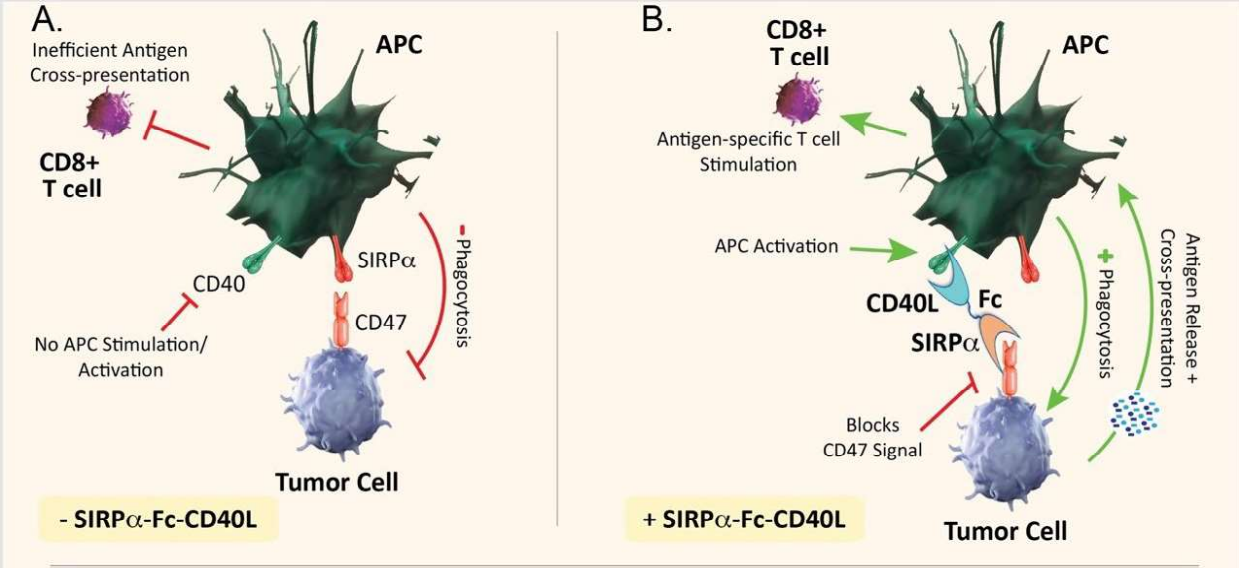
BCL-2 inhibitor that has been Food and Drug Administration (FDA) approved in combination with azacitidine for the treatment of newly diagnosed AML.

1.5 SL-172154

1.5.1 Mechanism of Action

The 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 MDS and AML. 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 has been observed compared to the separate administration of two individual antibodies against identical targets [de Silva, 2019]. As a result, Shattuck sought to develop a SIRPα-Fc-CD40L ARC™ fusion protein, SL-172154, 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 1A]. SIRPα-Fc-CD40L (SL-172154) can relieve this inhibitory signal through blockade of CD47 with the SIRPα domain of the ARC, while simultaneously providing an "eat me" signal via co-stimulation of CD40 by CD40L [Figure 1B]. This enhances tumor phagocytosis, APC activation, increased antigen processing/presentation, and induction of an antitumor antigen-specific CD8+ T cell response. Combination treatment of SIRPα-Fc-CD40L with checkpoint blocking agents increases CD40 target density which may stimulate a more potent and durable anti-tumor response.

Figure 1 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. Combinations with checkpoint blocking agents increase target density for the ARC and may stimulate a more potent and durable anti-tumor response.

1.5.2 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, 2019]. Detailed information is presented in the SL-172154 Investigator's Brochure (IB).

1.5.2.1 Pharmacology Studies

1.5.2.1.1 *In Vitro* Pharmacology

In vitro, SL-172154 was shown to bind to its cognate targets, CD47 and CD40, both individually and simultaneously. High binding affinity for CD47 and CD40 was noted as well as a slow off rate (K_D values of 0.628 nM and 4.74 nM, respectively), indicating a longer on target resident time. This longer resident time could be of benefit in the tumor microenvironment where CD47 is known to be expressed. CD40-mediated activity by SL-172154 was demonstrated in a NFκB 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 antibody-dependent cell-mediated cytotoxicity (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 SL-172154 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 and blocking Fc-γ receptors in this assay abrogated the phagocytosis induced by rituximab in combination with SL-172154.

The combination of SL-172154 with the hypomethylating agent, azacitidine, enhanced phagocytosis of AML and chronic myeloid leukemia (CML) tumor cell lines (Kasumi-3 and K562, respectively). A similar effect was observed with the combination of SL-172154 with the BCL-2-inhibitor, venetoclax. Upregulation of CD47, the target for SIRPα, and induction of the prophagocytic protein, calreticulin, was observed with azacitidine.

1.5.2.1.2 *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, 2019]. Furthermore, CD40 stimulation had a more prolonged effect on the same DC populations.

In the murine CT26 colorectal tumor xenograft model, mSIRPα-Fc CD40L given via intraperitoneal administration enhanced tumor control and rejection of both primary and rechallenge tumors, suggesting that a more robust memory response was generated, in comparison to murine anti CD47, murine anti CD40, or combination antibody therapy. Additionally, in two mouse CD20+ hematological tumor models (WEHI3 and A20), intraperitoneal administration of mSIRPα-Fc-CD40L in combination with murine anti-CD20 led to decreased tumor volumes in comparison to treatment with either mSIRPα-Fc-CD40L or anti-CD20 monotherapy. This effect on tumor growth inhibition could be abrogated by blocking the type I interferon response.

1.5.2.2 Toxicology Studies in Non-Human Primates

In two repeat dose toxicology studies, cynomolgus monkeys received SL-172154 at 0 (vehicle), 0.1, 1, 10, or 40 mg/kg by intravenous infusion (30 or 60 minutes) once weekly for up to 5 weeks. 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 intravenous 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 magrolimab [Sikic, 2019].

The principal SL-172154-related toxicity finding in the GLP toxicology study was the occurrence of dose-dependent infusion-related reactions 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 infusion-related reactions (IRRs) were coincident with the emergence of anti-drug antibody (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.

1.5.2.3 Toxicokinetic Studies

In two studies in cynomolgus monkeys, systemic exposure, as evaluated by maximum observed concentration (Cmax) and area under the serum concentration-time curve (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 hour 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 intravenous 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.

For further information, please refer to the SL-172154 IB.

1.6 Summary of Clinical Data

A brief summary of the clinical data is provided for SL-172154. Detailed information is presented in the current SL-172154 IB. As of 25 May 2023, SL-172154 has been administered IV to 79 subjects and intratumorally to 5 subjects with 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-seven subjects were enrolled into 7 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), 0.3 mg/kg (n=3, Schedule 2), 1.0 mg/kg (n=4, Schedule 2), 3.0 mg/kg (n=6, Schedule 2), 3.0 mg/kg (n=3, Schedule 1), and 10.0 mg/kg (n=5, Schedule 2). Subjects treated with IV SL-172154 at 3.0 mg/kg in Study SL03-OHD-101 cleared the 28-day dose-limiting toxicity (DLT) evaluation period with no DLTs. The maximum administered dose (MAD) level of SL-172154 evaluated in Study SL03-OHD-101 was 10.0 mg/kg given once weekly. One DLT (Grade 3 ALT increased) was reported in the 10.0 mg/kg cohort. A maximum tolerated dose (MTD) was not reached.

All subjects (100%) reported AEs with the most frequently (>20% of subjects) reported AEs being IRR (18 subjects, 67%), fatigue (12 subjects, 44%), nausea (9 subjects, 33%), constipation (6 subjects, 22%), and diarrhea (6 subjects, 22%). AEs considered related to SL-172154 per Investigator assessment were reported in 24 subjects (89%), with the most common (>15% of subjects) being IRR (18 subjects, 67%), fatigue (9 subjects, 33%), and nausea (6 subjects, 22%).

The most common Grade 3 or 4 TEAE (>5%) were AST increased, embolism, hypertension, IRR, lymphopenia and sepsis. Drug-related Grade 3 or 4 TEAEs were AST increased (n=2), lymphopenia (n=2), neutropenia, thrombocytopenia, back pain, muscular weakness, anemia, ALT increased and IRR each in one subject. Treatment-related Grade 3 ALT/AST elevations were reported in one subject treated at 10.0 mg/kg. The ALT/AST elevations normalized with withholding of treatment.

Six subjects (22%) reported serious TEAEs (embolism n=2, sepsis n=2, large intestine infection n=1, lower gastrointestinal hemorrhage n=1, small intestinal obstruction n=1); all were Grade 3, and none were considered drug-related.

No Grade 5 AEs have been reported and no AEs led to permanent discontinuation of SL-172154.

PK data for 27 subjects in Study SL03-OHD-101 (overall intravenous dose range, 0.1 to 10.0 mg/kg) were estimated using noncompartmental analysis. Following a single and multiple IV infusions of 0.1 to 10 mg/kg SL-172154, mean serum SL-172154 Cmax was reached at the end of infusion and ranged from 118 ng/mL to 115536 ng/mL. Serum SL-172154 concentrations showed multi-phasic decline and were quickly cleared with a half-life generally below 1.3 hour for all dose levels. In general, the increase in serum SL-172154 Cmax and AUC_{last} values with dose was greater than dose-proportional, a finding that is consistent with target-mediated drug disposition. There was a >500-fold increase for Cmax and AUC for a 100-fold increase in dose across the entire dose range (0.1 to 10 mg/kg). No accumulation of SL-172154 after multiple doses was observed (accumulation ratio, <1.56).

In the current study, as of May 25, 2023, 37 subjects with higher-risk MDS or AML received SL-172154 either as monotherapy (19 subjects; doses of 1, 3, or 6 mg/kg) or in combination with AZA (18 subjects; doses of 1, 3, or 6 mg/kg). Sixteen subjects (84.2%) in the monotherapy cohorts and 12 subjects (66.7%) in the SL-172154 + AZA cohorts had at least one SL-172154-related TEAE. Thirteen subjects (68.4%) in monotherapy cohorts and 8 subjects (44.4%) in SL-172154 + AZA cohorts experienced an IRR. One subject that received 6.0 mg/kg SL-172154 + AZA experienced a DLT of Gr 3 IRR. Based on the SMC's recommendation further enrollment into 6 mg/kg + AZA was stopped. SMC reviewed all the available safety data and selected 3 mg/kg SL-172154 as the dose for expansion cohorts. Enrollment is currently ongoing in the dose expansion cohorts.

SL-172154 is also being investigated in combination with either pegylated liposomal doxorubicin or mirvetuximab soravtansine in an ongoing Phase 1b Study in ovarian cancer. As of 25 May 2023, 15 subjects have been enrolled onto this study.

In summary, SL-172154 has demonstrated an AE profile that has been manageable and acceptable in the context of benefit-risk. No clinically significant findings were identified.

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. Transient decreases in hemoglobin (without evidence of hemolysis), platelets and lymphocytes has been observed following infusion of SL-172154. Overall, the

benefit-risk profile of SL-172154 supports the continued investigation of SL-172154 in subjects with advanced cancer.

1.7 Study Rationale

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 (see SL-172154 IB). In clinical trials, CD47-targeted agents have limited monotherapy activity, whereas combination with agents such as azacitidine or venetoclax that induce prophagocytic signals (e.g., calreticulin) in leukemic blasts have resulted in improved response rates [Vyas, 2018; Sallman, 2019a].

SL03-OHD-104 is designed as a Phase 1a/1b open-label trial to evaluate the safety, PK, PD, and preliminary efficacy of SL-172154 monotherapy as well as in combination with azacitidine or in combination with azacitidine and venetoclax. Azacitidine and venetoclax are commonly used in clinical practice in these patient populations, with well-described safety and PK profiles for the individual agents and the combination. This is the first clinical trial to investigate the combination of these agents with SL-172154. Each component is anticipated to have activity on distinct targets, and these agents combined with SL-172154 have the potential to further bridge innate and adaptive immunity, thus potentially improving treatment outcomes without increasing toxicity. No overlapping toxicities, other than fatigue, are anticipated with SL-172154. Hematologic toxicities (e.g., hemolysis, interference with crossmatch) have not been observed with SL-172154 in ongoing clinical trials.

Study SL03-OHD-104 will initially enroll approximately 5 subjects with relapsed or refractory disease (MDS or AML) to SL-172154 monotherapy dose escalation cohort at the starting dose of 1.0 mg/kg SL-172154. Subjects will be enrolled into sequential dose levels of SL-172154 and assessed for DLT during the first 28 days. This will inform the safety, tolerability, PK, PD, and preliminary anti-tumor activity profile of SL-172154 monotherapy by dose level.

While clinical response is possible with SL-172154 monotherapy, limited clinical responses have been observed with other investigational agents targeting CD47 and CD40 administered as monotherapy [Vonderheide, 2007; Vyas, 2018; Sallman, 2019a; Sikic, 2019]. The mechanism of action of SL-172154 suggests that combination therapy is likely to provide greater benefit. In addition, subjects with higher-risk MDS or AML often have rapidly progressing disease.

When the SL-172154 monotherapy cohort completes the DLT evaluation period in Dose Level 2 (3.0 mg/kg), enrollment may begin in parallel to the dose escalation cohorts investigating SL-172154 (starting dose 1.0 mg/kg) administered with azacitidine to maximize the potential for clinical benefit to participating subjects. Once the selected dose of SL-172154 administered with azacitidine is identified in dose escalation, enrollment of treatment-naïve subjects with AML to a safety run-in cohort (n=8) of SL-172154 administered with azacitidine and venetoclax will commence using the same SL-172154 dose.

The 3 mg/kg dose of SL-172154 was selected for the SL-172154 and azacitidine combination regimen and dose expansion cohorts are enrolling additional subjects to further evaluate the safety and efficacy of the combination regimen. In the dose expansion part of the study, approximately 20 treatment naïve subjects with higher-risk MDS will be enrolled to receive SL-172154 at the selected dose with azacitidine (Part A). In addition, approximately 20 treatment naïve AML subjects with at least one known TP53 gene mutation or deletion will be enrolled to receive SL-172154 at the selected dose with azacitidine (Part C). Once the SL-172154 dose in combination with azacitidine and venetoclax is confirmed during the safety run-in, approximately 20 treatment naïve subjects with AML (including safety run-in cohort and dose expansion) will be enrolled to receive SL-172154 with azacitidine and venetoclax (Part B).

Safety and efficacy will be further explored in Part D (with randomized control arm of azacitidine monotherapy). Approximately 60 treatment naïve subjects with higher-risk MDS will be randomized to three arms (approximately 20 subjects per arm). The three arms consist of two experimental arms at two dose levels of SL-172154 (1.0 mg/kg and 3.0 mg/kg) in combination with azacitidine, and one control arm for azacitidine monotherapy. The three arms will be stratified based on TP53 mutation status (TP53m vs TP53wt) and bone marrow blasts at baseline (<5% vs ≥5%). This will further evaluate the safety, and efficacy of different doses of SL-172154, and help determine the contribution of SL-172154 to the anti-leukemic activity in the azacitidine plus SL-172154 treatment.

SL-172154 will be administered on a weekly schedule for the first two cycles of treatment and biweekly during the third cycle and beyond. Although the optimal SL-172154 dosing schedule has not been established, less frequent dosing in later cycles is a reasonable approach to avoid frequent CD40 stimulation that may lead to chronic activation of APC and exhaustion of T cells [Rüter, 2010]. It is anticipated that the disease burden would be substantially reduced during the first two cycles (first 2 months of therapy) of treatment when SL-172154 is combined with azacitidine or azacitidine and venetoclax [DiNardo, 2020a]. Thus, when SL-172154 is combined with either regimen, biweekly dosing beyond this time frame could facilitate a continued anti-tumor immune response.

1.8 Potential Risks and Benefits

1.8.1 Potential Risks

Potential risks to participants 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 administered intravenously as a monotherapy was assessed in the Phase 1 first-in-human clinical trial, SL03-OHD-101, in subjects with relapsed, refractory ovarian cancer. Although the risks and potential benefits of SL-172154 have not been previously assessed in AML or MDS in other studies, the safety results from SL03-OHD-101 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) non-human primate (NHP) toxicology data; and (3) safety data from the SL03-OHD-101 study.

Adverse events reported with other CD47-SIRPα targeting agents and CD40 agonists: Anti-CD47 monoclonal antibodies (mAbs) and SIRPα-Fc fusion proteins have been evaluated in patients with hematologic malignancies and solid tumors. Adverse events 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 mAbs was transient infusion-related CRS characterized by fevers, rigors, chills, and other symptoms such as headache and back pain. 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 CD40 antibodies but remain a potential concern [Vonderheide, 2001; Vonderheide, 2007; Vonderheide, 2013a; Vonderheide, 2013b; Nowak, 2015; Sanborn, 2019].

Toxicities observed with SL-172154 in nonclinical toxicology studies in NHP: The underlying etiology of the SL-172154-related effects in NHP is most likely due to a combination of both the pharmacologic activity of the molecule and to immunologic reactions to SL-172154 administration. The following are potential contributory factors to the dose-dependent IRRs observed in NHP 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) post-dose changes in peripheral blood lymphocyte counts. The 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. 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 azacitidine and venetoclax: The combination of SL-172154 and azacitidine or SL-172154 with azacitidine and venetoclax has not previously been studied in humans. The AE profile reported for azacitidine or azacitidine and venetoclax in patients with AML has been reported in a Phase 3 study [DiNardo, 2020b]. Hematologic AEs reported in ≥ 20% of patients with AML receiving azacitidine or azacitidine with venetoclax included thrombocytopenia, neutropenia, febrile neutropenia, anemia, and leukopenia while non- hematological toxicities reported in ≥ 20% of patients included infections, nausea, constipation, diarrhea, vomiting, hypokalemia, pyrexia. The incidence of neutropenia and febrile neutropenia was higher with the combination of azacitidine and venetoclax in comparison to azacitidine alone. In addition, fatigue, peripheral edema, and decreased appetite occurred in ≥20% patients treated with azacitidine and venetoclax while these same AEs were reported in <20% of patients in the azacitidine alone arm. Fatigue has been reported following administration with CD47-SIRPα targeting agents as well as with CD40 agonist mAbs. In addition, fatigue is a frequently reported treatment-related AE (Investigator attribution) associated with intravenous SL-172154 monotherapy in the SL03-OHD-101 study (Section 1.6). Anemia without evidence of hemolysis, and transient decreases in lymphocyte and platelet counts have been observed with SL-172154. These hematologic effects are not a consequence of myelosuppression. The expression of CD40 on platelets and B cells may explain the hematologic effects observed with CD40 agonists.

Inwald et al. showed that the binding of sCD40L to CD40 induces P-selectin expression and partially activates $\alpha_{IIb}\beta_3$ without inducing platelet aggregation [Inwald, 2003]. We and others have shown that ligation of CD40 receptor on B cells by CD40 agonists lead to transient egress of B cells from the circulation [Vonderheide, 2007; Lakhani, 2021]. It is not expected that SL-172154 would exacerbate the myelosuppression commonly observed with azacitidine alone or in combination with venetoclax.

Potential risks of SL-172154 administration in SL03-OHD-104 study:

The potential risks noted below are based on observations in the SL-172154 NHP studies, the Phase 1 clinical studies, or select toxicities reported with other CD47 or CD40-targeted agents.

1) IRRs and CRS: In Study SL03-OHD-101, 45 treatment-related events of IRR were reported in 18 subjects. Thirteen subjects (48.1%) had IRRs that led to infusion interruption. IRRs did not lead to study drug withdrawal in any subject. The median number of IRR events in subjects experiencing an IRR was 2, with a range of 1 to 9. All SL-172154-related IRRs 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 IRRs resolved with no sequelae. Collectively, the frequency of subjects experiencing IRR events and the frequency of IRR events increased with increasing dose. Symptomatic manifestations of the IRR events variably include fever, chills, rigors, back pain and rash. Most of the IRRs were reported to be relatively short in duration and occurred near the end of the infusion or immediately post-infusion. All of the IRR events were readily managed with temporary interruption of the infusion and/or treatment medications; several subjects received premedications (such as diphenhydramine, famotidine, and acetaminophen) prior to their next dose. In the current Study, Thirteen of the 19 subjects (68.4%) who received monotherapy had 32 IRR events. The median number of IRR events was 3 with a range of 1 to 5. All IRR events were Grade 1 or 2, except for 1 subject each dosed with 3 mg/kg and 6 mg/kg who had Grade 3 events. All IRR events resolved with no sequelae. Most IRR events (68.8%) started during the SL-172154 infusion or less than 2 hours post-end-of-infusion (25.0%). Eight of the 18 subjects (44%) who received SL-172154 + AZA had 19 IRR events. The median number of IRR events was 1 with a range of 1 to 8. All IRR events were Grade 1 or 2, except for 1 subject dosed with 6 mg/kg who had Grade 3 events. One Grade 3 IRR (6 mg/kg SL-172154 + AZA) was deemed serious. All IRR events resolved with no sequelae. All IRR events started during the SL-172154 infusion.
2) No CRS has been observed in the SL03-OHD-101 study and one Gr 1 CRS has been reported in the current Study in a subject with AML in the setting of sepsis. 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, management guidelines (e.g., SL-172154 infusion adjustments/interruptions, rescue treatments), and extended monitoring when indicated. Recommendations to identify and manage infusion-related IRRs and CRS are outlined in the Toxicity Management Guidelines section of the protocol (Section 3.8).
3) 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-104 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 will be characterized. A guideline for monitoring and management of IRR including hypersensitivity reactions (HSRs) is included in Section 3.8.1.

4) 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). Treatment-related Grade 3 or 4 anemia (n=1), thrombocytopenia (n=1), neutropenia (n=1) and lymphopenia (n=2) were reported in SL03-OHD-101. In study SL03-OHD-104, complete blood counts will be assessed frequently on treatment to monitor for hematologic toxicity. Supportive therapy (growth factors, prophylactic antibiotics, and active treatment for infections) will be provided according to standard medical practice; dose modification for hematologic toxicity will follow recommendations provided in the protocol and product information for approved agents. To date, hemolysis has not been observed in SL03-OHD-101; the absence of hemolysis is likely due to the inactive Fc domain of SL-172154 [Chow, 2019]. To investigate the possible risk of interference with pre-transfusion 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 crossmatch resolution has been observed in subjects treated to date in SL03-OHD-101.
5) 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 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 alone or in combination with azacitidine or venetoclax.

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 administered to patients with cancer; (3) patients treated at each SL-172154 dose level would be followed for the duration of the DLT assessment period before escalating to the next higher dose level of SL-172154; (4) administration of SL-172154 in an oncology treatment center/hospital allows for close monitoring of subjects for AEs and for timely action; (5) guidelines for management of AEs based on established guidelines [Lee, 2014; Haanen, 2017; Puzanov, 2017; Rosello, 2017; Brahmer, 2018; Porter, 2018] are provided in the protocol; and (6) a Safety Monitoring Committee (SMC) will meet at least monthly during dose escalation and every 2 months during dose expansion to review emerging toxicities and assess the impact of these toxicities on study conduct.

1.8.2 Potential Benefits

The clinical benefits of SL-172154 in subjects with MDS and AML are unknown as no other 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

leukemias, lymphomas, myeloma, and intermediate and high-risk myelodysplasia. Encouraging preliminary anti-tumor activity has been observed in patients with hematologic malignancies receiving CD47 blockade alone as well as in combination with agents that provide additional 'eat me' signals (rituximab, azacitidine). Several anti-CD47 agents are in development including magrolimab, ALX-148, and TTI-662 of which the most advanced anti-CD47 development program is for magrolimab [Advani, 2018; Sallman, 2019a; Sallman, 2020a].

As a monotherapy, magrolimab has shown relatively low response rates: 10% in relapsed/refractory AML/MDS patients. In contrast, magrolimab in combination with azacitidine has demonstrated efficacy in MDS and AML, with a CR rate of 50% in previously untreated patients with MDS (n = 24), and 42% in previously untreated patients with AML (n = 43) [Sallman, 2019a; Sallman, 2020a]. The combination appears to compare favorably with historical data from azacitidine monotherapy [Fenaux, 2009] [DiNardo, 2020b]. Additionally, efficacy has been reported in patients with relapse and refractory non-Hodgkin's lymphoma (NHL) treated with either magrolimab [Advani, 2018] or ALX-148 (evorpacept) in combination with rituximab [Kim, 2020]. Clinical responses have also been reported in patients with relapse and refractory NHL treated with TTI-622 monotherapy [Patel, 2020]. Several different CD40 agonistic antibodies have been studied in early phase trials [Beatty, 2017]. Responses (1 CR and 5 PR among n=50 subjects) in diffuse large B cell lymphoma have been reported with a monotherapy CD40 agonist, dacetuzumab [Advani, 2009].

The mechanism of action of SL-172154 is designed to pair the costimulatory role of CD40L in augmenting the antigen cross-presenting ability of DCs with the increased phagocytic activity of macrophages through CD47-SIRPα binding. Importantly, because the ECDs of SIRPα and CD40L are physically linked to one another and localized to the TME, APCs and tumor cells receive these signals in a spatiotemporally coordinated manner, potentially leading to a more potent and durable anti-tumor response. The investigation of SL-172154 in AML and MDS is supported by the following factors: (1) mechanism of action of SL-172154 and potentiation of phagocytosis of leukemic cells *in vitro* by SL-172154 in combination with azacitidine or venetoclax; (2) reported clinical efficacy with magrolimab, a CD47-targeted antibody in combination with azacitidine, and (3) favorable adverse event profile of SL-172154 with no apparent overlapping toxicities, other than fatigue, with either of the combination agents. The possible benefits of the combination regimens proposed in this trial outweigh the potential risks for the patient population proposed for enrollment in SL03-OHD-104.

2. STUDY OBJECTIVES AND OUTCOME MEASURES

Primary Objectives	Outcome Measures
To evaluate the safety and tolerability of SL-172154 administered alone or with azacitidine OR azacitidine + venetoclax in subjects with higher-risk MDS or AML	• 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 safety laboratory values per NCI-CTCAE, version 5.0

	• AEs leading to treatment discontinuation, AEs leading to dose reduction of SL-172154 • Maximum tolerated dose (MTD) of SL-172154 in monotherapy and each combination regimen based on the rate of DLTs, or the Maximum Administered Dose (MAD; the highest dose administered).
To select the recommended Phase 2 dose (RP2D) for SL-172154 administered with azacitidine OR azacitidine + venetoclax in subjects with higher-risk MDS or AML	• Number and occurrence of DLTs as defined in the protocol • Available pharmacokinetic (PK) parameters • Available pharmacodynamic (PD) effects • Safety • Anti-tumor efficacy
Part D: • To evaluate safety and anti-tumor activity of SL-172154 at 1.0 mg/kg and 3.0 mg/kg administered with azacitidine vs azacitidine monotherapy in higher-risk MDS subjects • To evaluate safety and anti-tumor activity of SL-172154 at 1.0 mg/kg vs 3.0 mg/kg administered with azacitidine in higher-risk MDS subjects	• Safety endpoints as listed above • Complete remission (CR) based on Investigator assessed disease response according to International Working Group (IWG) 2006 criteria
Secondary Objectives	**Outcome Measures**
To assess preliminary evidence of anti-tumor efficacy of SL-172154 administered alone or with azacitidine OR azacitidine + venetoclax in subjects with higher-risk MDS or AML Part D: To assess preliminary evidence of anti-tumor efficacy of SL-172154 administered with azacitidine compared to azacitidine monotherapy in subjects with higher-risk MDS	• Investigator assessed disease response according to International Working Group (IWG) 2006 criteria (MDS) [Cheson, 2006] or European Leukemia Net (ELN) 2017 criteria (AML) [Dohner, 2017] ○ Complete remission (CR) ○ Objective response rate (ORR) defined as CR, partial remission (PR), marrow CR, or hematologic improvement (HI) for MDS, or CR, CR with incomplete hematologic improvement (CRi), PR, or MLFS for AML ○ Composite CR rate (CR and CRi) for AML ○ CR/CR with partial hematological recovery (CRh) for AML • Time to response • Duration of response (DOR) • Progression free survival (PFS) • Event free survival (EFS)

	• Overall Survival (OS) • Minimal residual disease (MRD)-negative response rate • Proportion of subjects with MDS with hematologic improvement
To evaluate immunogenicity to SL-172154 during and after treatment of SL-172154 administered alone or with azacitidine OR azacitidine + venetoclax in subjects with higher-risk MDS or AML	• Number/proportion of subjects with positive or negative anti-drug antibody (ADA) titer • ADA duration • Transient vs. persistent ADA
To assess the pharmacokinetic profile of SL-172154 when administered alone or with azacitidine OR azacitidine + venetoclax in subjects with higher-risk MDS or AML	• Maximum observed concentration (Cmax), time at which the maximum concentration is observed (Tmax), and minimum observed concentration (Cmin) following single and multiple doses of SL-172154 • Area under the serum concentration-time curve (AUC) • Terminal elimination half-life ($t_{1/2}$), Clearance (CL) and Volume of Distribution (Vz), as data permit
Exploratory Objectives	**Outcome Measures**
To assess the rate and duration of RBC and platelet transfusion independence in subjects with higher-risk MDS or AML receiving SL-172154 alone or with azacitidine OR azacitidine + venetoclax Part D: To assess the rate and duration of RBC and platelet transfusion independence in subjects with higher-risk MDS administered SL-172154 with azacitidine compared to azacitidine monotherapy	• Proportion of participants who have a 56-day or longer period with no RBC transfusions • Duration of RBC transfusion independence • Proportion of participants who have a 56-day or longer period with no platelet transfusions • Duration of platelet transfusion independence
To assess MRD in subjects with higher-risk MDS or AML receiving SL-172154 alone or with azacitidine OR azacitidine + venetoclax Part D: To assess MRD in subjects with higher-risk MDS administered SL-172154 with azacitidine compared to azacitidine monotherapy	• MRD assessed in bone marrow aspirate by next-generation sequencing (NGS) and/or flow cytometry
To assess pharmacodynamic biomarkers in peripheral blood and bone marrow	Pharmacodynamic biomarkers in peripheral blood and bone marrow aspirate may include:

aspirate prior to, on-treatment and following treatment with SL-172154 administered alone or with azacitidine OR azacitidine + venetoclax in subjects with higher-risk MDS or AML	• Changes in T cells subsets, B cells, macrophages and DCs • Evidence of SL-172154 localization (CD47 or CD40 receptor occupancy) on hematopoietic cells and/or leukemic cells in the bone marrow and peripheral blood

3. DESCRIPTION OF STUDY DESIGN

SL03-OHD-104 is an open label, multicenter, Phase 1a/1b trial in subjects with higher-risk (i.e., intermediate, high or very high risk by IPSS-R) MDS or AML as depicted in the Study Schema. The study is designed to evaluate the safety, PK, PD effects, and preliminary anti-tumor activity of SL-172154 monotherapy and SL-172154 administered with either azacitidine or azacitidine and venetoclax. Throughout the treatment period (monotherapy as well as combination regimens) for all subjects, an ongoing review of available safety data will be undertaken by a SMC as described in Section 7.8. Subjects will receive SL-172154 as monotherapy or administered with azacitidine with or without venetoclax 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 3.14.

The starting intravenous infusion dose of 1.0 mg/kg in Study SL03-OHD-104 is supported by safety data in the first-in-human, dose escalation Study SL03-OHD-101 in which SL-172154 was administered once weekly to 4 subjects at 1.0 mg/kg, 8 subjects at 3.0 mg/kg, and 5 subjects at 10.0 mg/kg. One DLT was reported at the MAD of 10.0 mg/kg (Section 1.6). Further information on the safety profile of SL-172154 is provided in the SL-172154 IB. Based on safety data obtained to date, a SL-172154 dose of 1.0 mg/kg was chosen as the initial dose level for evaluation in subjects with higher-risk MDS or AML in Study SL03-OHD-104.

In Study SL03-OHD-104, SL-172154 will be administered once weekly during Cycles 1 and 2 and biweekly during Cycle 3 and thereafter, in 28-day cycles; the first 28-day cycle will be the DLT evaluation period for each subject (Section 3.6). For all subjects in all cohorts, prophylactic premedication for IRR with dexamethasone, an antipyretic and antihistamines should be administered at least 30 minutes prior to each SL-172154 administration. For the dose and schedule of prophylactic premedications, please see Sections 3.7.3 and 3.7.4. Treatment will be administered in 28-day cycles until at least one of the study treatment discontinuation criteria is met.

The study will initially enroll sequential cohorts of approximately 5 subjects with relapsed or refractory disease (AML or higher-risk MDS) to the SL-172154 monotherapy dose escalation cohort. The planned dose escalation and duration of infusion for SL-172154 are outlined in Table 1; the starting SL-172154 monotherapy dose is 1.0 mg/kg.

When the SL-172154 monotherapy cohort completes the DLT evaluation period in Dose Level 2 (3.0 mg/kg), enrollment into the SL-172154 dose escalation in combination with azacitidine cohort may initiate in parallel (SL-172154 starting dose, 1.0 mg/kg). Sequential cohorts of approximately 5 subjects with relapsed/refractory AML or higher-risk MDS will be enrolled; the planned dose escalation and duration of infusion for SL-172154 are outlined in Table 2. Additionally, previously

untreated subjects with AML and known adverse cytogenetics (e.g., ELN adverse risk group) as well as previously untreated subjects with MDS with at least one TP53 gene mutation/deletion may be considered for enrollment into this cohort. Azacitidine (IV or SQ) will be administered at the standard dose and schedule. Dose escalation of SL-172154 administered with azacitidine will continue until a safe dose of SL-172154 is identified for the combination.

Once the selected dose of SL-172154 administered with azacitidine is identified in dose escalation, enrollment into a safety run-in cohort (n=8) of SL-172154 administered with azacitidine and venetoclax will commence using the same SL-172154 dose and duration of infusion. Treatment-naïve subjects with AML will be enrolled.

The following cohorts will utilize the modified toxicity probability interval (mTPI-2) design [Guo, 2017] with a target DLT rate of 20% for the MTD:

- SL-172154 monotherapy dose escalation
- SL-172154 and azacitidine dose escalation cohort
- SL-172154, azacitidine and venetoclax safety run-in cohort

The dose escalation decision rules based on mTPI-2 model are outlined in Section 9.1.1. In selecting the dose of SL-172154 for the combination regimen(s) to be evaluated in the dose expansion cohorts, 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 a selected dose for the SL-172154 and azacitidine combination regimen, a dose expansion cohort will enroll additional subjects to further evaluate the safety and efficacy of the combination regimen. In the dose expansion part of the study, approximately 20 treatment naïve subjects with higher-risk MDS will be enrolled to receive SL-172154 at the selected dose with azacitidine (Part A) and will include subjects with wild-type TP53 and TP53 gene mutation/deletion. Clinical outcomes are shown to be distinct between these patient populations [Daver, 2022]. In addition, approximately 20 treatment naïve AML subjects with a known TP53 gene mutation/deletion will be enrolled to receive SL-172154 at the selected dose with azacitidine (Part C).

Once the SL-172154 dose in combination with azacitidine and venetoclax is confirmed during the safety run-in, approximately 12 additional treatment-naïve subjects with AML will be enrolled into dose expansion (Part B) to have approximately 20 subjects receive SL-172154 with azacitidine and venetoclax.

3.1 Dose Escalation Cohorts

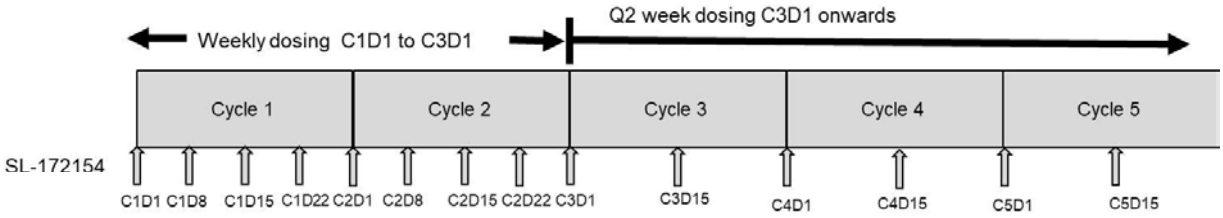
During dose escalation (monotherapy or combination regimen), the following guideline should be followed if an event of CRS occurs on Cycle 1 Day 8 or later:

Grade 2 CRS: SL-172154 dose should not be escalated by more than 50% between subsequent dose levels

Grade 3 CRS: SL-172154 dose should not be escalated by more than 25% between subsequent dose levels

3.1.1 SL-172154 Monotherapy Dose Escalation

Figure 2 SL-172154 Monotherapy



Subjects with AML or higher-risk MDS being treated in the relapsed/refractory setting will be enrolled in this cohort. SL-172154 (Dose Level 1, 1.0 mg/kg) will be administered once weekly by IV infusion on Days 1, 8, 15, and 22 during Cycles 1 and 2, and biweekly on Days 1 and 15 during Cycle 3 and thereafter (Figure 2). One cycle consists of 28 days. Premedication as prophylaxis for IRR with an antipyretic and antihistamines should be administered at least 30 minutes prior to each SL-172154 administration, as described in Section 3.7.3. Subjects will be enrolled in cohorts of approximately 5 subjects into sequential dose levels of SL-172154 and assessed for DLTs during the first cycle (28 days) of treatment. DLT criteria are defined in Section 3.6. The planned dose escalation and duration of infusion of SL-172154 is outlined in Table 1. At each dose level, a minimum 3-day stagger between dosing the first and second subject is required. Treatment will be administered in 28-day cycles until at least one of the study treatment discontinuation criteria is met (Section 3.14). Subjects will be followed according to the Schedule of Assessments in Section 6.1.

When the SL-172154 monotherapy cohort completes the DLT evaluation period in Dose Level 2 (3.0 mg/kg), the SL-172154 dose escalation in combination with azacitidine cohort (starting SL-172154 dose, 1.0 mg/kg) will open and enroll subjects in parallel as outlined in Section 3.2.1.

Table 1 SL-172154 Monotherapy Dosing

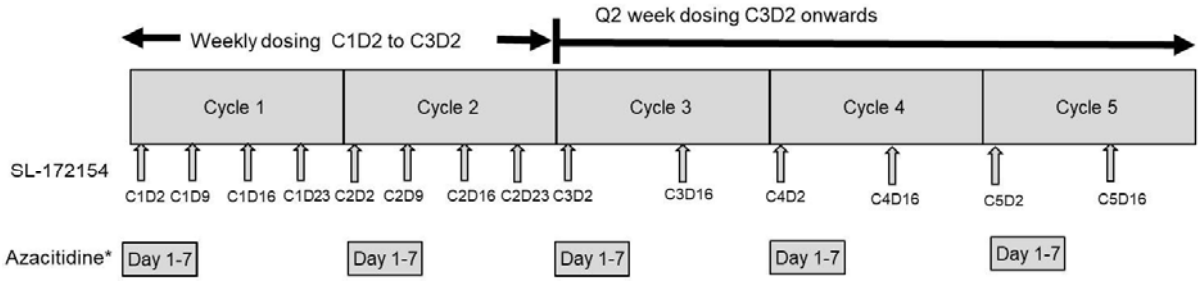
Dose Level (DL)	IV Dose of SL-172154[a,b]	Duration of Infusion
DL -1[c]	0.3 mg/kg	30 minutes (± 10 minutes)
DL 1 (starting dose)	1.0 mg/kg	60 minutes (± 10 minutes)
DL 2	3.0 mg/kg	180 minutes (± 15 minutes)
DL 3	6.0 mg/kg	180 minutes (± 15 minutes)
DL 4	10.0 mg/kg	180 minutes (± 15 minutes)

a. SL-172154 will be administered once weekly on Days 1, 8, 15, and 22 during Cycles 1 and 2 and biweekly on Days 1 and 15 during Cycle 3 and thereafter. One cycle consists of 28 days.
b. The actual body weight in kilograms (kg) will be used for 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. Dose level -1 at 0.3 mg/kg will be evaluated if 1.0 mg/kg is not safe per mTPI-2.

3.2 SL-172154 Dose Escalation in Combination Treatment Arms

3.2.1 SL-172154 Administered with Azacitidine

Figure 3 SL-172154 in Combination with Azacitidine



*5-2-2 schedule (i.e., azacitidine administration on Days 1-5 and 8-9) is allowed for azacitidine to avoid administration during weekends.

The subjects with higher-risk MDS or AML enrolled in SL-172154 dose escalation in combination with azacitidine cohorts will have relapsed/refractory disease; previously untreated subjects with AML and known adverse cytogenetics (e.g., ELN adverse risk group) and previously untreated subjects with higher-risk MDS with a TP53 gene mutation/deletion may also be eligible for this cohort.

When the SL-172154 monotherapy cohort completes the DLT evaluation period in Dose Level 2 (3.0 mg/kg), enrollment may begin in the dose escalation cohorts investigating SL-172154 administered with azacitidine. In this cohort, SL-172154 (starting dose, 1.0 mg/kg) will be administered by IV infusion once weekly on Days 2, 9, 16 and 23 during Cycles 1 and 2 and biweekly on Days 2 and 16 during Cycle 3 and thereafter (Figure 3). One cycle consists of 28 days.

To escalate the dose of SL-172154 in combination with azacitidine, the corresponding monotherapy dose level for SL-172154 will have been cleared for safety. For example, the SL-172154 monotherapy 6.0 mg/kg cohort must be cleared before opening the SL-172154 at 6.0 mg/kg in combination with azacitidine cohort. The planned dose escalation and duration of infusion of SL-172154 is outlined in Table 2. At each dose level, a minimum 3-day stagger between dosing the first and second subject is required. Prophylactic premedication for IRR with dexamethasone, an antipyretic and antihistamines should be administered at least 30 minutes prior to each SL-172154 administration as described in Section 3.7.3.

Subjects will be enrolled in cohorts of approximately 5 subjects into sequential dose levels of SL-172154 administered with azacitidine (75 mg/m^2, IV or SQ on Days 1 to 7 or alternative 5-2-2 schedule) and evaluated for DLTs during the 28-day DLT evaluation period which starts from the first dose of azacitidine. DLT criteria are defined in Section 3.6. Treatment will be administered in 28-day cycles until at least one of the study treatment discontinuation criteria is met (Section 3.14). During therapy, management of azacitidine-related toxicity should follow the guidelines provided in the country's current prescribing information (e.g., US Prescribing Information (USPI), Summary of Product Characteristics (SmPC), or Product Monograph). Subjects will be followed according to the Schedule of Assessments 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 azacitidine to either treatment-naïve subjects with higher-risk MDS (Part A) or treatment-naïve AML subjects with at least one known TP53 gene mutation or deletion (Part C).

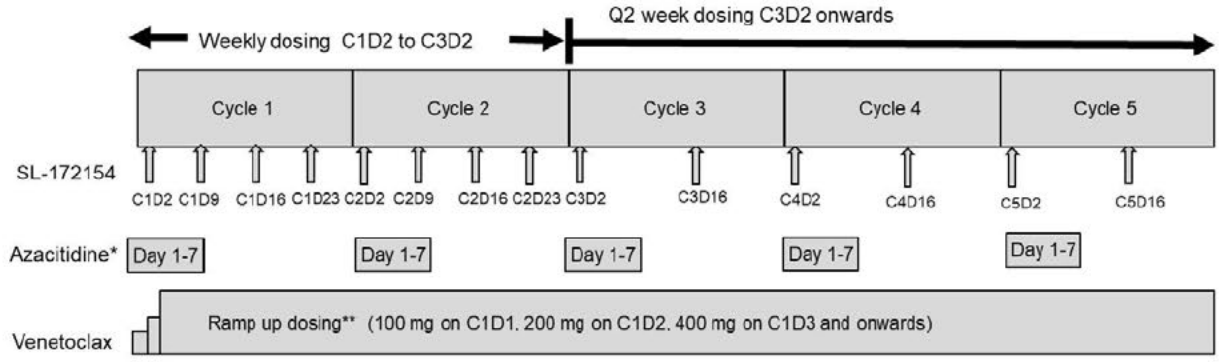
Table 2 SL-172154 Administered with Azacitidine

Dose Level (DL)	IV Dose of SL-172154[a,b]	Duration of Infusion	Combination Regimen 1
DL -1a[c]	0.3 mg/kg	30 minutes (± 10 minutes)	Azacitidine (75 mg/m^2) SQ or IV on Days 1 to 7 or use 5-2-2 schedule in each 28-day cycle. On days when both are administered, azacitidine administration should be completed at least 30 minutes prior to the start of the SL-172154 infusion.
DL 1a	1.0 mg/kg	60 minutes (± 10 minutes)	
DL 2a	3.0 mg/kg	180 minutes (± 15 minutes)	
DL 3a	6.0 mg/kg	180 minutes (± 15 minutes)	
DL 4a	10.0 mg/kg	180 minutes (± 15 minutes)	

a. SL-172154 will be administered once weekly on Days 2, 9, 16, and 23 during Cycles 1 and 2 and biweekly on Days 2 and 16 during Cycle 3 and thereafter. A cycle consists of 28 days.
b. The actual body weight in kilograms (kg) will be used for 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. Dose level -1a at 0.3 mg/kg will be evaluated if 1.0 mg/kg is not safe per mTPI-2.

3.2.2 SL-172154 Administered with Azacitidine and Venetoclax (Safety Run-In)

Figure 4 SL-172154 in Combination with Azacitidine and Venetoclax



*5-2-2 schedule (i.e., azacitidine administration on Days 1-5 and 8-9) is allowed for azacitidine to avoid administration during weekends.
**Modification is required for ramp-up dosing when a strong CYP3A inhibitor is co-administered.

Once the selected dose of SL-172154 administered with azacitidine is identified in dose escalation, enrollment to a safety run-in cohort of SL-172154 administered with azacitidine and venetoclax will commence using the same SL-172154 dose and duration of infusion. Treatment-naïve subjects with AML will be enrolled.

SL-172154 will be administered once weekly by IV infusion on Days 2, 9, 16 and 23 during Cycle 1 and 2 and biweekly on Days 2 and 16 during Cycle 3 and thereafter (Figure 4 and Table 3). One cycle consists of 28 days. Prophylactic premedication for IRR with dexamethasone and antipyretic and antihistamines should be administered at least 30 minutes prior to each SL-172154 administration as described in Section 3.7.3. Azacitidine (75 mg/m^2, IV or SQ on Days 1 to 7 or alternative 5-2-2 schedule) and venetoclax (target dose of 400 mg, oral, once daily) will be administered as described (Section 5.2 and Section 5.3) in 28-day cycles. A ramp-up schedule for venetoclax will be used with 100 mg (Day 1), 200 mg (Day 2), 400 mg (Day 3), and 400 mg once daily thereafter. A modified ramp-up schedule is required when a strong CYP3A inhibitor is co-administered (Section 16.7).

Subjects will be enrolled in cohorts of approximately 5 subjects to receive the selected dose level of SL-172154 administered with azacitidine and venetoclax, and evaluated for DLT during the 28-day DLT evaluation period which starts from the first dose of azacitidine and venetoclax; DLT criteria are defined in Section 3.6. Approximately eight subjects, in total, will be enrolled at a given dose in the safety run-in cohort evaluating SL-172154 administered with azacitidine and venetoclax prior to moving into the dose expansion cohort with this combination regimen. Treatment will continue until at least one of the study treatment discontinuation criteria is met (Section 3.14). During therapy, management of azacitidine-related or venetoclax-related toxicity should follow the guidelines provided in the country's current prescribing information (e.g., USPI, SmPC, or Product Monograph). Subjects will be followed according to the Schedule of Assessments in Section 6.2. Since this cohort is receiving venetoclax, additional safety assessment is required to monitor for tumor lysis syndrome (TLS) (Section 3.7.5 and Section 6.2 Schedule of Assessments).

The safety as well as the available PK, PD and efficacy data from these subjects will inform the dose of SL-172154 selected to be further evaluated in dose expansion (Part B) when administered in combination with azacitidine and venetoclax to treatment-naïve subjects with AML.

Table 3 SL-172154 Administered with Azacitidine and Venetoclax

Dose Level (DL)	SL-172154[a,b]	Combination Regimen 2
DL -1b[c]	1 dose level lower that was evaluated in the SL-172154 + azacitidine dose escalation portion of the study	Azacitidine (75 mg/m^2) SQ or IV on Days 1 to 7 or 5-2-2 schedule in each 28-day cycle. On days when both are administered, azacitidine administration should be completed at least 30 minutes prior to the start of the SL-172154 infusion. Venetoclax (target dose 400 mg) PO QD in each 28-day cycle.
DL 1b	Dose selected in combination with azacitidine in dose escalation	

a. SL-172154 will be administered once weekly on Days 2, 9, 16 and 23 during Cycles 1 and 2 and biweekly on Days 2 and 16 during Cycle 3 and thereafter. One cycle consists of 28 days.
b. The actual body weight in kilograms (kg) will be used for 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. Dose level -1 at 0.3 mg/kg will be evaluated if 1.0 mg/kg is not safe per mTPI-2.

3.3 Dose Expansion Cohorts

3.3.1 Part A: SL-172154 Administered with Azacitidine in Subjects with Higher-Risk MDS

Treatment-naïve subjects with higher-risk (intermediate, high, or very high per IPSS-R) MDS will be enrolled to receive SL-172154 and azacitidine at a dose and schedule identified in the dose escalation part of the study to further evaluate the safety, PD effects, and efficacy of this regimen. Prophylactic premedication for IRR with dexamethasone, an antipyretic and antihistamines should be administered at least 30 minutes prior to each SL-172154 administration, as described in Section 3.7.3. The goal is to enroll approximately 20 subjects with MDS at the potential RP2D for this combination regimen, including subjects with wild-type TP53 and TP53 gene mutation/deletion. Treatment will be administered in 28-day cycles until at least one of the study treatment discontinuation criteria is met (Section 3.14). Enrollment of subjects in Part A of dose expansion may occur in parallel with enrollment of subjects in Part B (SL-172154 administered with azacitidine and venetoclax) and Part C (SL-172154 administered with azacitidine to AML subjects with TP53 mutation/deletion) of dose expansion.

3.3.2 Part B: SL-172154 Administered with Azacitidine and Venetoclax in Subjects with AML

Once the SL-172154 dose in combination with azacitidine and venetoclax is confirmed during the safety run-in, approximately 12 additional subjects will be enrolled in the dose expansion cohort with this triplet combination regimen. Treatment-naïve subjects with AML will be enrolled to receive SL-172154, azacitidine, and venetoclax at a dose and schedule identified in the safety run-in part of the study to further evaluate the safety, PD effects, and efficacy of this regimen. Prophylactic premedication for IRR with dexamethasone, an antipyretic and antihistamines should be administered prior to each SL-172154 administration as described in Section 3.7.3. The goal is to enroll approximately 20 subjects with AML at the potential RP2D for the combination regimen, including both safety run-in and dose expansion. Treatment will be administered in 28-day cycles until at least one of the study treatment discontinuation criteria are met (Section 3.14). Enrollment of subjects in Part B of dose expansion may occur in parallel with enrollment of subjects in Part A and Part C (SL-172154 administered with azacitidine) of dose expansion.

3.3.3 Part C: SL-172154 Administered with Azacitidine in AML Subjects with TP53 Gene Mutation/Deletion

Treatment-naïve subjects with AML who have at least one TP53 mutation or deletion will be enrolled to receive SL-172154 and azacitidine at a dose and schedule identified in the dose escalation part of the study to further evaluate the safety, PD effects, and efficacy of this regimen. Prophylactic premedication for IRR with dexamethasone, an antipyretic and antihistamines should be administered at least 30 minutes prior to each SL-172154 administration as described in Section 3.7.3. The goal is to enroll approximately 20 treatment naïve subjects with TP53 mutant AML at the potential RP2D for the combination regimen. Treatment will be administered in 28-day cycles until at least one of the study treatment discontinuation criteria are met (Section 3.14).

Enrollment of subjects in Part C of dose expansion may occur in parallel with enrollment of subjects in Part A (SL-172154 administered with azacitidine) and/or Part B (SL-172154 administered with azacitidine and venetoclax) of dose expansion.

3.3.4 Part D (Randomized Cohorts): SL-172154 with Azacitidine vs Azacitidine monotherapy in HR-MDS Subjects

Approximately 60 previously untreated subjects with higher-risk (intermediate, high, or very high per IPSS-R) MDS will be randomized to three arms (approximately 20 subjects per arm): 3.0 mg/kg of SL-172154 in combination with azacitidine, 1.0 mg/kg of SL-172154 in combination with azacitidine, or azacitidine monotherapy. Subjects will be stratified based on TP53 mutation status (TP53m vs TP53wt) and baseline bone marrow blast count (<5% vs ≥5%). Prophylactic premedication for IRR with dexamethasone, antipyretics and antihistamines should be administered at least 30 minutes prior to each SL-172154 administration, as described in Section 3.7.3. Treatment will be administered in 28-day cycles until at least one of the study treatment discontinuation criteria is met (Section 3.14).

3.4 Selection of Recommended Phase 2 Dose (RP2D)

Selection of the RP2D for SL-172154 in combination with azacitidine or in combination with azacitidine and venetoclax will be based upon the totality of the safety, tolerability, PK, PD, and efficacy data in subjects treated with the respective regimen in dose escalation and dose expansion cohorts. The RP2D is a dose of SL-172154 that can be safely administered with azacitidine or azacitidine with venetoclax. In addition, preliminary efficacy of the combination regimens will be assessed to determine if the regimen warrants further evaluation in a Phase 2 study.

3.5 Evaluation of a Less Frequent Dosing Schedule

If safety and PD data support exploration of a less intensive dosing schedule, then subsequent cohort enrollment on an alternative less frequent schedule may be instituted. For example, SL-172154 may be administered once every two weeks in every cycle or once every 21 or 28 days. The starting dose on this less intensive schedule would be instituted at the current dose level of the selected schedule that is safe as defined by the mTPI-2 method [Guo, 2017] or a lower dose level based on emerging safety data. Any such evaluation of alternative dosing schedule(s) will be done by protocol amendment.

3.6 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 28 days of treatment (i.e., Cycle 1). However, there is provision in the criteria below for AEs that occur beyond this period to be considered in the determination of DLTs and RP2D. All toxicities except for CRS will be graded as per NCI CTCAE v5. CRS will be graded per the ASTCT Consensus Grading Criteria for CRS (Section 3.8.2). AEs clearly related to disease progression, intercurrent illness, or concomitant medications are not considered DLTs. Infection, bleeding, or other expected direct complication of cytopenias due to active underlying MDS or AML will not be considered a DLT. A DLT is defined as an event considered related or possibly related to SL-172154 and meets one of the following criteria:

- SL-172154 monotherapy cohorts: Grade 4 neutropenia or thrombocytopenia lasting ≥14 days from the start of the cycle in the absence of evidence of active AML or MDS.
- SL-172154 in combination with azacitidine or azacitidine and venetoclax: Grade 4 neutropenia or thrombocytopenia lasting ≥28 days from the start of the cycle in the absence of active AML or MDS.
- Any death not clearly related to underlying disease or intercurrent illness.
- Any Grade 3 elevations in AST, ALT, or total bilirubin.
  - Evidence of Hy's Law (AST or ALT ≥ 3 x upper limit of normal (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 or greater non-hematologic AE that requires permanent discontinuation of SL-172154.
- Any Grade 3 or greater non-hematologic AE **except** for those listed below:
  - Grade 3 fatigue lasting ≤ 7 days.
  - 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.
  - Vitiligo or alopecia of any grade.

Other toxicities may be considered a DLT as determined by the Investigator in conjunction with the SMC. The DLT-evaluable population is defined in Section 9.2.1.

3.7 Concomitant Medications, Treatments and Procedures

Investigators may prescribe concomitant medications or treatments deemed necessary to provide supportive care except for prohibited medications described in Section 3.7.1. Best supportive care should be provided (including but not limited to antibiotics, bisphosphonates, receptor activator of nuclear factor kappa B ligand [RANKL] inhibitors, transfusions, growth factor support, nutritional support, correction of metabolic disorders, hydration, anti-hyperuricemics, optimal symptom control, and pain management including palliative radiotherapy) for all subjects when clinically indicated.

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

Vaccines for Coronavirus Disease 2019 (COVID-19) are permitted as they are not live attenuated vaccines. 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.

3.7.1 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 SL-172154 therapy:

- Any investigational anti-cancer therapy not described in this protocol.
- Any concurrent chemotherapy (other than study medications), radiotherapy, hormonal or hormonal suppression therapy, immunotherapy, or biologic therapy administered for anti-cancer treatment.
- Non-steroidal immunosuppressive medications (except to treat a drug-related AE).
- Systemic corticosteroids > 10 mg of daily prednisone or equivalent except that the following are permitted:
  - Topical, intranasal, inhaled, ocular, intraarticular corticosteroids.
  - Physiological doses of replacement steroid (e.g., for adrenal insufficiency).
  - A brief course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., transfusion reactions, delayed-type hypersensitivity reaction caused by contact allergen).
  - Treatment for a drug-related AE (Section 3.8).
  - Corticosteroids used as prophylactic premedication for IRR.
- Live attenuated vaccines during the study through 30 days after the last dose of SL-172154.
- Adalimumab (Humira) should be avoided when subjects receive azacitidine.
- For venetoclax cohorts:
  - Use of P-gp substrates concomitantly with venetoclax. If concomitant use of P-gp substrate is unavoidable, separate dosing of the P-gp substrate by at least 6 hours before venetoclax administration.
  - When azole antifungals that are P-gp inhibitors must be used, they are permitted. If concomitant use of P-gp inhibitor is unavoidable, venetoclax dose should be reduced as described in Section 16.7, or follow country-specific prescribing information (e.g., USPI, SmPC, or Product Monograph).
  - When azole antifungals that are strong or moderate CYP3A inhibitors must be used, they are permitted. If strong or moderate CYP3A inhibitors must be used, the venetoclax dose should be reduced as described in Section 16.7 or follow the country's current prescribing information (e.g., USPI, SmPC, or Product Monograph).
  - Concomitant use of strong or moderate CYP3A inducers is to be avoided throughout the study treatment period. Treatment with a strong or moderate CYP3A inducers should stop 7 days prior to first dose of study treatment.

3.7.2 Medications To Be Used With Caution

SL-172154 is a therapeutic protein that may induce the transient release of cytokines including IL-6 which in turn, may inhibit the activity of cytochrome P450 (CYP450) enzymes including CYP3A4 activity [Evers, 2013]. Although not tested clinically, a drug-drug interaction may occur with the 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, therefore such drugs with a narrow therapeutic index should be used with caution. There may be an increased risk of side effects for drugs that are CYP450 substrates. Where possible consider substitutions for these medicinal products if therapeutic effects cannot be monitored.

A list of drugs that are CYP450 substrates including CYP3A substrates is available at: https://drug-interactions.medicine.iu.edu/Main-Table.aspx (Flockhart Table).

For subjects receiving venetoclax, concomitant use with a P-gp inhibitor or a strong or moderate CYP3A inhibitor should be avoided and alternative medications should be considered. In situations where the use of strong and moderate CYP3A inhibitors or P-gp inhibitors is not avoidable, the venetoclax dose should be reduced as described in Section 16.7, or follow country-specific prescribing information.

Subjects receiving venetoclax should avoid grapefruit products, Seville oranges, and starfruit during treatment as they contain inhibitors of CYP3A. Refer to the country's current prescribing information of venetoclax (e.g., USPI, SmPC, or Product Monograph) for contraindications and dose modifications for use with CYP3A inhibitors and inducers, and P-gp inhibitors.

3.7.3 Prophylactic Premedication for Infusion-Related Reactions (IRR) (All Subjects)

Prophylactic premedication for IRR with dexamethasone 8 mg IV, an antipyretic and antihistamines [e.g., acetaminophen 650 to 1000 mg PO; diphenhydramine 25 to 50 mg (or equivalent) PO or IV; famotidine 20 mg PO or IV (or equivalent)] should be administered at least 30 minutes prior to each SL-172154 administration. The dose and administration method of prophylactic premedication can be modified at the Investigator's discretion. Premedication with dexamethasone 8 mg, IV or oral, one day prior to scheduled day of SL-172154 infusion is also allowed at the Investigator's discretion.

For subjects who experience IRR, see the toxicity management guidelines Section 3.8.1. If the measures implemented in study SL03-OHD-104 (prophylaxis noted above and extended duration of infusion) are not sufficient for prevention of IRRs, the SMC may recommend modifications of prophylactic premedication for IRR based on emerging safety.

3.7.4 Prophylactic Premedication for Cytokine Release Syndrome (CRS)

For subjects who experienced CRS, see the toxicity management guidelines of CRS in Section 3.8.2.

3.7.5 Recommendations for Prophylaxis and Management of Tumor Lysis Syndrome (Subjects Receiving Venetoclax)

There is a potential risk for TLS in subjects with AML who receive venetoclax, especially in those with elevated leukocyte count, circulating blasts, elevated pretreatment lactate dehydrogenase (LDH) levels, renal dysfunction, and dehydration. In addition, on-target effect of venetoclax could lead to rapid cell death and pose a risk for TLS. Subjects enrolled in the study who will receive venetoclax should be assessed for the risk of TLS, and to mitigate risk, TLS prophylaxis and monitoring may be implemented. Prophylactic reductions of potassium, inorganic phosphorus or uric acid above normal range are recommended prior to beginning study treatment and continue

based on the ongoing risk of TLS. Below are the minimum recommendations for TLS prophylaxis and management for subjects receiving venetoclax in this study. Prophylaxis and monitoring procedures for TLS should be implemented as per regional guidelines or institutional standards:

- Consider hospitalization on or before Cycle 1 Day1 prior to administration of the initial dose of venetoclax-containing study treatment regimen and remain in the hospital for at least 24 hours after reaching the final dose level of the concurrent administration of venetoclax/azacitidine in Cycle 1.
- Administration of uric acid reducing agent, adequate oral and IV hydration while monitoring the fluid status of the subject prior to and during the ramp-up of venetoclax in the first cycle should be based on institutional guidelines.
- TLS chemistry tests may be drawn (calcium, inorganic phosphorus, potassium, uric acid and creatinine) on the first, second and third day of venetoclax dosing at predose (within 4 hours prior to dosing), 6 to 8 hours post-dose, and 24 hours after reaching final dose.
- Additional laboratory assessments may be performed, per Investigator discretion, post-dose during ramp-up and up to 48 hours after reaching the final dose (i.e., 400 mg) if clinically indicated.
- Abnormal chemistry tests should be corrected promptly,
- If a subject meets criteria for clinically significant laboratory of clinical TLS (Table 4), no additional venetoclax should be administered until resolution.

For continued dosing of venetoclax, monitoring for evidence of TLS during treatment and managing abnormalities of serum creatinine, uric acid and electrolytes promptly is recommended. For subjects at higher risk (i.e., circulating blasts) more intensive measures should be considered.

Refer to Section 16.4 for recommended guidelines on the management of TLS.

Table 4 Tumor Lysis Syndrome Classification

Metabolic Abnormality	Criteria for Classification of Laboratory of TLS[a]	Criteria for Classification of Clinical TLS[b]
Hyperuricemia	Uric acid > 8.0 mg/dL (475.8 µmol/L)	N/A
Hyperphosphatemia	Phosphorus > 4.5 mg/dL (1.5 mmol/L)	N/A
Hyperkalemia	Potassium > 6.0 mmol/L	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium < 7.0 mg/dL (1.75 mmol/L) or ionized calcium < 4.5 mg/dL (1.12 mmol/L)[c]	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trouseau's sign, Chvostek's sign, laryngospasm, bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute kidney injury[d]	N/A	Increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/L) or the presence of oliguria (average urine output of < 0.5 mL/kg/hr over a 6-hour period)

a. Laboratory TLS requires two or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward.
b. Clinical TLS requires the presence of laboratory TLS plus one or more findings from clinical TLS column.
c. Corrected calcium = measure calcium level in mg/dL + 0.8 x(4-albumin in g/dL).
d. Acute kidney injury, unless attributable to another cause, represents clinical TLS even if criteria for laboratory TLS are not satisfied.

Abbreviations: TLS = tumor lysis syndrome; N/A = not applicable

Source: [Howard, 2011]

3.8 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. These guidelines are not meant to be prescriptive, and Investigators should always use clinical judgement in the determination of dosing. Investigators should always err on the side of caution if treatment-related toxicity is suspected. Subjects should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, infections). In the absence of a clear alternative etiology, the possibility of an immune-related AE should be considered.

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 SL-172154. Only one level dose reduction is

permitted for AE management and then SL-172154 administration should be interrupted. If SL-172154 is skipped, azacitidine dosing may continue per schedule. Investigators always have the option to perform a more conservative dose modification if clinically indicated (i.e., dose interruption as opposed to dose reduction). If any adverse event deemed to be related to SL-172154 that requires a dose hold of more than 28 days, please contact the medical monitor as it may result in permanent discontinuation of SL-172154.

Table 5 SL-172154 Dose Reduction for Management of Toxicities

Starting Dose Level (mg/kg)	Dose Level Reduction (mg/kg)
0.3	Interrupt SL-172154 until toxicity resolves to ≤ Grade 1 or baseline and then restart at same dose level.
1.0	0.3
3.0	1.0
6.0	3.0
10.0	6.0

3.8.1 Management of Infusion-Related Reactions

General Guidance for Infusion-Related Reactions (IRRs) [Rosello, 2017; Porter, 2018]	
Premedications for IRR prophylaxis must be administered at least 30 minutes prior to each SL-172154 administration as outlined in Section 3.7.3 Subjects must be monitored for signs and symptoms of IRRs with prompt institution of treatment. Subjects should be notified that symptoms may occur during the first infusion and for up to several hours afterwards or with subsequent infusions. 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 soon as possible, as noted in Section 6.6.7.1**	
Severity (Symptoms)	**Management**
Grade 1	• Infusion interruption not indicated. • Vital signs should be measured after the onset of an IRR approximately every 15 minutes through the end of the infusion followed by approximately every 15 minutes for one hour after end of the SL-172154 infusion and then approximately every 30 minutes for the second hour after the end of SL-172154 infusion. Monitor subjects with close observation in an outpatient or inpatient setting for a minimum of 12 hours or 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 end of the infusion followed by approximately every 15 minutes for one hour after end of the SL-172154 infusion and then approximately every 30 minutes for the second hour after end of the SL-172154 infusion. Begin IV infusion of normal saline and treat symptoms with an antipyretic and histamine 1 and 2 (H1 and H2) antihistamines as per prophylaxis described in Section 3.7.3; 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 for a minimum of 12 hours or until recovery from symptoms. Consider admission to hospital. • If the infusion is interrupted, then restart the infusion after resolution of symptoms at no more than 50% of the rate in mg/min at which the reaction symptoms occurred. • If symptoms recur when the infusion is restarted, then no further SL-172154 will be administered at this visit. • For subsequent infusions, SL-172154 may be administered at one dose level lower at 50% of the rate in mg/min at which the reaction occurred (e.g. 1.0 mg/kg for 120 minutes ± 15 minutes when a dose reduction is required for the original dose of 3.0 mg/kg), OR, if the original dose is administered, the infusion must be administered at 50% of the rate in mg/min at which the reaction occurred (e.g. 3.0 mg/kg for 360 minutes ± 15 minutes when the original dose was 3.0 mg/kg).

	• If further symptoms are not experienced for the next 2 doses of SL-172154, the dose of SL-172154 (if decreased to one dose level lower) may be re-escalated to the original dose and the infusion rate may be escalated at intervals and increments as clinically appropriate. The investigator may discontinue SL-172154 in the event of recurrent IRR based on the severity of the symptoms.

General Guidance for Infusion-Related Reactions (IRRs), cont.	
Severity (Symptoms)	**Management**
Grade 3	• Immediately discontinue infusion of SL-172154. • Vital signs should be measured after the onset of an IRR approximately every 15 minutes through the end of the infusion followed by approximately every 15 minutes for one hour after end of the SL-172154 infusion and then approximately every 30 minutes for the second hour after end 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, 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 a minimum of 12 hours or until recovery from symptoms. Consider admission to hospital. • Rechallenge should not be attempted in cases of true anaphylaxis. In other cases, once subject has completely recovered, carefully consider if it is safe for the subject to receive SL-172154 at the next scheduled dose with premedication (e.g., corticosteroids, antihistamines, antipyretic) and slow infusion (≤50% of the rate at which the reaction occurred). The next two subsequent infusions of SL-172154 (after an event of Grade 3 event of infusion-related reaction) must be administered at one dose level lower in an inpatient or outpatient setting with prolonged observation for a minimum of 12 hours after the completion of the infusion. If no further symptoms, dose may be re-escalated to original dose and infusion rate may be escalated at intervals and increments as clinically appropriate. If symptoms recur, permanently discontinue SL-172154.
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 through the end of the infusion followed by approximately every 15 minutes for one hour after end of the SL-172154 infusion and then approximately every 30 minutes for the second hour after end of the SL-172154 infusion. Manage severe IRRs per institutional standards (e.g., epinephrine, diphenhydramine, famotidine, 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.

3.8.2 Management of Cytokine Release Syndrome (CRS)

Table 6 ASTCT Consensus Grading Criteria for CRS

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 an 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.

Source: [Lee, 2019]

General Guidance for Cytokine Release Syndrome (CRS) [Lee, 2014; Lee, 2019; BREYANZI® USPI, 2021]	
CRS is a non-antigen-specific, systemic inflammatory response that occurs as result of high-level immune activation with concomitant elevations of cytokines (e.g., IL-6, IL-10, TNF-α, IL-2, IFNɣ). CRS can be fatal or life-threatening reactions. Evaluate for and treat other causes of fever, hypoxia, and hypotension. Determine CRS grade per the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading criteria for CRS in Table 6 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 mAbs (e.g., sarilumab) or anti-IL-6 mAbs (e.g., siltuximab). **If CRS events occur, ad hoc labs should be collected as soon possible as noted in Section 6.6.7.1**	
Severity (ASTCT CRS Consensus Grading)	**Management**
Any Grade	• Permanently discontinue SL-172154 if any grade CRS occurring 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 a minimum of 12 hours or until recovery from symptoms. • Maintain IV access. Symptomatic treatment with an antipyretic, antiemetics, analgesics, histamine 1/histamine 2 (H1/H2) antihistamines as needed; monitor fluid balance; assess for infection. Consider opioids (e.g., meperidine) for rigors. Regularly evaluate for signs of further deterioration. Resume SL-172154 when all symptoms/ clinical features for CRS resolved, and follow the guidelines below: • Subjects who have experienced Grade 1 CRS with C1D1 should be hospitalized for C1D8 dosing [SL-172154 monotherapy cohort] or those who have experienced Grade 1 CRS with C1D2 should be hospitalized for C1D9 dosing [Combination cohorts], or next subsequent infusions of SL-172154 after the first event of Grade 1 CRS; subjects should be under prolonged observation for a minimum of 12 hours after the completion of the infusion. • For subsequent infusions, infuse SL-172154 for at least twice the infusion time (± 15 minutes) Consider premedication (e.g., antipyretic, antihistamines) per institutional guidelines.

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. Monitor subjects with close observation in an outpatient or inpatient setting for a minimum of 12 hours or until recovery from symptoms. Consider admission to hospital for management of symptoms, organ dysfunction or administration of therapy. • Closely monitor cardiac and other organ functions. • Monitor subjects with continuous cardiac telemetry and pulse oximetry. • Start IV infusion with normal saline. Administer oxygen if needed. Treat with an antipyretic, H1/H2 antagonists (diphenhydramine 50 mg IV plus famotidine 20 mg IV), and/or methylprednisolone 1-2 mg/kg or equivalent dose of corticosteroid every 6 hours 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 CRS. o Administer tocilizumab at a dose of 8 mg/kg over 1 hour (not to exceed 800 mg). o Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. o Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses. • 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. <u>Resume SL-172154 at one dose level lower when all symptoms/ clinical features for CRS resolved and follow the guidelines below:</u> • Subjects who have experienced Grade 2 CRS with C1D1 should be hospitalized for C1D8 and C1D15 dosing [SL-172154 monotherapy cohort] or those who have experienced Grade 2 CRS with C1D2 should be hospitalized for C1D9 and C1D16 dosing [Combination cohorts], or next two subsequent infusions of SL-172154 after the first event of Grade 2 CRS. Subjects should be under prolonged observation for a minimum of 12 hours after the completion of the infusion. • For subsequent infusions, infuse SL-172154 for at least twice the infusion time (± 15 minutes) Premedicate with dexamethasone 20 mg, antipyretic, H1/H2 antihistamines, and manage per institutional guidelines.

Grade 3	• Interrupt SL-172154.
	  ○ 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 management of symptoms related to organ dysfunction: admit to the hospital for close monitoring and management.
	• Monitor subjects with continuous cardiac telemetry and pulse oximetry.
	• Consider performing an echocardiogram 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, corticosteroids, bronchodilators, oxygen, fluids, meperidine for rigors, etc.). Epinephrine is the drug of choice in an anaphylactic reaction and its administration should not be delayed.
	• Administer tocilizumab at a dose of 8 mg/kg over 1 hour (not to exceed 800 mg).
	  ○ Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen.
	  ○ Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.
	• Second-line therapies:
	  ○ 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.
	  ○ anti-TNF-α mAbs (infliximab) or soluble TNF-α receptor (etanercept), or IL-1R-based inhibitors (anakinra).
	<u>Resume SL-172154 at one dose level lower only when all symptoms/ clinical features for CRS resolve within 72 hours and follow the guidelines below</u>:
	• Subjects who have experienced Grade 3 CRS with C1D1 should be hospitalized for C1D8 and C1D15 dosing [SL-172154 monotherapy cohort], or those who have experienced Grade 3 CRS with C1D2 should be hospitalized for C1D9 and C1D16 dosing [Combination cohorts],or next two subsequent infusions of SL-172154 after the first event of Grade 3 CRS. Subjects should be under prolonged observation for a minimum of 12 hours after the completion of the infusion.
	• For subsequent infusions, infuse SL-172154 for at least twice the infusion time (± 15 minutes) (Premedicate with dexamethasone 20 mg, antipyretic, H1/H2 antihistamines, and manage per institutional guidelines.

Grade 4	• Permanently discontinue SL-172154.
	• Hospitalization required for management of symptoms related to organ dysfunction: admit to the hospital for close monitoring and 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.
	• Consider intensive-care supportive therapy.
	• Monitor subjects with continuous cardiac telemetry and pulse oximetry.
	• Consider performing an echocardiogram 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, corticosteroids, bronchodilators, oxygen, fluids, meperidine for rigors, etc.). Epinephrine is the drug of choice in an anaphylactic reaction and its administration should not be delayed.
	• Administer tocilizumab at a dose of 8 mg/kg over 1 hour (not to exceed 800 mg).
	  ○ Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen.
	  ○ Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.
	• Second-line therapies:
	  ○ 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.
	  ○ anti-TNF-α mAbs (infliximab) or soluble TNF-α receptor (etanercept), or IL-1R-based inhibitors (anakinra).

3.8.3 Management of Hepatotoxicity

General Guidance for Hepatotoxicity	
Monitor signs, symptoms and laboratory evidence of liver dysfunction. Evaluate alternative etiologies: review medications for hepatotoxic drugs and alcohol history; perform liver screen: hepatitis A, B, C serology, hepatitis E polymerase chain reaction (PCR), antinuclear antibody (ANA)/smooth muscle antibody/liver kidney microsomal antibodies /soluble liver antibody/liver-pancreas antigen/liver cytosol iatrogene antibodies, iron studies. Consider imaging for progressive disease/thrombosis. Guidelines are based on elevations in ALT, AST and bilirubin per CTCAEv5. Discontinue SL-172154 for Hy's law as follows: 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 (Symptoms)	**Management**
Grade 1	• Continue SL-172154 with close monitoring. • Monitor liver function at least weekly; if liver function is stable, reduce frequency of blood tests.
Grade 2	• Reduce dose of SL-172154 by one dose level. • Monitor liver function ~every 3 days. If persistent or rising liver chemistries or significant clinical symptoms, interrupt SL-172154. • Consider hepatology consult and liver biopsy is optional. • If an immune etiology is suspected, start oral prednisone 0.5-1.0 mg/kg/day (or equivalent of methylprednisolone) with 4-week taper. • Resume SL-172154 when toxicity ≤ G1 and corticosteroid taper to ≤ 10 mg/day prednisone or equivalent.
Grade 3	• Hold SL-172154. • Permanently discontinue SL-172154 for liver function test abnormality that meets following criteria in subjects who enroll with AST/ALT/total bilirubin ≤ ULN: AST or ALT > 8 x ULN or total bilirubin > 5 x ULN. • Permanently discontinue SL-172154 for liver function test abnormality that meets following criteria in subjects who enroll with AST/ALT/total bilirubin > ULN: AST or ALT > 8 x baseline or total bilirubin > 5 x baseline. • If persistent or rising liver chemistries, or significant clinical symptoms and an immune etiology is suspected, start oral prednisone 0.5-1.0 mg/kg/day (or equivalent of methylprednisolone) with 4-week taper. Obtain hepatology consult and assessments as above, monitor liver function daily; consider liver biopsy. • Other Grade 3 laboratory abnormalities: re-challenge may be considered only after consultation with hepatologist.

Grade 4	• Permanently discontinue SL-172154. • Consider hospitalization; obtain hepatology consult; assessments as above; monitor liver function daily; consider liver biopsy. • If an immune etiology is suspected, immediately start methylprednisolone 1-2 mg/kg (start with 2 mg/kg for Grade 4) or equivalent. • If refractory after 3 days, consider mycophenolate mofetil (MMF). Avoid the use of infliximab in immune mediated hepatitis.

3.8.4 Management of Non-hematologic and Hematologic AEs Not Specified

The SL-172154 dose may be held for SL-172154-related AEs that occur, including AEs that constitute a DLT. For the management of other AEs:

Severity (Symptoms)	Dose Modification
Any Grade	• 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. Any suspected immune-related AE (irAE) should be managed per Institutional guidelines.
Grade 1	• No dose modifications.
Grade 2	• For Grade 2 non-hematologic AEs, consider dose reducing SL-172154 by one dose level until AE resolves to ≤Grade 1 or baseline.
Grade 3	• Hold SL-172154 until resolution to ≤Grade 1 or baseline. • For non-hematologic AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days with optimal management, resume SL-172154. Otherwise, discontinue SL-172154. • Note: For Grade 3 hematologic and non-hematologic labs, decision to hold should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.
Grade 4	• Discontinue SL-172154 for all grade ≥ 4 non-hematologic events. • For Grade 4 non-hematologic labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor). • Discontinue SL-172154 for Grade 4 neutropenia and thrombocytopenia of ≥ 28 days from start of cycle in absence of evidence of active AML or MDS.

If SL-172154 is permanently discontinued for any reason, subject should complete the Post Treatment visit and continue in the survival follow-up portion of the study. At the Investigator's discretion, the subject may continue to receive approved agents, either azacitidine alone or in combination with venetoclax, during the survival follow-up period; in such instances, this therapy will be considered subsequent anticancer therapy and be recorded on the appropriate electronic case report form (eCRF). If a dose delay occurs, then PK and PD assessments should be performed on the actual day of study drug administration, and not on the original scheduled administration day.

3.9 Toxicity Management Guidelines for Azacitidine

When toxicity is considered to be attributed to azacitidine, azacitidine dose should be modified based on the current country's prescribing information (e.g., USPI, SmPC, or Product Monograph). Recommendations for management of cytopenias associated with azacitidine are outlined in Section 16.5; if the country-specific prescribing information is different, those guidelines should be used.

3.10 Toxicity Management Guidelines for Azacitidine and Venetoclax

When toxicity is considered to be attributed to the combination of azacitidine and venetoclax, dosage modification should follow the current country's prescribing information (e.g., USPI, SmPC, or Product Monograph). Recommendations for management of cytopenias are outlined in Section 16.6; if the country-specific prescribing information is different, those current guidelines should be used. Please also see Management of Tumor Lysis Syndrome in Section 3.7.5.

3.11 Participant Withdrawal of Consent

- A participant may withdraw consent for participation in this study at any time at his/her own request; or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. 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 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 withdrawal of consent for further treatment with study medication, a Post Treatment visit should be conducted, as shown in the Schedule of Assessments (SOA) in Section 6. See SOA for data to be collected at the time of discontinuation of study treatment and for any further evaluations that need to be completed. Every effort must be made to continue follow-up of participants for protocol-specified safety follow-up procedures to capture AEs, SAEs, and unanticipated problems.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

3.12 Lost to Follow-up

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

3.13 Premature Termination or Suspension of the 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 agencies 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 GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further development of the investigational product (IP)
- Determination of unexpected, significant, or unacceptable risk to participants

3.14 Study Treatment Discontinuation Criteria

Subjects will receive the assigned study treatment (e.g., SL-172154 monotherapy or SL-172154 and azacitidine administered with or without venetoclax, or azacitidine monotherapy) until any of the following events occur during the study:

- Documented disease progression
- 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 decision to withdraw from further treatment on the study
- Subject becomes eligible for and consents to transplant
- Occurrence of pregnancy
- Significant noncompliance with protocol requirements
- Death
- Termination of the study by the Sponsor

A subject meeting the response criteria of relapsed or progressive disease, or determination of clinical progression is considered a sufficient reason to discontinue study drug treatment. However, if the determination of progression is equivocal for a subject with AML, the Investigator may continue study drug treatment when a subject with transfusion dependence at baseline become post-treatment transfusion independent. Transfusion dependence at baseline

is defined by transfusion requirement during the 4-week period prior to the first dose of study drug treatment. Post-treatment transfusion independence is defined as no transfusion for ≥ 56 days at any time point after the first dose of study drug treatment. When the determination of progression is equivocal for a subject with MDS, the investigator may continue study drug treatment until relapse/ disease progression is confirmed after 4 weeks from an initial finding unless there is clinical deterioration.

In the event of study treatment discontinuation, subjects should be strongly encouraged to complete all scheduled assessments at the Post Treatment visit and the Survival Follow-up contacts.

3.15 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 eCRF.

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

Participants who discontinue IP for any reason other than withdrawal of consent will be followed for survival and will be contacted approximately every 3 months until death or the end of the study, whichever occurs first. During Survival Follow-up, relevant information regarding subsequent anticancer therapy(ies) for AML or MDS will be collected and entered in the eCRF.

In addition, for subjects that proceed to HCT, HCT-relevant information will be collected and entered in the eCRF. Refer to Section 6.13 for additional details.

3.16 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 on study treatment will receive standard of care treatment as determined by their health care provider after completion of the study.

3.17 COVID-19 Risk Assessment

Shattuck Labs has developed a separate COVID-19 risk assessment policy to address conduct of clinical trials during the COVID-19 pandemic to ensure subject safety as well as management of potential implications to data integrity. A copy of this document is available upon request.

4. STUDY POPULATION

Participants with higher-risk MDS or AML described below 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

Participants must meet 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. For subjects with AML, confirmation of AML diagnosis by 2016 WHO criteria [Arber, 2016] (WHO classification, excluding acute promyelocytic leukemia [APL]).
4. Subjects with MDS must have:
   a. morphologically confirmed diagnosis of MDS by 2016 WHO criteria [Arber, 2016] with <20% blasts in bone marrow per bone marrow biopsy/aspirate or peripheral blood.
   b. confirmation of intermediate, high or very high risk category by IPSS-R.

   Subjects with a diagnosis of any of the following are excluded: Atypical CML, juvenile myelomonocytic leukemia (JMML), chronic myelomonocytic leukemia (CMML), and unclassifiable MDS/myeloproliferative neoplasm (MPN).
5. [*Dose Escalation Cohort – SL-172154 Monotherapy*] Subjects with AML must have relapsed/refractory disease (≥5% blasts by manual aspirate differential, flow cytometry, or immunohistochemistry) following at least 1 prior line of therapy but no more than 4 prior lines of therapy. Subjects with higher-risk MDS must have relapsed/refractory disease following at least 1 prior line of therapy but no more than 4 prior lines of therapy.
   a. Prior hydroxyurea or other supportive care in the form of transfusions or growth factors will not be considered prior therapy.
   b. Subjects who have undergone allogeneic-HCT are eligible if they are at least 6 months post-HCT, have relapsed AML or MDS as defined above, are not on treatment or prophylaxis for graft versus host disease (GVHD) for at least 6 weeks before the first dose of study treatment, and have no active GVHD.
   c. Subjects must not be eligible for rescue chemotherapy and allogeneic-HCT per local or institutional guidelines at the time of screening.
6. [*Dose Escalation Cohort – SL-172154 Administered with Azacitidine*] Subjects with relapsed/refractory AML and MDS (as defined in Inclusion criterion 5) following at least 1 prior line of therapy but no more than 4 prior lines of therapy.
   a. Treatment for MDS preceding secondary AML will not be considered as a prior line of therapy for secondary AML.
   b. Prior hydroxyurea or other supportive care in the form of transfusions or growth factors will not be considered prior therapy.
   c. Subjects who have undergone allogeneic-HCT are eligible if they are at least 6 months post-HCT, have relapsed AML or MDS as defined above, are not on treatment or prophylaxis for GVHD for at least 6 weeks before the first dose of study treatment, and have no active GVHD.
   d. Subjects must not be eligible for rescue chemotherapy and allogeneic-HCT per local or institutional guidelines at the time of screening.

In addition, previously untreated subjects meeting either of the following criteria are eligible for this cohort:

a. Previously untreated subjects with AML with known adverse cytogenetics who fall into the adverse ELN risk group and who are unlikely to benefit from standard intensive induction therapy or refuse intensive induction therapy at time of enrollment.
b. Previously untreated subjects with MDS with documentation of at least one TP53 gene mutation or deletion based on local test. Prior MDS therapy with lenalidomide or other supportive care in the form of transfusions or growth factors is allowed.

7. [*Dose Expansion Cohort Part A: SL-172154 Administered with Azacitidine*]: Subjects diagnosed with MDS must be previously untreated. Prior MDS therapy with lenalidomide, luspatercept or other supportive care in the form of transfusions or growth factors is allowed. Up to 1 cycle of prior therapy with a hypomethylating agent is permitted. Subjects with newly diagnosed treatment-related MDS are also eligible for enrollment.

8. [*Dose Escalation – Safety Run-in Cohort AND Dose Expansion Cohort Part B: SL-172154 Administered with Azacitidine and Venetoclax*]: Subjects with AML must be previously untreated as defined by:
   a. Subject must be ineligible for induction therapy with a standard cytarabine and anthracycline induction regimen due to age or co-morbidities as defined by the following:
      - ≥ 75 years of age
      - ≥ 60 to 74 years of age with at least one of the following co-morbidities:
        - Eastern Cooperative Oncology Group (ECOG) Performance Status of 2
        - History of congestive heart failure (CHF) requiring treatment
        - Ejection fraction ≤ 50%
        - Chronic stable angina
        - DLCO ≤ 65% or FEV1 ≤ 65%
        - Creatinine clearance ≥ 30 mL/min to < 45 ml/min
        - Documented contraindication to anthracycline or cytarabine based therapy
   b. Subjects with AML with known adverse cytogenetics who fall into the adverse ELN risk group and who are unlikely to benefit from standard intensive induction therapy or refuse intensive induction therapy at time of enrollment are also eligible.
   c. Subjects with newly diagnosed secondary AML and who are unlikely to benefit from standard intensive induction therapy or refuse intensive induction therapy at time of enrollment are eligible for enrollment. Subjects with secondary AML after MDS must not have received prior chemotherapy or no more than 2 cycles of prior hypomethylating agent for MDS.

9. [*Dose Expansion Cohort Part C: SL-172154 Administered with Azacitidine*]: Subjects with previously untreated *de novo* AML or secondary AML with TP53 gene mutation or deletion and who are unlikely to benefit from standard intensive induction therapy or refuse intensive induction therapy at time of enrollment are eligible. All subjects must have

documentation of at least one TP53 gene mutation/deletion based on local test. Subjects with secondary AML after MDS must not have received prior chemotherapy or no more than 2 cycles of prior hypomethylating agent for MDS.

10. ECOG Performance Status of 0, 1, or 2.

11. Laboratory values must meet the following criteria:

Laboratory parameter	Threshold value
White blood cell count (WBC)	≤ 20 x 10^9/L (Hydroxyurea is permitted to meet this criterion)
Creatinine clearance (CrCl)	≥ 30 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

12. Willing to provide consent for bone marrow aspirate samples at baseline and on-treatment for exploratory research as described in the Schedule of Assessments (Section 6).

13. For subjects with relapsed/refractory disease, recovery from prior anti-cancer treatments including surgery, radiotherapy, chemotherapy or any other anti-cancer therapy to baseline or ≤ Grade 1. (NOTE: Low-grade or controlled toxicities (e.g., alopecia) may be allowed upon agreement by the Medical Monitor)

14. Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test within 72 hours of the first dose of study treatment. NOTE: Females are defined as being of childbearing potential unless they are surgically sterile (i.e., have undergone a complete hysterectomy, bilateral tubal ligation/occlusion, bilateral oophorectomy or bilateral salpingectomy), have a congenital or acquired condition that prevents childbearing or are naturally post-menopausal for at least 12 consecutive months (see Section 16.3 for additional details). Documentation of post-menopausal status must be provided. To avoid pregnancy, FCBP must use a highly effective method of contraception (i.e., <1% failure rate), as described in Section 16.3, at least 14 days prior to initiation of study treatment, and continue use during treatment and for 30 days (which exceeds 5 half-lives) after the last dose of SL-172154, or for the duration required by local prescribing information after the last dose of azacitidine (i.e., for sites in UK, at least 6 months after the last dose of azacitidine in either combination regimen).

15. Male subjects with female partners of childbearing potential must have azoospermia from a prior vasectomy, an underlying medical condition, or agree to use a highly effective method of contraception (i.e., <1% failure rate) during treatment and for 30 days (which exceeds 5 half-lives) after the last dose of SL-172154, or for the duration required by local prescribing information after the last dose of azacitidine (i.e., for sites in UK, at least 3 months; for sites in Canada, at least 6 months). See Section 16.3 for further details on contraception requirements.

16. [*Dose Expansion Cohort Part D: SL-172154 Administered with Azacitidine vs azacitidine monotherapy*]*:* Subjects diagnosed with MDS must be previously untreated. Prior MDS therapy with lenalidomide, luspatercept or supportive care in the form of transfusions or growth factors is allowed. No prior therapy with a hypomethylating agent is permitted. Subjects with newly diagnosed treatment-related MDS are also eligible for enrollment. TP53 mutation status results based on local test must be available prior to randomization.

4.2 Exclusion Criteria

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

1. [*Monotherapy and Combination Regimen Dose Escalation Cohorts*]: Prior treatment with:
   - CAR-T cell therapy within 3 months from the first dose of the study drug.
   - Prior treatment with anti-CD47 targeting agent or CD40 agonist within 28 days prior to first dose of study treatment.
   - Prior treatment with signal-regulatory protein alpha (SIRPα)-targeting agent.
   - Other experimental therapies for AML or MDS within 14 days or at least 5 half-lives (whichever is shorter) prior to first dose of study treatment.
2. Evidence of active CNS involvement with leukemia.
3. Subjects requiring agents other than hydroxyurea to control blast counts within 14 days prior to first dose of study treatment.
4. Evidence of active bleeding or bleeding diathesis or major coagulopathy (including familial).
5. [*Only for Cohorts Including Venetoclax in the Regimen*] Subject has received strong and/or moderate CYP3A inducers within 7 days prior to the first dose of venetoclax.
6. Use of systemic corticosteroids (>10 mg daily prednisone equivalent) or other non-steroidal immunosuppressive medication, current or within 14 days of the first dose of study treatment with the following exceptions (i.e., the following are allowed within 14 days of first dose):
   - Topical, intranasal, inhaled, ocular, intraarticular corticosteroids
   - Physiological doses of replacement steroid (e.g., for adrenal insufficiency)
   - Steroid premedication for hypersensitivity reactions (e.g., reaction to IV contrast) or a brief course of treatment of non-autoimmune conditions (e.g., transfusion reactions, delayed-type hypersensitivity reaction caused by contact allergen).
7. Receipt of live attenuated vaccine within 30 days of first dose of SL-172154 treatment.
8. Subject has active, uncontrolled infection (e.g., viral, bacterial, or fungal). Subjects are eligible if infection is controlled with antibiotics, antivirals and/or antifungals.
9. [*Only for Cohorts Including Venetoclax in the Regimen*] Subject has a malabsorption syndrome or other condition that precludes enteral route of administration.
10. Subject with:

- Symptomatic peptic ulcer disease or gastritis,
- active diverticulitis, or
- other serious gastrointestinal disease associated with diarrhea within 6 months of first dose of study treatment.

11. Clinically significant or uncontrolled cardiac 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 (AV) block without a pacemaker, circulatory collapse requiring vasopressor or inotropic support, or arrhythmia not stabilized on therapy)
12. Subject has chronic respiratory disease that requires continuous oxygen, or significant history of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, hepatic, cardiovascular disease, or any other medical condition that in the opinion of the Investigator would adversely affect his/her participation in the study.
13. Subjects who have had any major surgical procedure within 14 days of first dose of study treatment.
14. Subject is a woman who is pregnant or breast feeding or planning to become pregnant or breast feed while receiving study treatment in this study.
15. Psychiatric illness/social circumstances that would limit compliance with study requirements and substantially increase the risk of AEs or compromise ability to provide informed consent.
16. Presence of another malignancy that requires active therapy and that in the opinion of the Investigator and Sponsor would interfere with the monitoring of disease assessments in this study.
17. Known hypersensitivity to any of the study medications including excipients of azacitidine.
18. Has undergone solid organ transplantation.
19. Known or active human immunodeficiency virus (HIV) infection
20. Known or active infection with hepatitis B (positive for hepatitis B surface antigen [HBsAg]) or hepatitis C virus ([HCV]; if HCV antibody (Ab) test is positive check for HCV ribonucleic acid [RNA]).

    NOTE: Hepatitis B virus (HBV): Subjects who are hepatitis B core antibody (HbcAb)-positive, but HbsAg-negative are eligible for 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 trial but are not subsequently treated in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reason, eligibility criteria, and any SAEs related to study procedure(s).

5. PHARMACEUTICAL PRODUCT INFORMATION

5.1 Investigational Product (SL-172154)

5.1.1 Investigational Product Description

Investigational product name	SL-172154
Formulation description	Solution containing SL-172154 10 mg/mL. Refer to the Study Pharmacy Manual (SPM) for further description of the drug product.
Dosage form	Supplied as frozen liquid solution in a glass vial.
Unit dose strength(s) / Dose level(s)	SL-172154 10 mg/mL Refer to Sections 3.1 and 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 aluminum seal. See the SPM for additional detail.
Route / Administration / Duration	• Delivered as IV solution via a syringe pump or IV infusion pump. See the SPM for additional details. • Duration of infusion depends on the dose. (See Table 1 and Table 2 (Section 3.1.1 and Section 3.2.1, respectively) for infusion time for each dose level. 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. • Prophylactic premedication for IRR is to be administered at least 30 minutes prior to each SL-172154 administration as follows: dexamethasone (8 mg IV), acetaminophen (650 to 1000 mg PO), diphenhydramine (25 to 50 mg, or equivalent, PO or IV), and famotidine (20 mg PO or IV or equivalent).
Dosing Instructions	Determine the number of vials needed based on the assigned dose level (in mg/kg) and the subject's weight (in kg). See the SPM for instructions on IP preparation and information on compatible administration materials. Doses of SL-172154 are to be administered as an IV infusion via an infusion or syringe pump that can ensure precision to at least 0.1 mL/min.

Secondary packaging / Quality / Label type	This is an open label study. Each vial of SL-172154 will be supplied in a single vial carton. See SPM for details.
Manufacturer / Source of procurement	Manufactured for Shattuck Labs by [redacted]

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

5.1.2 Preparation, Handling, 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 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 less than or equal to 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 Cycle 1 Day 1 weight throughout the study (mg/kg) if there is no significant change in their weight from the weight recorded at the Cycle 1 Day 1 visit. A change

in weight (i.e., increase or decrease) of the subject by 10% OR greater will require re-calculation of dose (mg/kg).

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

5.1.4 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 1.8.1. 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 3.8.2 for toxicity management recommendations). When tocilizumab is not available, consider using a drug with similar mechanism of actions such as anti-IL-6 receptor mAbs (e.g. sarilumab) or anti-IL-6 mAbs (e.g., siltuximab).

Subjects will be monitored prior to, during, and for at least 4 hours after the completion of each SL-172154 infusion. Monitoring time may be shortened to 2 hours at Cycle 4 Day 1 and beyond if no IRR or CRS was observed with the last four consecutive doses. Monitoring time after the completion of each SL-172154 infusion can be further shortened to 1 hour at Cycle 6 Day 1 and beyond if no IRR or CRS was observed with the last four consecutive doses. Vital signs will be measured as outlined in the SOA in Section 6 as needed.

Subjects who are administered azacitidine monotherapy in the control arm of Part D will be monitored according to institutional standard of procedures.

5.1.5 Treatment of SL-172154 Overdose

An overdose of SL-172154 is defined as the administration of a 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 3.8) 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 must be reported as an SAE (Section 7.6).

- 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 Azacitidine

Azacitidine 75 mg/m^2 will be administered either IV (10-40 minute infusion) or subcutaneously once daily for 7 days (Days 1 to 7 or alternative 5-2-2 schedule) in 28-day cycles (Table 7 and Table 8). Azacitidine is to be administered beginning on Day 1 of each cycle for all subjects, regardless of combination regimen cohort assignment. When SL-172154 is to be administered on the same day as azacitidine, the azacitidine administration should be completed at least 30 minutes prior to the start of the SL-172154 infusion. Refer to the country's current prescribing information of azacitidine (e.g., USPI, SmPC, or Product Monograph). for details regarding preparation, handling, administration, storage, instructions, and precautions; subjects should be premedicated with anti-emetics for nausea and vomiting.

Table 7 Azacitidine Dosing During Cycles 1 and 2

28-day Cycles	D1	D2	D3	D4	D5	D6	D7	D8	D9	D16	D23
SL-172154 dosing		X							X	X	X
Azacitidine dosing (7-day schedule)	X	X	X	X	X	X	X				
Azacitidine dosing (5-2-2 schedule)	X	X	X	X	X			X	X		

On days when both SL-172154 and azacitidine are administered, azacitidine administration should be completed at least 30 minutes prior to the start of the SL-172154 infusion.

Table 8 Azacitidine Dosing During Cycle 3 and Thereafter

28-day Cycles	D1	D2	D3	D4	D5	D6	D7	D8	D9	D16	D23
SL-172154 dosing		X								X	
Azacitidine dosing (7-day schedule)	X	X	X	X	X	X	X				
Azacitidine dosing (5-2-2 schedule)	X	X	X	X	X			X	X		

On days when both SL-172154 and azacitidine are administered, azacitidine administration should be completed at least 30 minutes prior to the start of the SL-172154 infusion.

5.3 Venetoclax

Venetoclax 400 mg will be administered orally, once daily, with food (Table 9 and Table 10). A 3-day ramp-up dosing during Cycle 1 will be performed, with the dose of venetoclax 100 mg on Day 1 and 200 mg on Day 2; on Day 3, the target dose of 400 mg will be administered and

continued until Day 28. In all subsequent 28-day cycles, the dose of venetoclax will be 400 mg daily. Subjects will self-administer venetoclax by mouth once daily. Tablets must be swallowed whole and must not be broken, chewed, or crushed. Refer to the country's current prescribing information of venetoclax (e.g., USPI, SmPC, or Product Monograph) for details regarding preparation, handling, administration, storage, instructions and precautions.

Table 9 Venetoclax Dosing During Cycles 1 and 2

28-Day Cycles	D1	D2	D3	D4	D5	D6	D7	D8	D9	D16	D23
SL-172154 dosing		X							X	X	X
Azacitidine dosing (7-day schedule)	X	X	X	X	X	X	X				
Azacitidine dosing (5-2-2 schedule)	X	X	X	X	X			X	X		
Venetoclax PO administration	3-day ramp-up[a,b]			Once daily							
	100 mg	200 mg	400 mg	400 mg							
Venetoclax PO administration when a strong CYP3A inhibitor is co-administered	4-day ramp-up[a, b]			Once daily							

On days when both SL-172154 and azacitidine are administered, azacitidine administration should be completed at least 30 minutes prior to the start of the SL-172154 infusion.

a. Chemistry tests should be drawn at predose (within 4 hours prior to dosing of venetoclax), 6 to 8 hours after each new dose during ramp-up, and 24 hours after reaching final dose.
b. Note ramp-up is only in Cycle 1.

Table 10 Venetoclax Dosing During Cycle 3 and Thereafter

28-Day Cycles	D1	D2	D3	D4	D5	D6	D7	D8	D9	D16	D23
SL-172154 dosing		X								X	
Azacitidine dosing (7-day schedule)	X	X	X	X	X	X	X				
Azacitidine dosing (5-2-2 schedule)	X	X	X	X	X			X	X		
Venetoclax PO administration	Once daily										

On days when both SL-172154 and azacitidine are administered, azacitidine administration should be completed at least 30 minutes prior to the start of the SL-172154 infusion.

5.4 Drug 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 study drug supplies received from the Sponsor, the amount of SL-172154, azacitidine or venetoclax 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 agents 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 SPM for further detailed instructions on product accountability.

When subjects self-administer venetoclax, compliance will be assessed through review of a dosing diary. The Investigator or designee should query the subject during clinic visits and document in the source documents. A record of the number of tablets dispensed to, taken and returned by each subject is to be maintained and reconciled with study treatment and compliance records. The Investigator must make every effort to bring non-compliant subjects into compliance. Treatment start and stop dates, including dates for treatment delays and/or dose modifications will be recorded in the eCRF.

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

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

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

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 by the Investigator to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the informed consent 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.
- In the SL-172154 plus azacitidine arm or azacitidine and venetoclax arm, if SL-172154 dose is held, then the next scheduled dose of azacitidine (and venetoclax) can be administered per the schedule, without any delay.
- Beginning with Cycle 2, if the start of a subsequent cycle (e.g., Day 1) is delayed due to azacitidine-related or venetoclax-related toxicities (e.g., cytopenia), SL-172154 dose

should also be delayed. Consequently, the current cycle length is extended (i.e., the cycle lasts longer than 28 days).

6.1 Schedule of Assessments: SL-172154 Monotherapy Dose Escalation Cohorts Only

Assessment[a]	Scrn[b]	Cycle 1						Cycle 2					Cycle 3 and Subsequent Cycles		Q3 Cycle	PTV[c]	SFU
		D1	D2	D3	D8	D15	D22	D1	D2	D8	D15	D22	D1	D15			
Informed Consent	X																
Eligibility Evaluation[d]	X																
Demographics	X																
Medical and Disease History	X																
Cancer treatment history	X																
TSH, free T4[e]	X																
Antiviral testing[e] (HBV/HCV)	X																
12-lead ECG[f]	X																
ECHO/MUGA[f]	X																
Type and Screen (ABO/Rh), Blood phenotyping and DAT[g]	X																
Physical Examination	X	X			X	X	X	X					X				
Vital signs[h]	X	X			X	X	X	X		X	X	X	X	X			
Pulse oximetry[h]	X	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[i1]					X[i1]				
Clinical Chemistry[e]	X	X	X		X	X	X	X	X		X		X			X	
Hematology[e]	X	X[e1]	X	X	X[e1]	X[e1]	X	X[e1]	X		X		X	X[e2]		X	
Coagulation[e] (PT, aPTT, INR, d-dimer, fibrinogen)	X					X											
Blood sample for SL-172154 PK[j]		X				X		X					X			X[j1]	X[j1]
Blood sample for ADA[j]		X				X		X					X			X[j1]	X[j1]
Blood sample for receptor occupancy[j]		X				X											
Blood sample for cytokines[k]		X	X	X				X	X								
Bone marrow aspirate/biopsy for local disease assessment[l]	X							X					X[l]		X[l]		

Assessment[a]	Scrn[b]	Cycle 1						Cycle 2					Cycle 3 and Subsequent Cycles		Q3 Cycle	PTV[c]	SFU
		D1	D2	D3	D8	D15	D22	D1	D2	D8	D15	D22	D1	D15			
Bone marrow aspirate sample[l] (send for research)	X							X					X[l]		X[l]		
Bone marrow aspirate for receptor occupancy[l]	X							X[l1]					X[l1]				
Hematologic improvement assessment for MDS subjects (every cycle beginning in Cycle 2)								X					X				
SL-172154 IV administration[m] [monotherapy cohort]		X			X	X	X	X		X	X	X	X	X			
Concomitant Medications	←---------- X ----------→															X	
Adverse Events[n]	←---------- X ----------→															X	
Transfusion Log	X	From 8 weeks (subjects with MDS) or from 4 weeks (subjects with AML) prior to first dose throughout end of treatment date														X	
Survival Contact[o] (q3 months ± 14d)																	X

Abbreviations: ADA = anti-drug antibody; aPTT = activated partial thromboplastin time; C = cycle; D = day; DAT = direct anti-globulin test; ECHO = echocardiogram; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FCBP = females of childbearing potential; HBV = hepatitis B virus; HCV = hepatitis C virus; INR = international normalized ratio; IV = intravenous; MDS = myelodysplastic syndrome; MUGA = multigated acquisition; PO = oral administration; PT = prothrombin time; PTV = Post Treatment Visit; SCRN = screening visit; SFU = Survival Follow-up; SQ = subcutaneous administration; TSH = thyroid stimulating hormone; q = every

a. **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. Laboratory tests can be performed up to 3 days prior to the scheduled dose.

b. **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 any of the study drugs. 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 SL-172154: hematology, clinical chemistry, ECOG status, and physical exam.

c. **Post Treatment visit (PTV)**: visit should occur 30 days (±7 days) from the last dose of study treatment. In addition to the assessments to be performed at the Post Treatment Visit, additional information, if available, should be collected regarding the subject. Beginning at the Post Treatment Visit and during Survival Follow-up, initiation of any subsequent anti-cancer therapy should also be reported. For subjects who proceed to HCT, HCT-relevant information should also be collected and entered in the eCRF. Should the subject be followed by another physician, the study Investigator should contact the subject's hematologist/oncologist/transplant physician to obtain this information. See Section6.14 for details.

d. **Eligibility evaluation**: Subjects must meet all eligibility criteria prior to first dose of SL-172154.

e. **Hematology/Clinical Chemistry/ Coagulation/Thyroid Function (TSH, free T4)/Antiviral Testing**: will be performed at local laboratories according to the laboratory's normal procedures. See Section 6.6.7 for a list of laboratory tests required.
   1) Additional hematology sample will be collected at 2 hrs after the end of infusion in Cycle 1 on D1, D8 and D15 and on Cycle 2 D1. Microscopic examination of peripheral blood smear per local assessment is encouraged for 2 hour-post EOI hematology samples.
   2) Hematology will be performed on Day 15 of Cycles 1, 2, 3, 4, 5 and 6 only.

f. **Cardiac Assessments**: 12-lead electrocardiogram (ECG) and an echocardiogram (ECHO) or multigated acquisition (MUGA) scan must be performed at screening to serve as a baseline for comparison in the event of a cardiac AE/SAE. ECHO/MUGA scan or ECG performed within 30 days of first dose in this study does not need to be repeated during Screening.

g. **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 and all requested information is available, this can be used for baseline assessment.

h. **Vital Signs**: Blood pressure (BP), heart rate (HR), temperature (T) and respiratory rate (RR) must be measured after the subject has been at rest (a semi-supine or sitting position) for at least 5 minutes (min). Pulse oximetry will be collected to coincide with vital sign time points noted below.
   1) **Collect vital signs/pulse oximetry during Cycle 1 on D1, D8, D15, D22**: Predose (within 30 min of starting the infusion), at the end of infusion (EOI) and then 0.5 hour [hr] (± 5 min), 2 hr (± 10 min), 4 hr (± 10 min) after the EOI for SL-172154.
   2) **Collect vital signs/pulse oximetry dosing days ≥ C2D1**: Predose (within 30 min of starting the infusion) and at the end of infusion (EOI) (± 5 min) of SL-172154.
   3) For subjects experiencing any grade IRR, vital signs should be measured after the onset of an IRR approximately every 15 minutes through the end of the infusion followed by approximately every 15 minutes for one hour after end of the SL-172154 infusion and then approximately every 30 minutes for the second hour after end of the SL-172154 infusion.

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 72 hrs of first dose of any study drug on Cycle 1 Day 1. FCBP must start using a highly effective method of contraception (i.e., <1% failure rate) at least 14 days prior to initiation of study treatment and continue use during treatment and for 30 days (which exceeds 5 half-lives) after the last dose of SL-172154.
   1) Repeat this test every 8 weeks during SL-172154 treatment (i.e., C3D1, C5D1, C7D1, etc. for every 8 weeks; C2D1, C3D1, C4D1, etc..

j. **Pharmacokinetic (PK)/anti-drug antibody (ADA)/Receptor occupancy (RO):** Blood sample collection timings for PK/ADA/RO measurement are outlined in Section 6.1.1 in supplementary Table 11. Blood volumes required will be provided in the Study Laboratory 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 subject has a positive or unknown ADA test at the Post Treatment visit, an additional blood sample should be collected for ADA and PK assessment within 45-90 days of last dose of study treatment.

k. **Cytokines**: Blood sample collection timing for cytokine assessments are outlined in Section 6.1.1 in supplementary Table 11. Blood volumes required will be provided in the SLM. Cytokines 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.

l. **Bone marrow aspirate**: See Section 8.1 for details regarding bone marrow aspirates for disease assessment during the study. See 6.10 and Table 15 for bone marrow assessment schedule for SL-172154 monotherapy for research.
   1) **Alternative dates** for C2D1, C3D1, C5D1 bone marrow aspirate are available in Table 15 (Section 6.10).

m. **SL-172154 administration**: Subjects will be monitored prior to, during, and for at least 4 hours after the completion of each SL-172154 infusion. Monitoring time may be shortened to 2 or 1 hours in later cycles. See Section 5.1.4 for details. 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 1 Day 9, 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).

n. **AE Monitoring**: 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). 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 will 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.

o. **Survival Follow-Up (SFU)**: All subjects will be contacted after discontinuing study therapy to collect survival status. Subjects should be contacted every 3 months (± 14 days) until death, withdrawal of consent, lost to follow-up or end of study. Contact may include clinic visit, telephone contact, email or mail to document survival status. Initiation of any subsequent anti-cancer therapy should also be reported. For subjects who proceed to HCT, HCT-relevant information should also be collected and entered in the eCRF. Should the subject be followed by another physician, the study Investigator should contact the subject's hematologist/oncologist/transplant physician to obtain this information. See Section 6.13 for details.

6.1.1 PK, ADA, and Cytokines Sampling Schedule (SL-172154 Monotherapy Dose Escalation Cohorts)

Table 11 PK, ADA, Blood Receptor Occupancy, and Cytokines Sampling Schedule (SL-172154 Monotherapy Cohorts)

	C1D1 / C2D1								C1D2 / C2D2	C1D3	C1D15			
Sample	Predose	EOI	0.5h post-EOI	1h post-EOI	1.5h post-EOI	2h[d] post-EOI	4h post-EOI	6h post-EOI	24h post-EOI	48h post-EOI	Predose	EOI	2h[d] post-EOI	4h post-EOI
Collection window	Within 30 min prior	±5 min	±5 min	±10 min	±10 min	±10 min	±30 min	±30 min	±30 min	±30 min	Within 30 min prior	±5 min	±10 min	±30 min
SL-172154 PK[a]	X	X	X[b]	X	X	X	X	X			X	X	X	X
ADA[a]	X										X			
Receptor occupancy (blood)	X[c]					X[c]					X[c]		X[c]	
Cytokines	X	X				X			X	X				

Abbreviations: ADA = anti-drug antibodies; C = cycle; D = day; EOI = end of SL-172154 infusion; PK = pharmacokinetics

Note: SL-172154 dose of 0.3 mg/kg requires a 30 min infusion (± 10 min), dose of 1.0 mg/kg requires a 60 min infusion (± 10 min), doses of 3.0 mg/kg or higher require a 180 min infusion (± 15 min). See Table 1.

a. Predose samples for SL-172154 PK and ADA will also be collected on C3D1 and every 3 cycles thereafter (e.g., C6D1, C9D1, etc.).
b. SL-172154 PK sample at 0.5h post-EOI is collected on C1D1 only.
c. Blood samples for receptor occupancy analysis will be collected for C1D1 and C1D15.
d. Post-SL-172154 infusion hematology sample is collected at the same time (see Schedule of assessments in 6.1).

6.2 Schedule of Assessments: SL-172154 Combination Cohorts, Dose Escalation or Dose Expansion (SL-172154 with Azacitidine or Azacitidine and Venetoclax)

Assessment[a]	Scrn[b]	Cycle 1							Cycle 2							Cycle 3 and Subsequent Cycles				Q3 Cycle	PTV[c]	SFU
		D1	D2	D3	D4	D9	D16	D23	D1	D2	D3	D4	D9	D16	D23	D1	D2	D3-D7 (or D9)	D16			
Informed Consent	X																					
Eligibility Evaluation[d]	X																					
Demographics	X																					
Medical and Disease History	X																					
Cancer treatment history	X																					
TSH, free T4[e]	X																					
Antiviral testing[e] (HBV/HCV)	X																					
12-lead ECG[f]	X																					
ECHO/MUGA[f]	X																					
Type and Screen (ABO/Rh), Blood phenotyping, DAT[g]	X																					
Physical Examination[p]	X	X				X	X	X	X							X					X	
Vital signs[h]	X		X			X	X	X		X			X	X	X		X		X			
Pulse oximetry[h]	X		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[i1]							X[i1]						
Clinical Chemistry[e]	X	X	X	X		X	X	X	X		X			X		X					X	
Hematology[e]	X	X	X[e1]	X	X	X[e1]	X[e2]	X	X	X[e1]	X	X	X	X[e2]	X	X			X[e2]		X	
Coagulation[e] (PT, aPTT, INR, d-dimer, fibrinogen)	X						X															
Blood sample for SL-172154 PK[j]			X				X			X												
Blood sample for ADA[j]			X				X			X							X				X[j1]	X[j1]

Assessment[a]	Scrn[b]	Cycle 1							Cycle 2							Cycle 3 and Subsequent Cycles				Q3 Cycle	PTV[c]	SFU
		D1	D2	D3	D4	D9	D16	D23	D1	D2	D3	D4	D9	D16	D23	D1	D2	D3-D7 (or D9)	D16			
Blood sample for receptor occupancy[j]			X				X															
Blood sample for cytokines[k]			X	X	X					X	X											
Bone marrow aspirate/biopsy for local disease assessment[l]	X									X						X[l1]	X[l2]			X[l]		
Bone marrow aspirate sample[l] (send for research)	X									X						X[l1]	X[l2]			X[l]		
Bone marrow aspirate for receptor occupancy[l]	X									X[l3]							X[l3]					
Hematologic improvement assessment for MDS subjects (every cycle beginning in C2)									X							X						
SL-172154 IV administration[m] [combination cohort]			X			X	X	X		X			X	X	X		X		X			
Azacitidine administration, IV or SQ (7 consecutive days or 5-2-2 schedule permitted)		←----------→ D1 to D7							←----------→ D1 to D7							←----------→ D1 to D7						
Venetoclax PO administration (if assigned)		←---------- Once Daily ----------→																				
Dispense venetoclax; review subject dosing diary		X							X							X						
Concomitant Medications	←---------- X ----------→																				X	
Adverse Events[n]	←---------- X ----------→																				X	
Transfusion Log	X	From 8 weeks (subjects with MDS) or from 4 weeks (subjects with AML) prior to first dose throughout end of treatment date																			X	
Survival Contact[o] (q3 months ± 14d)																						X

Abbreviations: ADA = anti-drug antibody; aPTT = activated partial thromboplastin time; C = cycle; D = day; DAT = direct anti-globulin test; ECHO = echocardiogram; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FCBP = females of childbearing potential; INR = international normalized ratio; HBV = hepatitis B virus; HCV = hepatitis C virus; IV = intravenous; MDS = myelodysplastic syndrome; MUGA = multigated acquisition; PO = oral administration; PT = prothrombin time; PTV = Post Treatment Visit; SCRN = screening visit; SFU = Survival Follow-up; SQ = subcutaneous administration; TSH = thyroid stimulating hormone; q = every

a. **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. Laboratory tests can be performed up to 3 days prior to the scheduled dose.
b. **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 any of the study drugs. 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, ECOG status, and physical exam.
c. **Post Treatment visit (PTV)**: visit should occur 30 days (± 7 days) from the last dose of study treatment. In addition to the assessments to be performed at the Post Treatment Visit, additional information, if available, should be collected regarding the subject. Beginning at the Post Treatment Visit and during Survival Follow-up. Initiation of any subsequent anti-cancer therapy should also be reported. For subjects who proceed to HCT, HCT-relevant information should also be collected and entered in the eCRF. Should the subject be followed by another physician, the study Investigator should contact the subject's hematologist/oncologist/transplant physician to obtain this information. See Section 6.13for details.
d. **Eligibility evaluation**: Subjects must meet all eligibility criteria prior to first dose of any study drug.
e. **Hematology/Clinical Chemistry/Coagulation/Thyroid Function (TSH, free T4)/Antiviral Testing**: will be performed at local laboratories according to the laboratory's normal procedures. See Section 6.6.7 for list of laboratory tests required. For subjects receiving venetoclax, chemistry tests to monitor for TLS should also be performed (calcium, inorganic phosphorus, potassium, uric acid and creatinine) on the first, second and third day of venetoclax dosing at predose (within 4 hours prior to dosing), 6 to 8 hours after each new dose during ramp-up, and 24 hours after reaching final dose. If the modified ramp-up schedule is used with strong CYP3A inhibitors, a uric acid test is required on fourth day of venetoclax dosing.
    1. Additional hematology sample will be collected at 2 hrs after the end of infusion in Cycle 1 on D2, D9 and D16 and on Cycle 2 D2. Microscopic examination of peripheral blood smear per local assessment is strongly encouraged for 2 hour-post EOI hematology samples.
    2. Hematology will be performed on Day 16 of Cycles 1, 2, 3, 4, 5 and 6 only.
f. **Cardiac Assessments**: 12-lead electrocardiogram (ECG) and an echocardiogram (ECHO) or multigated acquisition (MUGA) scan must be performed at screening to serve as a baseline for comparison in the event of a cardiac AE/SAE. ECHO/MUGA scan or ECG performed within 30 days of first dose in this study does not need to be repeated during Screening.
g. **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 and all requested information is available, this can be used for baseline assessment.
h. **Vital Signs**: Blood pressure (BP), heart rate (HR), temperature (T) and respiratory rate (RR) must be measured after the subject has been at rest (a semi-supine or sitting position) for at least 5 minutes (min). Pulse oximetry will be collected to coincide with vital sign time points noted below.
    1) **Collect vital signs/pulse oximetry during Cycle 1 on D2, D9, D16, D23:** Predose (approximately 30 min of starting the infusion), then every 15 min (±5 min) during the first hour of infusion, every 30 min (±10 min) from second hour onwards through one hour post end of SL-172154 infusion, and 2 hr (± 10 min), 4 hr (± 10 min) after the EOI for SL-172154.
    2) **Collect vital signs/pulse oximetry dosing days ≥ C2D2:** Predose (approximately 30 min of starting the infusion), then every 15 min (±5 min) during the first hour of infusion and every 30 min (±10 min) from second hour onwards through one hour post end of SL-172154 infusion.
    3) For subjects experiencing any grade IRR, vital signs should be measured after the onset of an IRR approximately every 15 minutes through the end of the infusion followed by approximately every 15 minutes for one hour after end of the SL-172154 infusion and then approximately every 30 minutes for the second hour after end of the SL-172154 infusion.
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 72 hrs of first dose of any study drug on Cycle 1 Day 1. FCBP must start using a highly effective method of contraception (i.e., <1% failure rate) at least 14 days prior to initiation of study treatment, and continue use during treatment and for 30 days (which exceeds 5 half-lives) after the last dose of SL-172154, or for the duration required by local prescribing information after the last dose of azacitidine (i.e., for sites in UK, at least 6 months after the last dose of azacitidine in either combination regimen).
    1) Repeat this test every 8 weeks during SL-172154 treatment (i.e., C3D1, C5D1, C7D1, etc. for every 8 weeks).
j. **Pharmacokinetic (PK)/anti-drug antibody (ADA)/Receptor Occupancy (RO)**: Blood sample collection timings for PK/ADA/RO measurement are outlined in Section 6.2.1 in Table 12. Blood volumes required will be provided in the 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) All subjects should have an additional blood sample collected for ADA assessment within 45-90 days of the last dose of study treatment.
k. **Cytokines**: Blood sample collection timing for cytokine assessments are outlines in Section 6.2.1 in Supplementary Table 12. Blood volumes will be provided in the SLM. Cytokines 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.

l. **Bone marrow aspirate**: See Section 8.1 for details regarding bone marrow aspirates for disease assessment during the study. See Section 6.10 and Table 16 for details of the schedule for bone marrow assessments for SL-172154 in combination with azacitidine or azacitidine + venetoclax. If a baseline bone marrow sample could not be collected, an archival bone marrow sample (if available) should also be provided. In addition, a peripheral blood sample should be collected during screening and submitted for translational or biomarker research. If a peripheral blood sample was submitted during screening, on-study peripheral blood samples should also be collected for translational or biomarker research at the time of on-study bone marrow collection (Table 16).
   1) Bone marrow aspirate on Day 1 in Cycle 8 and thereafter.
   2) Bone marrow aspirate on Day 2 in Cycle 3 and Cycle 5.
   3) **Alternative dates** for C2D2, C3D2, C5D2 bone marrow aspirate are available in Table 16 (Section 6.10).

m. **SL-172154 administration**: Subjects will be monitored prior to, during, and for at least 4 hours after the completion of each SL-172154 infusion. Monitoring time may be shortened to 2 or 1 hour in later cycles. See Section 5.1.4 for details. 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 1 Day 9, 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 2) is delayed, the current cycle length is extended (e.g., the cycle lasts longer than 28 days). On days when both SL-172154 and azacitidine study drugs are administered, azacitidine administration should be completed at least 30 minutes prior to the start of the SL-172154 infusion.

n. **AE Monitoring**: 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). Subjects will be followed continuously for AEs during the study and for 30 days after the last dose of study medications (SL-172154 and/or azacitidine or venetoclax). After a subject is discontinued from SL-172154 or study therapy due to progressive disease or for other reasons, any ongoing AE should be followed until resolution (or return to baseline) and documented in the eCRF. If another anti-cancer agent is started within 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 will 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.

o. **Survival Follow-Up (SFU)**: All subjects will be contacted after discontinuing study therapy to collect survival status. Subjects should be contacted every 3 months (± 14 days) until death, withdrawal of consent, lost to follow-up or end of study. Contact may include clinic visit, telephone contact, email or mail to document survival status. Initiation of any subsequent anti-cancer therapy should also be reported. For subjects who proceed to HCT, HCT-relevant information should also be collected and entered in the eCRF. Should the subject be followed by another physician, the study Investigator should contact the subject's hematologist/oncologist/transplant physician to obtain this information. See Section 6.13 for details.

p. **Physical Examination**: full physical exam is only required at screening and PTV, on treatment physical exams should be performed per standard of care.

6.2.1 PK, ADA, and Cytokines Sampling Schedule (SL-172154 Combination Dose Escalation or Dose Expansion Cohorts)

Table 12 PK, ADA, Blood Receptor Occupancy, and Cytokines Sampling Schedule (SL-172154 Combination Cohorts)

	C1D2 / C2D2								C1D3 / C2D3	C1D4	C1D16			
Sample	**Predose**	**EOI**	**0.5h post-EOI**	**1h post-EOI**	**1.5h post-EOI**	**2h[d] post-EOI**	**4h post-EOI**	**6h post-EOI**	**24h post-EOI**	**48h post-EOI**	**Predose**	**EOI**	**2h[d] post-EOI**	**4h post-EOI**
Collection window	Within 30 min prior	±5 min	±5 min	±10 min	±10 min	±10 min	±30 min	±30 min	±30 min	±30 min	Within 30 min prior	±5 min	±10 min	±30 min
SL-172154 PK[a]	X	X	X[b]	X	X	X	X	X			X	X	X	X
ADA[a]	X										X			
Receptor occupancy (blood)	X[c]					X[c]					X[c]		X[c]	
Cytokines	X	X				X			X	X				

Abbreviations: ADA = anti-drug antibodies; C = cycle; D = day; EOI = end of SL-172154 infusion; PK = pharmacokinetics

Note: SL-172154 dose of 0.3 mg/kg requires a 30 min infusion (± 10 min), dose of 1.0 mg/kg requires a 60 min infusion (± 10 min), doses of 3.0 mg/kg or higher require a 180 min infusion (± 15 min). See Table 2.

a. From Cycle 3 onwards, predose samples for SL-172154 ADA will also be collected on D2 of every cycle.
b. SL-172154 PK sample at 0.5h post-EOI is collected on C1D2 only.
c. Blood samples for receptor occupancy analysis will be collected for C1D2 and C1D16.
d. Post-SL-172154 infusion hematology sample is collected at the same time (see Schedule of assessments 6.2).

6.3 Schedule of Assessments: Dose Expansion Cohort Part D (SL-172154 in Combination with Azacitidine in Previously Untreated HR-MDS Subjects)

Assessment[a]	Scrn[b]	Cycle 1							Cycle 2							Cycle 3 and Subsequent Cycles				Q3 Cycle	PTV[c]	SFU
		D1	D2	D3	D4	D9	D16	D23	D1	D2	D3	D4	D9	D16	D23	D1	D2	D3-D7 (or D9)	D16			
Informed Consent	X																					
Eligibility Evaluation[d]	X																					
Demographics	X																					
Medical and Disease History	X																					
Cancer treatment history	X																					
TSH, free T4[e]	X																					
Antiviral testing[e] (HBV/HCV)	X																					
12-lead ECG[f]	X																					
ECHO/MUGA[f]	X																					
Physical Examination[o]	X	X				X	X	X	X							X					X	
Vital signs[g]	X		X			X	X	X		X			X	X	X		X		X			
Pulse oximetry[g]	X		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[h] (serum or urine; FCBP only)	X								X[h1]							X[h1]						
Clinical Chemistry[e]	X	X	X	X		X	X	X	X		X			X		X					X	
Hematology[e]	X	X	X	X	X	X	X[e1]	X	X	X	X	X	X	X[e1]	X	X			X[e1]		X	
Coagulation[e] (PT, aPTT, INR, d-dimer, fibrinogen)	X						X															
Ferritin	X																					
C-Reactive Protein	X																					
Blood sample for SL-172154 PK[i]			X	X			X			X	X											
Blood sample for ADA[i]			X				X			X							X				X[i1]	X[i1]

Assessment[a]	Scrn[b]	Cycle 1							Cycle 2							Cycle 3 and Subsequent Cycles				Q3 Cycle	PTV[c]	SFU
		D1	D2	D3	D4	D9	D16	D23	D1	D2	D3	D4	D9	D16	D23	D1	D2	D3-D7 (or D9)	D16			
Blood sample for receptor occupancy[i]			X				X															
Blood sample for complement analysis[j]			X							X												
Blood sample for cytokines[j]			X	X						X	X											
Bone marrow aspirate/biopsy for local disease assessment[k]	X															X				X		
Bone marrow aspirate sample[k] (send for research)	X															X				X		
Hematologic improvement assessment (every cycle beginning in C2)									X							X						
SL-172154 IV administration[l]			X			X	X	X		X			X	X	X		X		X			
Azacitidine administration, IV or SQ (7 consecutive days or 5-2-2 schedule permitted)		←----------→ D1 to D7							←----------→ D1 to D7							←----------→ D1 to D7						
Concomitant Medications	←---------- X ----------→																				X	
Adverse Events[m]	←---------- X ----------→																				X	
Transfusion Log	X	From 8 weeks prior to first dose throughout end of treatment date																			X	
Survival Contact[n] (q3 months ± 14d)																						X

Abbreviations: ADA = anti-drug antibody; aPTT = activated partial thromboplastin time; C = cycle; D = day; ECHO = echocardiogram; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FCBP = females of childbearing potential; INR = international normalized ratio; HBV = hepatitis B virus; HCV = hepatitis C virus; IV = intravenous; MDS = myelodysplastic syndrome; MUGA = multigated acquisition; PO = oral administration; PT = prothrombin time; PTV = Post Treatment Visit; SCRN = screening visit; SFU = Survival Follow-up; SQ = subcutaneous administration; TSH = thyroid stimulating hormone; q = every

a. **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. Laboratory tests can be performed up to 3 days prior to the scheduled dose.
b. **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 any of the study drugs. 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, ECOG status, and physical exam.
c. **Post Treatment visit (PTV)**: visit should occur 30 days (± 7 days) from the last dose of study treatment. In addition to the assessments to be performed at the Post Treatment Visit, additional information, if available, should be collected regarding the subject. Beginning at the Post Treatment Visit and during Survival Follow-up, initiation of any subsequent anti-cancer therapy should also

be reported. For subjects who proceed to HCT, HCT-relevant information should also be collected and entered in the eCRF. Should the subject be followed by another physician, the study Investigator should contact the subject's hematologist/oncologist/transplant physician to obtain this information. See Section 6.13 for details.

d. **Eligibility evaluation**: Subjects must meet all eligibility criteria prior to first dose of any study drug.
e. **Hematology/Clinical Chemistry/Coagulation/Thyroid Function (TSH, free T4)/Antiviral Testing**: will be performed at local laboratories according to the laboratory's normal procedures. See Section 6.6.7 for list of laboratory tests required.
   1. Hematology will be performed on Day 16 of Cycles 1, 2, 3, 4, 5 and 6 only.
f. **Cardiac Assessments**: 12-lead electrocardiogram (ECG) and an echocardiogram (ECHO) or multigated acquisition (MUGA) scan must be performed at screening to serve as a baseline for comparison in the event of a cardiac AE/SAE. ECHO/MUGA scan or ECG performed within 30 days of first dose in this study does not need to be repeated during Screening.
g. **Vital Signs**: Blood pressure (BP), heart rate (HR), temperature (T) and respiratory rate (RR) must be measured after the subject has been at rest (a semi-supine or sitting position) for at least 5 minutes (min). Pulse oximetry will be collected to coincide with vital sign time points noted below.
   1) **Collect vital signs/pulse oximetry during Cycle 1 on D2, D9, D16, D23:** Predose (approximately 30 min of starting the infusion), then every 15 min (±5 min) during the first hour of infusion, every 30 min (±10 min) from second hour onwards through one hour post end of SL-172154 infusion, and 2 hr (± 10 min), 4 hr (± 10 min) after the EOI for SL-172154.
   2) **Collect vital signs/pulse oximetry dosing days ≥ C2D2:** Predose (approximately 30 min of starting the infusion), then every 15 min (±5 min) during the first hour of infusion and every 30 min (±10 min) from second hour onwards through one hour post end of SL-172154 infusion.
   3) For subjects experiencing any grade IRR, vital signs should be measured after the onset of an IRR approximately every 15 minutes through the end of the infusion followed by approximately every 15 minutes for one hour after end of the SL-172154 infusion and then approximately every 30 minutes for the second hour after end of the SL-172154 infusion.
h. **Pregnancy Test**: A serum pregnancy test (beta-human chorionic gonadotropin [β-hCG]) or urine pregnancy test must be performed at screening for all FCBP within 72 hrs of first dose on Cycle 1 Day 1. FCBP must start using a highly effective method of contraception (i.e., <1% failure rate) at least 14 days prior to initiation of study treatment, and continue use during treatment and for 30 days (which exceeds 5 half-lives) after the last dose of SL-172154, or for the duration required by local prescribing information after the last dose of azacitidine (i.e., for sites in UK, at least 6 months after the last dose of azacitidine).
   1) Repeat this test every 8 weeks during SL-172154 treatment (i.e., C3D1, C5D1, C7D1, etc. for every 8 weeks).
i. **Pharmacokinetic (PK)/anti-drug antibody (ADA)/Receptor Occupancy (RO)**: Blood sample collection timings for PK/ADA/RO measurement are outlined in Section 6.3.1 in Table 13. Blood volumes required will be provided in the 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) All subjects should have an additional blood sample collected for ADA assessment within 45-90 days of the last dose of study treatment.
j. **Cytokines/Complement Analysis**: Blood sample collection timing for cytokine assessments and complement analysis are outlined in Section 6.3.1 in Supplementary Table 13. Blood volumes will be provided in the SLM. Cytokines 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.
k. **Bone marrow aspirate**: See Section 8.1 for details regarding bone marrow aspirates for disease assessment during the study. See Section 6.10 and Table 17 for details of the schedule for bone marrow assessments. If a baseline bone marrow sample could not be collected, an archival bone marrow sample (if available) should also be provided. In addition, a peripheral blood sample should be collected during screening and submitted for translational or biomarker research. If a peripheral blood sample was submitted during screening, on-study peripheral blood samples should also be collected for translational or biomarker research at the time of on-study bone marrow collection (Table 17).
l. **SL-172154 administration**: Subjects will be monitored prior to, during, and for at least 4 hours after the completion of each SL-172154 infusion. Monitoring time may be shortened to 2 or 1 hour in later cycles. See Section 5.1.4 for details. 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 1 Day 9, 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 2) is delayed, the current cycle length is extended (e.g., the cycle lasts longer than 28 days). On days when both SL-172154 and azacitidine study drugs are administered, azacitidine administration should be completed at least 30 minutes prior to the start of the SL-172154 infusion.
m. **AE Monitoring**: 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). Subjects will be followed continuously for AEs during the study and for 30 days after the last dose of study medications (SL-172154 and/or azacitidine). After a subject is discontinued from SL-172154 or study therapy due to progressive disease or for other reasons, any ongoing AE should be followed until resolution (or return to baseline) and documented in the eCRF. If another anti-cancer agent is started within 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 will 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.

n. **Survival Follow-Up (SFU)**: All subjects will be contacted after discontinuing study therapy to collect survival status. Subjects should be contacted every 3 months (± 14 days) until death, withdrawal of consent, lost to follow-up or end of study. Contact may include clinic visit, telephone contact, email or mail to document survival status. See Section 6.13 for details.
o. **Physical Examination**: full physical exam is only required at screening and PTV, on treatment physical exams should be performed per standard of care.

6.3.1 PK, ADA, Receptor Occupancy, Complement analysis and Cytokines Sampling Schedule for Dose Expansion Cohort Part D (SL-172154 in Combination with Azacitidine in Previously Untreated HR-MDS Subjects)

Table 13 PK, ADA, Receptor Occupancy, Complement analysis, and Cytokine Sampling Schedule Part D (SL-172154 in Combination with Azacitidine)

	C1D2 / C2D2									C1D16			
Sample	Predose	EOI	0.5h post-EOI	1h post-EOI	1.5h post-EOI	2h post-EOI	4h post-EOI	6h post-EOI	24h[a] post-EOI	Predose	EOI	2h post-EOI	4h post-EOI
Collection window	Prior to SL-172154 dose	±5 min	±5 min	±10 min	±10 min	±10 min	±30 min	±30 min	±60 min	Prior to SL-172154 dose	±5 min	±10 min	±30 min
SL-172154 PK[b]	X	X	X[b]	X	X	X	X	X	X	X	X	X	X
ADA[c]	X									X			
Receptor occupancy[d]	X					X			X	X		X	
Cytokines	X					X			X				
Complement Analysis	X					X		X	X				

Abbreviations: ADA = anti-drug antibodies; C = cycle; D = day; EOI = end of SL-172154 infusion; PK = pharmacokinetics
Note: SL-172154 dose of 1.0 mg/kg requires a 60 min infusion (± 10 min) and 3.0 mg/kg require a 180 min infusion (± 15 min). See Table 2

a. 24h post-EOI sample will be collected on D3 of the cycle.
b. SL-172154 PK sample at 0.5h post-EOI is collected on C1D2 only.
c. ADA samples are collected predose. From Cycle 3 onwards ADA will only be collected on D2 of every cycle.
d. Blood samples for receptor occupancy analysis will be collected for C1D2 and C1D16.

6.4 Schedule of Assessments: Dose Expansion Cohort Part D (Azacitidine Monotherapy in Previously Untreated HR-MDS Subjects)

Assessment[a]	Scrn[b]	Cycle 1					Cycle 2			Cycle 3 and Cycle 4		Cycle 5 onwards	Q3 Cycle	PTV[c]	SFU
		D1	D2	D3	D8[a1]	D15	D1	D8[a1]	D15	D1	D15	D1			
Informed	X														
Eligibility Evaluation[d]	X														
Demographics	X														
Medical and Disease History	X														
Cancer treatment history	X														
TSH, free T4[e]	X														
Antiviral testing[e] (HBV/HCV)	X														
12-lead ECG[f]	X														
ECHO/MUGA[f]	X														
Physical Examination[m]	X	X					X			X		X		X	
Vital signs[g]	X	X			X	X	X	X	X	X		X		X	
Pulse oximetry[g]	X	X			X	X	X	X	X	X		X		X	
Height (screening only) / Weight	X	X					X			X		X		X	
ECOG Performance Status	X	X				X	X		X	X		X		X	
Pregnancy test[h] (serum or urine; FCBP only)	X									X		X			
Clinical Chemistry[e]	X	X				X	X		X	X		X		X	
Hematology[e]	X	X			X	X[e1]	X	X	X[e1]	X	X[e1]	X[e1]		X	

Assessment[a]	Scrn[b]	Cycle 1					Cycle 2			Cycle 3 and Cycle 4		Cycle 5 onwards	Q3 Cycle	PTV[c]	SFU
		D1	D2	D3	D8[a1]	D15	D1	D8[a1]	D15	D1	D15	D1			
Coagulation[e] (PT, aPTT, INR, d-dimer, fibrinogen)	X														
Blood sample for immunophenotyping[i]			X	X											
Blood sample for complement analysis[i]			X	X											
Blood sample for cytokines[i]			X	X											
Bone marrow aspirate/biopsy for local disease assessment[i]	X									X[i1]		X	X		
Bone marrow aspirate/biopsy (send for research[i]	X									X[i1]		X	X		
Hematologic improvement assessment (every cycle beginning in C2)							X			X		X			
Azacitidine administration, IV or SQ (7 consecutive days or 5-2-2 schedule permitted)		←----------→ D1 to D7					←---------- → D1 to D7			←---- → D1 to D7					
Concomitant Medications	←---------- X ----------→													X	
Adverse Events[k]	←---------- X ----------→													X	
Transfusion Log	X	From 8 weeks prior to first dose throughout end of treatment date												X	
Survival Contact[l](q3 months ± 14d)															X

Abbreviations: ADA = anti-drug antibody; aPTT = activated partial thromboplastin time; C = cycle; D = day; ECHO = echocardiogram; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FCBP = females of childbearing potential; INR = international normalized ratio; HBV = hepatitis B virus; HCV = hepatitis C virus; IV = intravenous; MDS = myelodysplastic syndrome; MUGA = multigated acquisition; PO = oral administration; PT = prothrombin time; PTV = Post Treatment Visit; SCRN = screening visit; SFU = Survival Follow-up; SQ = subcutaneous administration; TSH = thyroid stimulating hormone; q = every

a) **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. Laboratory tests can be performed up to 3 days prior to the scheduled dose.
   1) Day 8 assessments can be performed within ±3 days
b) **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 the study drug. 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, ECOG status, and physical exam.
c) **Post Treatment visit (PTV):** visit should occur 30 days (± 7 days) from the last dose of study treatment. In addition to the assessments to be performed at the Post Treatment Visit, additional information, if available, should be collected regarding the subject. Beginning at the Post Treatment Visit and during Survival Follow-up, initiation of any subsequent anti-cancer therapy should also be reported. For subjects who proceed to HCT, HCT-relevant information should also be collected and entered in the eCRF. Should the subject be followed by another physician, the study Investigator should contact the subject's hematologist/oncologist/transplant physician to obtain this information. See Section 6.13 for details.
d) **Eligibility evaluation:** Subjects must meet all eligibility criteria prior to first dose of study drug.
e) **Hematology/Clinical Chemistry/Coagulation/Thyroid Function (TSH, free T4)/Antiviral Testing:** will be performed at local laboratories according to the laboratory's normal procedures. See Section 6.6.7 for list of laboratory tests required.
   1) Hematology should be performed on Day 15 of Cycles 1 through 4. If hematology assessment is performed on Day 15 of Cycle 5 or later, please provide the results.
f) **Cardiac Assessments:** 12-lead electrocardiogram (ECG) and an echocardiogram (ECHO) or multigated acquisition (MUGA) scan must be performed at screening to serve as a baseline for comparison in the event of a cardiac AE/SAE. ECHO/MUGA scan or ECG performed within 30 days of first dose in this study does not need to be repeated during Screening.
g) **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 at rest (a semi-supine or sitting position) for at least 5 minutes (min). Collect vital signs/pulse oximetry predose (approximately 30 min of administration of azacitidine).
h) **Pregnancy Test:** A serum pregnancy test (beta-human chorionic gonadotropin [β-hCG]) or urine pregnancy test must be performed at screening for all FCBP within 72 hrs of first dose of any study drug on Cycle 1 Day 1. FCBP must start using a highly effective method of contraception (i.e., <1% failure rate) at least 14 days prior to initiation of azacitidine and continue use during treatment and for the duration required by local prescribing information after the last dose of azacitidine (i.e., for sites in UK, at least 6 months after the last dose of azacitidine).
   1) Repeat this test every 8 weeks during azacitidine treatment (i.e., C3D1, C5D1, C7D1, etc. for every 8 weeks).
i) **Immunophenotying/Cytokines/Complement Analysis:** Blood sample collection timing for immunophenotying, cytokine assessments and complement analysis are outlined in Section 6.4.1 in Supplementary Table 14. Blood volumes will be provided in the SLM. Cytokines 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.
j) **Bone marrow aspirate:** See Section 8.1 for details regarding bone marrow aspirates for disease assessment during the study. See Section 6.10 for details of the schedule for bone marrow assessments for azacitidine. If a baseline bone marrow sample could not be collected, an archival bone marrow sample (if available) should also be provided. In addition, a peripheral blood sample should be collected during screening and submitted for translational or biomarker research. If a peripheral blood sample was submitted during screening, on-study peripheral blood samples should also be collected for translational or biomarker research at the time of on-study bone marrow collection Table 17.
   1) Bone marrow assessment is performed on C3D1 only.
k) **AE Monitoring:** 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). Subjects will be followed continuously for AEs during the study and for 30 days after the last dose of azacitidine. After a subject is discontinued from azacitidine 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 will 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.
l) **Survival Follow-Up (SFU):** All subjects will be contacted after discontinuing study therapy to collect survival status. Subjects should be contacted every 3 months (± 14 days) until death, withdrawal of consent, lost to follow-up or end of study. Contact may include clinic visit, telephone contact, email or mail to document survival status. Initiation of any subsequent anti-cancer

therapy should also be reported. For subjects who proceed to HCT, HCT-relevant information should also be collected and entered in the eCRF. Should the subject be followed by another physician, the study Investigator should contact the subject's hematologist/oncologist/transplant physician to obtain this information. See Section 6.13 for details.

m) **Physical Examination**: full physical exam is only required at screening and PTV, on treatment physical exams should be performed per standard of care.

6.4.1 Immunophenotying, Complement analysis and Cytokines Sampling Schedule for Dose Expansion Cohort Part D (Azacitidine Monotherapy in Previously Untreated HR-MDS Subjects)

Table 14 Immunophenotyping, Complement analysis, and Cytokine Sampling Schedule Part D (Azacitidine Monotherapy)

	C1D2		
Sample	**Predose**	**2h post-EOI**	**24h[a] post-EOI**
Collection window	Prior to azacitidine dose	±10 min	±60 min
Immunophenotyping	X	X	X
Cytokines	X	X	X
Complement Analysis	X	X	X

Abbreviations: C = cycle; D = day; EOI = end of infusion

a. 24h post-EOI sample will be collected on C1D3.

6.5 Demographics, Medical History, and Screening Assessments

6.5.1 Informed Consent

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

6.5.2 Eligibility Criteria

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

6.5.3 Subject Demographics

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

6.5.4 Medical History

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

6.5.5 Concomitant Medications

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

6.5.6 Documentation of TP53 Gene Mutation/Deletion (Applicable as Entry Criterion for AML Subjects Enrolled to Part C Dose Expansion Cohort and for HR-MDS Subjects Enrolled to Part D Dose Expansion Cohort)

Documentation of the presence of at least one TP53 gene mutation/deletion based on local evaluation is required for enrollment in Part C of the dose expansion cohort.

Results of TP53 gene mutation/deletion based on local evaluation must be available prior to randomization in Part D of the dose expansion cohort.

6.5.7 Randomization

Following review of eligibility by the Investigator and Sponsor, sites will obtain a unique randomization number from the Randomization and Trial Supply Management (RTSM) system. Any completed randomization will be treated as an irreversible event and all randomized subjects will be included in study analyses and reports. Randomization codes cannot be reused once assigned via the study randomization system.

6.6 Safety Evaluations

6.6.1 Physical Examination

A complete physical examination should be performed by a qualified physician or their designee per the schedule described in Section 6. 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) 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.

6.6.2 ECOG Performance Status

Participant's performance status will be assessed using the ECOG performance status tool (Section 16.8).

6.6.3 Pulse Oximetry

Oxygen saturation will be measured with a pulse oximeter at room air without supplementation. Refer to SOA tables for details on when to collect pulse oximetry (Section 6).

6.6.4 Vital Signs

Vital signs should be assessed in a semi-supine or sitting position at rest and will include temperature (T), systolic and diastolic blood pressure (BP), heart rate (HR), and respiratory rate (RR). BP and RR measurements should be preceded by at least 5 min of rest for the participant in a quiet setting without distractions. Refer the SOA tables for details on when to collect vital signs (Section 6).

6.6.5 Electrocardiogram

A single, screening 12-lead ECG will be obtained as outlined in the SOA using an onsite standard of care ECG machine that automatically calculates HR and measures PR, QRS, QT, and corrected 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.

6.6.6 Echocardiogram/Multigated Acquisition (MUGA) scans

A screening ECHO or MUGA scan will be obtained as outlined in the SOA to assess left ventricular ejection fraction. ECHOs or MUGA scans should be performed as clinically indicated

during the conduct of the study. Any treatment emergent abnormalities of clinical consequence should be reported as AEs.

6.6.7 Local and Central Laboratory Assessments

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

For subjects receiving venetoclax, the following additional laboratory assessments should be performed:

- Blood samples for serum chemistry tests to monitor for TLS should be drawn (calcium, inorganic phosphorus, potassium, uric acid and creatinine) on the first, second and third day of venetoclax dosing at predose (within 4 hours prior to dosing) and 6 – 8 hours post-dose during ramp-up, and 24 hours after reaching final dose. If the modified venetoclax ramp-up is used with strong CYP3A inhibitors (Section 16.7), samples should be drawn on the fourth day of venetoclax dosing.
- International normalized ratio (INR) should be monitored more frequently in subjects using warfarin concomitantly with venetoclax.

<table>
<tr><th colspan="3">Local Clinical Labs</th></tr>
<tr><th>Hematology</th><th colspan="2">Clinical Chemistry</th></tr>
<tr><td>Hemoglobin
Hematocrit
Platelet Count
Red Blood Cell Count
White Blood Cell Count</td><td>Blood urea nitrogen or Urea
Creatinine
Glucose
Sodium
Potassium
Calcium

Aspartate aminotransferase
Alkaline phosphatase
Total and direct bilirubin
Alanine aminotransferase</td><td>Magnesium
Phosphorus
Total Protein
Albumin
Lactate dehydrogenase
Bicarbonate or CO_2
Uric acid (in subjects administered venetoclax)</td></tr>
<tr><th>WBC Differential</th><th></th><th>Thyroid</th></tr>
<tr><td>Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td><td></td><td>Thyroid stimulating hormone
Free thyroxine 4</td></tr>
<tr><th>Coagulation</th><th>Serum/Urine Pregnancy Test</th><th>Antiviral Testing</th></tr>
<tr><td>Prothrombin time and International- normalized ratio
Activated partial thromboplastin time
Fibrinogen
D-Dimer</td><td>β-human chorionic gonadotropin</td><td>Hepatitis B: HbsAg / HBV core Ab
Hepatitis C: HCV Ab / HCV RNA viral load</td></tr>
<tr><td colspan="3">Other</td></tr>
<tr><td colspan="3">Ferritin and C-Reactive Protein (Screening)</td></tr>
<tr><th colspan="3">Blood Type and Screen (Except in Part D)</th></tr>
<tr><td>ABO/Rh
D, C, E</td><td>Kell, Kidd
Direct antiglobulin test (DAT)</td><td>Duffy, MNS
Antibody Screen</td></tr>
</table>

Refer to the SOA in Section 6 for the timing and frequency of central laboratory tests performed on peripheral blood samples. A separate SLM detailing the preparation, storage, and shipping requirements for these samples collected during the study will be provided.

Central Laboratory Tests on Peripheral Blood Samples[a]	
Pharmacokinetics	SL-172154 serum concentration
Immunogenicity	Anti-drug antibodies (ADA) to SL-172154
Protein analysis (serum)	Assessment of potential immune regulators such as cytokines/chemokines and complement activation proteins
Receptor occupancy	Flow cytometry-based measurement for receptor occupancy of SL-172154 on CD47 and CD40 in select subsets of peripheral blood mononuclear cells

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

Refer to the SOA in Section 6 for the timing and frequency of central laboratory tests performed on peripheral blood and bone marrow aspirates. A separate SLM detailing the preparation, storage, and shipping requirements for these samples collected during the study will be provided.

Central Laboratory Tests on Bone Marrow Aspirates[a]	
Minimal Residual Disease (MRD) Assessment (exploratory research)	Monitor MRD in subjects that attain CR/CRi/MLFS by multiparametric flow cytometry and/or NGS
Immune Profiling	Lymphoid and myeloid subsets will be evaluated for activation and function Evidence of SL-172154 localization on hematopoietic cells and/or malignant cells in the bone marrow by multiparametric flow cytometry
Receptor Occupancy (except in Part D)	Flow cytometry-based measurement for receptor occupancy of SL-172154 on CD47 and CD40 expressing cells in bone marrow mononuclear cells

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

6.6.7.1 Ad Hoc Labs for IRR or CRS AEs

Ad hoc labs should be collected as noted if IRR or CRS events occur.

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

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

a. Refer to the SLM for sample collection procedures, handling, storage and shipment instructions. PK will be measured with each corresponding ADA sample.

b. Specific biomarker, PK, ADA, and local clinical samples should be collected as soon as possible if an event of CRS or IRR occurs.

6.6.7.2 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 Section 16.3.

6.6.7.3 Blood Type and Screen (ABO/Rh) and DAT (except in Part D)

SL-172154 does bind RBCs but has not been shown to cause hemolysis in NHPs. However, treatment with SL-172154 may make phenotyping difficult due to expected coating of the RBC membrane. Thus, blood phenotyping, type and screen (ABO/Rh), and DAT should be performed at screening before exposure to SL-172154. At screening, the following testing should be performed: 1) ABO and D group (ABO/Rh) type and antibody screen and antibody identification if required; 2) DAT; 3) phenotype/genotype for, at a minimum, the minor antigens Rh C/c E/e, K, Jk, Fy and MNSs. If the subject has had transfusion within 21 days of C1D1 (e.g., Screening period) and the type/screen/DAT information is known, this information can be reported in the eCRF 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.

6.7 Pharmacokinetics

The sampling schedule for PK of SL-172154 was determined based on observed PK in the Phase 1 trial of SL-172154 monotherapy administered to subjects with ovarian cancer. The sampling schedule for PK assessment of SL-172154 is outlined in the Tables in Section 6

6.8 Anti-Drug Antibody and Neutralizing Antibody Assessment

The presence of ADA for SL-172154 will be assessed in samples collected according to the SOA (Section 6). Blood samples will also be collected for ADA/neutralizing antibody assessment within 45 to 90 days of last dose of study treatment.

6.9 Pharmacodynamic Assessments in Blood

6.9.1 Cytokine and Chemokine Analysis

Levels of serum cytokines or chemokines have been shown to increase following administration immune modulating therapies and some chemotherapy agents including azacitidine. The assessment of cytokines or chemokines production after administration of SL-172154 in combination with azacitidine or azacitidine monotherapy may provide context to AEs observed in subjects following administration of SL-172154 or azacitidine as monotherapy or SL-172154 administered in combination with azacitidine with or without venetoclax and may act as PD markers of activity. Refer to Tables in Section 6 for the schedule of the sample collection for these analyses.

6.9.2 Complement activation Analysis

The infusion-related reactions associated with the administration of immunotherapies and certain cancer drugs have been shown to involve the activation of the complement system, in a process called Complement activation-related pseudoallergy (CARPA). The concentration of the complement activation proteins (C3a, C4a, C5a, sC5b-9) may provide context to AEs in subjects following administration of SL-172154 administered with azacitidine in combination. To ascertain that complement activation is due to SL-172154 only and not because of the combination with azacitidine, samples will be collected in the azacitidine monotherapy control arm albeit in the minimum time point. Refer to Tables in 6 for the schedule of the sample collection for these analyses.

6.9.3 Receptor Occupancy and Immunophenotype

Receptor occupancy of SL-172154 on CD47 and CD40 in peripheral blood cells will be measured by multiparameter flow cytometry. This analysis will provide evidence that SL-172154 is engaging the expected targets on different cell subsets and allows receptor occupancy to be calculated and assessed across SL-172154 dosing groups. In addition, activation markers will be assessed on different immune cell subsets across all dose groups. Refer to Tables in Section 6 for the schedule of the sample collection for these analyses.

6.10 Bone Marrow Assessments

Bone marrow aspirates must be performed for all subjects for diagnostic evaluation (includes response assessment) and biomarker analysis (includes exploratory research) at designated timepoints throughout the study as outlined in Section 6 Any results for bone marrow aspirates performed in addition to those required per protocol should also be captured in the eCRF. Further details on sample collection, processing, and shipping procedures will be provided in the SLM.

A portion of the aspirate must be processed according to the institutional standard procedures for diagnostic evaluation; however, a sample of the bone marrow aspirate should also be collected for

biomarker assessments at a central laboratory at the timepoints listed below. All samples should be prepared, labeled, and shipped as outlined in the SLM.

Bone marrow for disease assessments should be performed and a sufficient bone marrow aspirate for central laboratory analysis should be collected and submitted according to Table 15, Table 16, and Table 17. If a baseline bone marrow sample could not be collected, an archival bone marrow sample (if available) should also be provided. In addition, a peripheral blood sample should be collected during screening and submitted for translational or biomarker research. If a peripheral blood sample was submitted during screening, on-study peripheral blood samples should also be collected for translational or biomarker research at the time of on-study bone marrow collection.

Table 15 Bone Marrow Assessment for SL-172154 Monotherapy

Timepoints	Visit Dates	BM Test for Disease Assessment	Submission of BM Specimens for Biomarker Analysis	Submission of BM Specimens for RO Analysis
Baseline	**Screening**	Required	Required	Required
End of Cycle 1	**C2D1** (Alternative date: C1D22, C1D23, C2D2, C2D8, C2D9)	Required	Required	Required
End of Cycle 2	**C3D1** (Alternative date: C2D22, C2D23, C3D2, C3D15, C3D16)	*Only for AML subjects with resistant disease at end of Cycle 1*	Required	Required
End of Cycle 4	**C5D1** (Alternative date: C4D15, C4D16, C5D2, C5D15, C5D16)	Required	Required	Required
End of Cycle 7	**C8D1** (±7 days)	Required	Required	Not required
End of Cycle 10*	**C11D1*** (±7 days)	Required	Required	
End of Cycle 13*	**C14D1*** (±7 days)	Required	Required	
End of Cycle 19*	**C20D1*** (±7 days)	Required	Required	
End of Cycle 25* and thereafter	**C26D1*** and Day 1 of every 6 cycles (e.g. 6 months) thereafter (±7 days)	Required	Required	
At time of relapse/progression		If clinically feasible	Not required	
When a subject discontinues study treatment as (s)he becomes eligible for and is planned to proceed to HCT.		Strongly encouraged	Required (if performed)	
Unscheduled timepoint prior to the end of Cycle 13 for subjects with AML who achieve CR, CRi, or MLFS, or for subjects with MDS who achieve CR or marrow CR		If clinically indicated,	Required (if performed)	

*In the event that a subject experiences prolonged response or stable disease beyond Cycle 7, less frequent bone marrow assessment is permitted after consultation with the Sponsor Medical Monitor.

Abbreviations: AML = acute myeloid leukemia; BM = bone marrow; C= Cycle; D = day; HCT = hematopoietic cell transplantation, C = complete remission, CRi = CR with incomplete hematologic recovery: MLFS = morphologic leukemia-free state: MDS = myelodysplastic syndrome; RO = receptor occupancy.

Table 16 Bone Marrow Assessment Schedule for SL-172154 in Combination with Azacitidine or Azacitidine and Venetoclax (Dose Escalation and Dose Expansion cohorts; Parts A, B and C)

Timepoints	Visit Dates	BM Test for Disease Assessment	Submission of BM Specimens for Biomarker Analysis	Submission of BM Specimens for RO Analysis
Baseline	**Screening**	Required	Required	Required
End of Cycle 1	**C2D2** (Alternative date: C1D23, C1D24, C2D3, C2D9, C2D10)	Required	Required	Required
End of Cycle 2	**C3D2** (Alternative date: C2D23, C2D24, C3D3, C3D16, C3D17)	*Only for AML subjects with resistant disease at end of Cycle 1*	Required	Required
End of Cycle 4	**C5D2** (Alternative date: C4D16, C4D17, C5D3, C5D16, C5D17)	Required	Required	Required
End of Cycle 7	**C8D1** (±7 days)	Required	Required	Not required
End of Cycle 10*	**C11D1*** (±7 days)	Required	Required	
End of Cycle 13*	**C14D1*** (±7 days)	Required	Required	
End of Cycle 19*	**C20D1*** (±7 days)	Required	Required	
End of Cycle 25* and thereafter	**C26D1*** and Day 1 of every 6 cycles (e.g. 6 months) thereafter (±7 days)	Required	Required	
At time of relapse/progression		If clinically feasible	Required (if performed)	
When a subject discontinues study treatment as (s)he becomes eligible for and is planned to proceed to HCT.		Strongly encouraged	Required (if performed)	
Any unscheduled timepoint		If clinically indicated,	Required (if performed)	

*In the event that a subject experiences prolonged response or stable disease beyond Cycle 7, less frequent bone marrow assessment is permitted after consultation with the Sponsor Medical Monitor.

Abbreviations: AML = acute myeloid leukemia; BM = bone marrow; C= Cycle; D = day; HCT = hematopoietic cell transplantation, C = complete remission, CRi = CR with incomplete hematologic recovery: MLFS = morphologic leukemia-free state: MDS = myelodysplastic syndrome; RO = receptor occupancy

Table 17 Bone Marrow Assessment Schedule for SL-172154 in Combination with Azacitidine or Azacitidine Monotherapy Treatment (Dose Expansion cohort Part D)

Timepoints	Visit Dates	BM Test for Disease Assessment	Submission of BM Specimens for Biomarker Analysis
Baseline	**Screening**	Required	Required
End of Cycle 2	**C3D1** (±7 days)	Required	Required
End of Cycle 4	**C5D1** (±7 days)	Required	Required
End of Cycle 7	**C8D1** (±7 days)	Required	Required
End of Cycle 10*	**C11D1*** (±14 days)	Required	Required
End of Cycle 13*	**C14D1*** (±14 days)	Required	Required
End of Cycle 19*	**C20D1*** (±14 days)	Required	Required
End of Cycle 25* and thereafter	**C26D1*** and Day 1 of every 6 cycles (e.g. 6 months) thereafter (±14 days)	Required	Required
At time of relapse/progression		If clinically feasible	Required (if performed)
When a subject discontinues study treatment as (s)he becomes eligible for and is planned to proceed to HCT.		Strongly encouraged	Required (if performed)
Any unscheduled timepoint		If clinically indicated,	Required (if performed)

*In the event that a subject experiences prolonged response or stable disease beyond Cycle 7, less frequent bone marrow assessment is permitted after consultation with the Sponsor Medical Monitor.

BM = bone marrow; C= Cycle; D = day; HCT = hematopoietic cell transplantation,: MDS = myelodysplastic syndrome

6.10.1 Bone Marrow Aspirate Sample for Disease Assessment (Local Laboratory)

Response assessment as determined by the leukemic blast percentage should be performed locally per institution standard practice.

At Screening, cytogenetic (chromosomal) analysis by karyotyping and fluorescent *in situ* hybridization (FISH) should be performed from the diagnostic bone marrow aspirate per institution standard practice for treatment-naïve subjects; relapsed/refractory subjects will have cytogenetic analysis repeated during the Screening period. Historic cytogenetic data will be accepted if done within 30 days prior to the first dose of study treatment. A de-identified copy of these results at baseline will be provided to the Sponsor. A de-identified copy of local assessment of bone marrow after study drug treatment was initiated may be provided to the Sponsor if requested.

Documentation of TP53 gene mutation/deletion by local testing will serve as entry criterion for subject with previously untreated MDS with TP53m enrolled in the Dose Escalation Cohort of SL-172154 administered with azacitidine and for subjects with AML enrolled in Part C Cohort of dose expansion.

6.10.2 Bone Marrow Aspirate Sample (Central Laboratory)

6.10.2.1 Bone Marrow Aspirate for MRD Assessment by Flow Cytometry

Multiparameter flow cytometry (MFC), for detecting leukemia-associated immunophenotypes (LAIPs) is the current standard method for MRD assessment. The CD markers in line with the consensus recommendations from European Leukemia Network AML working party [Schuurhuis, 2018] will be selected for MFC. This is an exploratory analysis and would not be used to guide treatment decisions.

6.10.2.2 Bone Marrow Aspirate for Molecular Genetic Profiling

Molecular profiling may be performed to assess genetic aberrations in the bone marrow aspirate collected at Screening and during disease assessment from subjects with AML or MDS. These molecular genetic markers may be the basis for MRD evaluation in subjects with AML who achieve CR/CRi/MLFS or subjects with MDS who achieve CR/marrow CR. In addition, a peripheral blood sample may also be collected at the same timepoints for similar molecular profiling of genetic aberrations. These are exploratory analyses and would not be used to guide treatment decisions.

6.10.2.3 Bone Marrow Aspirates for Receptor Occupancy Analyses (Dose Escalation and Dose Expansion cohorts; Parts A, B and C)

Receptor occupancy of SL-172154 on CD47 and CD40 on bone marrow cells will be measured by flow cytometry, using bone marrow aspirate specimens collected in the SL-172154 monotherapy cohorts, on Cycle 2 Day 1, Cycle 3 Day 1 (if a bone marrow aspirate is required), and Cycle 5 Day 1, and in the combination cohorts, on Cycle 2 Day 2, Cycle 3 Day 2 (if a bone marrow aspirate is required), and Cycle 5 Day 2.

If this timepoint designated above is not feasible, make every effort to perform a bone marrow aspirate within 24 hours from the completion of a SL-172154 dose (as an example for SL-172154 monotherapy, the bone marrow aspirate should be performed on Cycle 2 Day 2 within 24 hours after the SL-172154 dose was completed on Cycle 2 Day 1; as an example for the combination therapy, the bone marrow aspirate should be performed on Cycle 2 Day 3 within 24 hours after SL-172154 dose was completed on Cycle 2 Day 2).

Alternatively, a bone marrow aspirate can be performed on the day of a prior dose (e.g., Cycle 1 Day 22 for monotherapy; Cycle 1 Day 23 for combination therapy) or on the day of a subsequent dose (e.g., Cycle 2 Day 8 for monotherapy; Cycle 2 Day 9 for combination therapy); in these cases, the bone marrow aspirate must be performed after completion of that day's SL-172154 infusion.

If this is still not feasible, make every effort to perform bone marrow aspirate within 24 hours from the completion of a SL-172154 dose (as an example for SL-172154 monotherapy, bone marrow aspirate should be performed on Cycle 1 Day 23 within 24 hours after SL-172154 dose was completed on Cycle 1 Day 22; as an example for the combination therapy, bone marrow aspirate should will be performed on Cycle 1 Day 24 within 24 hours after from the completion of when SL-172154 dose was completed on Cycle 1 Day 23).

6.10.2.4 Bone Marrow Aspirate for Translational or Biomarker Research

Translational or biomarker research may be performed on bone marrow aspirates collected on-study to better understand AML and MDS, and mechanism of action of and response to SL-172154 (monotherapy or in combination regimen).

These analyses include but are not limited to cytogenetics and molecular genetic testing, immune profiling, and MRD status assessment. Comparative examination of pre-dosing profiles of participants may uncover known or novel candidate biomarkers/profiles which could be used to predict response to treatment with SL-172154 or provide new insights into AML/MDS and medically related conditions. Comparative examination of post-dosing profiles in conjunction with pre-dosing profiles may yield known and novel candidate biomarkers/profiles and new insights which relate to the action of SL-172154. Performance of these investigations may be conditional on the results of the clinical trial principally, but not exclusively, on the primary measures of the clinical trial outcome, and samples may be selected for analysis on the basis of the clinical outcome. Unless stated otherwise, these investigations may be performed irrespective of whether a response to SL-172154 (monotherapy or in combination regimen) is observed.

6.11 Transformation to Acute Myeloid Leukemia (Only for MDS Subjects)

Transformation to AML will be monitored in subjects who enter the study with a diagnosis of MDS, and will be included as part of the safety assessment throughout the course of the study. Transformation to AML should be reported if documented at any time from signing of ICF through death, lost to follow-up, withdrawal of consent for further data collection, or study closure (whichever is later), whether or not it is thought to be related to treatment with study drugs. Documentation supporting the diagnosis of transformation to AML (e.g., confirmatory histology or cytology results) should be collected and documented on the appropriate eCRFs. MDS subjects with transformation to AML will discontinue study treatment on this trial and enter the follow-up part of the study; any subsequent anti-cancer therapy initiated for these subjects should be collected in the eCRF.

6.12 Transfusion Assessment

The following should be recorded for all transfusions the subject received within 4 weeks (subjects with AML) or 8 weeks (subjects with MDS) prior to first dose of study treatment, during study treatment, and until 30 days after the last dose of study treatment or at the time of the Post Treatment Visit, whichever occurs later:

- Type of blood product transfusion (e.g., RBC or platelets)
- Number of units
- Reason for transfusion
- Date of transfusion
- Hemoglobin value for which each RBC transfusion is given
- Platelet value for which each platelet transfusion is given

RBC transfusions administered for surgical procedures, significant hemorrhagic events, or other reasons documented as unrelated to disease-associated anemia will not be counted in the assessment of baseline transfusion burden, efficacy, or progressive disease status.

6.13 Information Collected at Post Treatment Visit and During Survival Follow-Up Period

In addition to the assessments noted in the Schedule of Assessment table (Section 6) to be performed at the Post Treatment Visit (PTV), additional information should be collected regarding the subject. Beginning at the PTV and during Survival Follow-up, the start date and agent name of subsequent anticancer therapy(ies) for AML or MDS will be collected and entered in the eCRF. The PTV should occur 30 days (±7 days) from the last dose of study treatment. If the PTV occurs earlier than 30 days after the last dose of study treatment, safety information up to 30 days after the last dose of study treatment will be collected during Survival Follow-up. In addition, for subjects that proceed to HCT, HCT-relevant information (e.g., type of transplant, GVHD and transplant-related complications) may also be collected and entered in the eCRF. Should the subject be followed by another physician, the study Investigator should contact the subject's hematologist/oncologist/transplant physician to obtain this information.

6.14 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 adverse events (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. 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 each of the study drugs (SL-172154, azacitidine, or venetoclax). 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 Post Treatment Visit, 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 adverse events.

7.1 Definitions for Safety Parameters

Event	Definition
Adverse Event (AE)	The AE observation period starts at the time of signing informed consent and includes baseline or washout periods, even if no study treatment has been administered. An AE is defined as any untoward medical occurrence in a subject to whom the IP has been administered, regardless of whether the event is considered related to that product. An AE is also defined as an undesirable medical condition due to a study-related procedure.
Adverse Reaction (AR)	AR is an untoward and unintended response in a subject to an IP. A causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	An AE or suspected AR that is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes: • Death (Note: death is an outcome not an event) • A life-threatening AE (an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe) • Inpatient hospitalization or prolongation of existing hospitalization • A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions • A congenital anomaly/birth defect. • Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
Laboratory test(s) that meet definition of an AE or SAE	• Any laboratory test result that meets the definition of an AE or SAE or requires holding or discontinuation of IP or requires corrective therapy, must be documented appropriately. • Ad hoc labs should be collected as noted in Section 6.6.7.16.7.7.1 above 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 documents. Clinically significant abnormal laboratory findings are those which are not associated

Event	Definition
	with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. All laboratory tests with clinically significant abnormal values during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator. If such values do not return to normal/baseline within a period judged reasonable by the Investigator, the etiology should be identified, and the results must be 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. Product reference safety information is contained in the current Guidance for Investigators in Section 6.0 of the Investigator's Brochure provided to the Investigator by the Sponsor.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	Suspected Adverse Reaction (causality related AE) that is serious and unexpected.

7.1.1 Events Not Qualifying as AE or SAE

The following are not considered to be AEs or SAEs:

- Medical or surgical procedures (e.g., endoscopy, appendectomy). The condition that leads to the procedure is considered the AE.
- Elective procedures, planned hospitalizations, and procedures for treatment of conditions noted in the subject's medical history (present prior to signing the ICF) that have not worsened are not considered AEs.
- Situations where an untoward medical occurrence did not occur (i.e., admission to hospital for social circumstances).
- Anticipated day-to-day fluctuations of pre-existing medical conditions that were present at start of study. These conditions are considered part of the subject's medical history and must be adequately documented on the appropriate page of the CRF.
- Clear progression of disease under study should not be reported as an AE or SAE (unless the Investigator considers the progression of underlying neoplasia to be atypical in its nature, presentation or severity from the normal course of the disease in a particular subject). Signs and symptoms that are clearly consistent with the expected progression of the underlying cancer should not be reported as an adverse event, and hospitalizations due

to the progression of cancer do not necessarily qualify for an SAE. 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 participant 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 CRF, and the diagnosis will be clearly described.
- Laboratory abnormalities: An isolated, out-of-range laboratory result in the absence of any associated, clinical finding may or may not be considered an AE. The Investigator's evaluation should be based on a consideration of the overall clinical context.

7.1.2 Adverse Events Commonly Associated with AML or MDS Study Population and/or Progression of Disease

Certain AEs are anticipated to occur in the study population (AML or higher-risk MDS) at some frequency independent of drug exposure. These are discussed as AEs commonly associated with the disease or progression of disease. Such events include known consequences of the underlying disease under investigation (e.g., symptoms, disease progression).

Cytopenias (anemia, neutropenia, or thrombocytopenia) are part of the natural history of AML and MDS. Persistent cytopenias at the same CTCAE grade as at baseline are not to be reported as adverse events, unless they fulfill a seriousness criteria, result in permanent discontinuation of a study drug, or the Investigator had an identifiable cause other than the underlying disease. Any clinically relevant abnormal laboratory assessment between screening and prior to administration of the first dose of study treatment will be recorded in the subject's medical history.

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 study treatment (SL-172154, azacitidine, or venetoclax) assessed. In a clinical trial, the IP must always be suspect. To help assess causality, the following guidelines are used.

- **Related** – There is reasonable causal relationship between the study drug 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 study drug and the AE. Information on whether the event responds to interruption of study drug and/or re-challenge is lacking or unclear.
- **Unlikely Related** – There is a temporal relationship to study drug administration, but there is not a reasonable causal relationship between the study drug and the AE (i.e., the AE is doubtfully related to study drug).
- **Not Related** – There is not a temporal relationship to study drug administration (e.g., too early, too late, or study drug 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 the Guidance for Investigators, Section 6 of the current SL-172154 IB. "Unexpected," as used in this definition, also refers to AEs or Ars that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug not specifically mentioned as occurring with the IP under investigation.
- **Expected** – AEs that are common and known to occur for the IP being studied. Expectedness refers to the awareness of AEs previously observed, not on what might be anticipated from the properties of the IP.

7.3 Timing for Event Assessment and Follow-Up

All AEs occurring while on-study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution. The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review of source documents 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 Procedure
Adverse Event	Subjects will be followed continuously for AEs during the study and for 30 days after the last dose of IP. After a subject is discontinued from IP due to progressive disease or for other reasons, any ongoing AE should be followed until resolution (or return to baseline) and documented in the eCRF, regardless of whether the event(s) is attributed to trial medication. If another anti-cancer agent is started within 30 days of the last dose of SL-172154, only SAEs and AEs that occur before the new anticancer therapy should be recorded. The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to trial medication, and action taken. Follow-up information should be provided, as necessary. AEs will be followed either until resolution, or the event is considered stable. It will be left to the Investigator's clinical judgment to decide if an AE is of sufficient severity to require the subject's removal from treatment. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the subject must undergo an end of treatment assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.
Serious Adverse Event	An SAE Form should be completed 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** Email: [redacted] eFax number: [redacted]

7.5 Reporting of Pregnancy

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

A FCBP must discontinue 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 an SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the Investigator's attention after the subject has discontinued study treatment must be promptly reported to the Sponsor.

7.6 Reporting of Overdose, Misuse of IP, or Suspected Transmission of Infectious Agent

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

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

7.7 Study Halting Rules

Administration of IP will be halted if a fatal SAE 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, etc.) of the temporary halt and the disposition of the study.

7.8 Safety Oversight

An SMC will be implemented in this study and will consist of Investigators and Sponsor representatives. SMC meetings will be conducted monthly (or more frequently if required) during dose escalation and approximately every 2 months during dose expansion to review and discuss safety data and communicate results of ongoing analyses during dose escalation and dose expansion provided subjects have been enrolled and data are available to be reviewed. The SMC will operate in accordance with the SMC charter which will define roles and accountabilities and the process for safety review. Throughout the conduct of the study, safety data will be reviewed by the Sponsor for each subject on an ongoing basis. Additionally, periodic safety reviews will be undertaken by the SMC as defined in the SMC charter. As dose escalation proceeds, the SMC will consider data from Study SL03-OHD-104 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 pharmacokinetic data from Study SL03-OHD-101 will be shared with the SMC for SL03-OHD-104. 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. 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. EFFICACY ASSESSMENTS

Disease evaluations will include bone marrow examinations, MRD assessment, hematologic parameters (e.g., hemoglobin, ANC, platelet counts), and physical examination of extramedullary disease of AML. Survival status will also be collected.

All efficacy assessments must be performed until relapse/progression, discontinuation of study treatment for a subsequent HCT, or withdrawal of consent, even if the subject is discontinued from study therapy. If a subject discontinues study treatment for reasons other than relapse/progression, disease assessments should continue until disease relapse/progression or the initiation of a subsequent AML or MDS anti-cancer therapy. Disease assessment will be performed as outlined in the Schedule of Assessments (Section 6).

8.1 Bone Marrow Aspirate for Disease Assessment

Bone marrow aspirates must be performed at screening for all subjects. The bone marrow aspirate during screening should be performed after all other eligibility criteria have been met. Refer to Section 6.1 and Section 6.2 for the schedule of additional bone marrow aspirates obtained during the study.

A sufficient bone marrow aspirate must be collected for clinical disease assessment and biomarker assessments. Bone marrow aspirate samples must be collected for all subjects. If a bone marrow aspirate sample is not evaluable, another aspirate sample should be performed within 7 days. Any results for bone marrow assessments performed as standard of care throughout the study should also be captured in the eCRF. A portion of bone marrow aspirate performed for disease assessment at selected timepoints (see Section 6.10) will be sent to a central lab for exploratory research outcome measures.

8.1.1 AML Response Criteria

Response will be evaluated based on guidelines by the 2017 ELN Response Criteria in AML [Dohner, 2017]. Subject's response is based on the most recent bone marrow results and recent hematology values. Hematology values for up to 2 weeks from the bone marrow evaluation can be used to determine the response. As a significant number of subjects in this study might have antecedent hematologic illness, hematologic response including transfusion independence will also be evaluated.

All subjects who completed at least one cycle of study treatment will be assessed by the Investigators using the 2017 ELN Response Criteria for AML as described below. Assessments

will be performed for response assessment as described in Section 6.10.1. Additionally, for subjects with cytogenetic abnormalities at the baseline bone marrow test, cytogenetic CR should be reported per 2003 IWG AML response criteria [Cheson, 2003] when the result is available for subjects with CR. Cytogenetic CR is defined as reversion to a normal karyotype at CR.

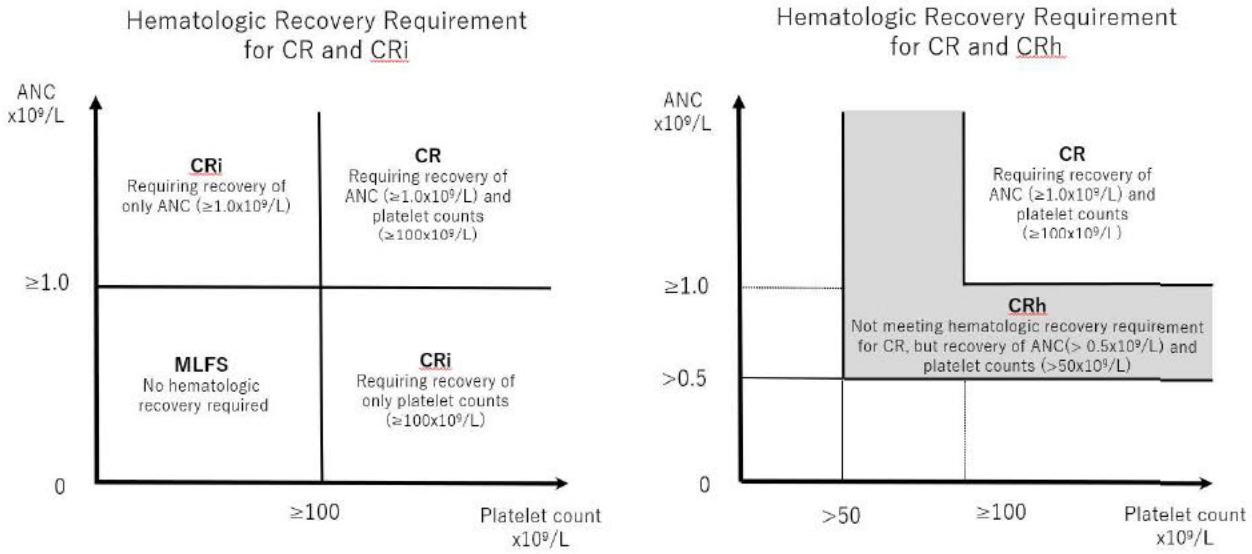
Category	ELN Response Criteria
CR without minimal residual disease (CR_{MRD-})	If studied pretreatment, CR with negativity for a genetic marker by RT-qPCR or NGS, or CR with negativity by MFC
Complete Remission (CR)	• Bone marrow blasts <5% • Absence of circulating blasts and blasts with Auer rods • Absence of extramedullary disease • ANC ≥1.0 x 10^9/L • Platelet count ≥100 x 10^9/L
CR with incomplete hematologic recovery (CRi)	All CR criteria except for residual neutropenia (<1.0 x 10^9/L) or thrombocytopenia (<100 x 10^9/L)
Morphologic leukemia-free state (MLFS)	• Bone marrow blasts <5% • Absence of circulating blasts and blasts with Auer rods • Absence of extramedullary disease • No hematologic recovery required
Partial remission (PR)	• All hematologic criteria of CR • Decrease of bone marrow blast percentage to 5% to 25%, AND • Decrease of pretreatment bone marrow blast percentage by at least 50%
Stable disease (SD)	• Absence of CR_{MRD-}, CR, CRi, PR, MLFS, AND • Progressive disease criteria not met
Progressive Disease	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: • >50% increase in marrow blasts over baseline (minimum 15% point increase is required in cases with <30% blasts at baseline); or persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in ANC to an absolute level (>0.5 x 10^9/L and/or platelet count to >50 x 10^9/L untransfused) **OR** • >50% increase in peripheral blasts (WBC x %blasts) to >25 x 10^9/L (in absence of differentiation syndrome) **OR** • New extramedullary disease

Hematologic relapse (after CR_{MRD-}, CR, CRi)	Bone marrow blasts ≥5%, or reappearance of blasts in the blood, or development of extramedullary disease
Molecular relapse (after CR_{MRD-})	If studied pretreatment, reoccurrence of MRD as assessed by RT-qPCR, NGS, or by MFC.

For subjects who achieve CR, locally assessed MRD status will be reported as MRD-negative or MRD-positive if performed at the investigational site. MRD-negative is defined as the best MRD value which is less than 10^{-3} residual blasts per leukocytes as measured in the bone marrow.

Additionally, CRh (complete remission with partial hematologic recovery) will be evaluated separately from the ELN response criteria. CRh is defined as all CR criteria except for partial hematological recovery of peripheral blood counts (e.g., platelets >50 x 10^9/L and ANC >0.5 x 10^9/L), as described in Figure 5.

Figure 5 Hematologic Recovery Requirements for CR, CRh, and CRi



Abbreviations: ANC: absolute neutrophil count; CR: complete remission; Cri: complete remission with incomplete hematologic recovery; MLFS: morphologic leukemia-free state; CRh: complete remission with partial hematologic recovery.

To determine transfusion dependence or independence, RBC transfusion history should be collected for 4 weeks prior to initiating study treatment for AML subjects regardless of hemoglobin level.

8.1.2 MDS Response Criteria

Response for subjects with MDS will be evaluated based on guidelines by the IWG 2006 MDS response criteria [Cheson, 2006]. Subject's response is based on the most recent bone marrow results and recent hematology values. Hematology values for up to 2 weeks from the bone marrow evaluation can be used to determine the IWG response. As a significant number of subjects in this

study might have antecedent hematologic illness, hematologic response including transfusion independence will also be evaluated.

To determine transfusion burden at baseline, RBC transfusion history should be collected for 8 weeks prior to initiating study treatment. Only RBC transfusions administered for a mean hemoglobin level below 9 g/dL are to be considered for the determination of transfusion dependence or independence at baseline; transfusions for intercurrent disease (e.g., bleeding, surgical procedure, etc.) should not be considered.

All subjects who completed at least one cycle of study treatment will be assessed by the Investigators using the IWG 2006 MDS response criteria as described below. Bone marrow assessments should be performed to assess disease response as described in Section 6.10.

Category	IWG Response criteria (response must last at least 4 weeks)
Complete Remission (CR)	Requires all of the following maintained for a minimum of four weeks. When reporting the CR achievement date, report the first date when CR was achieved (not the four week date in which CR was maintained). Bone marrow evaluation: ≤ 5% myeloblasts with normal maturation of all cell lines Peripheral blood evaluation: • Hemoglobin ≥ 11 g/dL untransfused without erythropoietic support • ANC ≥ 1.0 x 10^9/L without myeloid growth factor support • Platelets ≥ 100 x 10^9/L without thrombopoietic support • 0% blasts in blood
PR	All CR criteria if abnormal before treatment except: • Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5% • Cellularity and morphology not relevant
Marrow CR	• Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment • Peripheral blood: if hematologic improvement (HI) responses, they will be noted in addition to marrow CR
SD	• Failure to achieve at least PR, but no evidence of progression for > 8 weeks
Relapse after CR or PR	At least 1 of the following: • Return to pretreatment bone marrow blast percentage • Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets • Reduction in (hemoglobin) Hgb concentration by ≥1.5 g/dL or transfusion dependence
Cytogenetic CR	• Disappearance of the chromosomal abnormality without appearance of new ones in subjects who achieve CR
Disease Progression	For Subjects with: • Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts • 5% - 10% blasts: ≥ 50% increase to > 10% blasts • 10% - 20% blasts ≥ 50% increase to > 20% blasts

	And any of the following: • At least 50% decrement from maximum remission/response in granulocytes or platelets • Reduction in Hgb by ≥ 2 g/dL • Transfusion dependence

Response assessment for HI will be performed at each cycle beginning in Cycle 2 regardless of whether a bone marrow test is performed. HI will be assessed according to the IWG 2006 MDS criteria. Responses must last at least 8 weeks. The transfusion policy for the individual subject prior to therapy should be maintained on treatment if not otherwise clinically indicated. A maximum variation between pre- and on-study practice of 1 g/dL (or 0.6 mmol/L) in terms of transfusion threshold is recommended.

Hematologic Improvement[a]	IWG 2006 Response Criteria (response must last at least 8 weeks)
Erythroid response (pretreatment, <11g/dL)	• Hgb increase of ≥1.5 g/dL • Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk. Only RBC transfusions given for a Hgb of ≤9.0 g/dL pretreatment will count in the RBC transfusion response evaluation
Platelet response (pretreatment, <100 x 10^9/L)	• Absolute increase of ≥30 x 10^9/L for subjects starting with >20 x 10^9/L platelets • Increase from <20 x 10^9/L to >20 x 10^9/L and by at least 100%
Neutrophil response (pretreatment, <1.0 x 10^9/L)	• At least 100% increase and an absolute increase of >0.5 x 10^9/L
Progression or relapse after HI[b]	At least 1 of the following: • At least 50% decrement from maximum response levels in granulocytes or platelets • Reduction in hemoglobin by ≥ 1.5 g/dL • Transfusion dependence

Abbreviations: Hgb = hemoglobin; RBC = red blood cell; HI = hematologic improvement.

a. Pretreatment counts should be the averages of at least 2 measurements (not influenced by transfusions, i.e., no RBC transfusions for 2 weeks and no platelet transfusions for 1 week) at least 1 week apart. If the Screening result is less than 7 days prior to Cycle 1 Day 1, an historical result reported ≥7 days prior to Cycle 1 Day 1 should be reported.

b. In the absence of another explanation, such as acute infection, repeated courses of chemotherapy, gastrointestinal bleeding, hemolysis, etc. It is recommended that the 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

9. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

9.1 Study Design and Sample Size Determination

9.1.1 Dose Escalation Cohorts and Safety Run-In Cohort

The monotherapy and combination dose escalation will utilize an mTPI-2 design [Guo, 2017] with the target DLT rate of 20% for the maximum tolerated dose. For SL-172154, azacitidine and venetoclax combination safety run-in, the number of DLTs will be evaluated based on the same mTPI-2 design. The DLT-evaluable population is defined in Section 9.2.1.

The mTPI-2 design employs a simple Beta-Binomial Bayesian model with decision rules based on the unit probability mass from the posterior probability of DLT rate. With the target DLT rate of 20%, 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 (0.15, 0.25) is to stay at the current dose, subintervals below 0.15 is to escalate to next higher dose, and subintervals above 0.25 is to de-escalate to the next lower dose. Subjects will be enrolled in cohorts of approximately 5 subjects during the dose escalation. After each cohort of approximately 5

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 20%. The maximum number of subjects evaluated for DLT for each dose level will be 15 subjects (about 3 cohorts of 5 subjects) if the dose escalation decision is to stay at the current dose from the first 2 cohorts. Based on the above design, the dose escalation decision rules for each dose level are:

- Dose escalate if the observed DLT rate <14%;
- Stay at the current dose if the observed DLT rate between 14%-24%;
- Dose de-escalate if the observed DLT rate ≥25%

See Table 18 for dose escalation decision rules based on the total number of subjects evaluable for DLT and the number of subjects with DLT observed. The operating characteristics of the mTPI-2 design based on 10,000 simulations are in Table 19.

Table 18 Dose Escalation Decision Rules for Each Dose Level Based on mTPI-2

Number of subjects with DLTs	Number of DLT-Evaluable Subjects												
	3	4	5	6	7	8	9	10	11	12	13	14	15
0	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	D	S	S	S	E	E	E	E	E	E	E	E
2	DU	D	D	D	D	D	S	S	S	S	S	S	E
3	DU	DU	DU	DU	D	D	D	D	D	D	S	S	S
4	.	DU	DU	DU	DU	DU	DU	D	D	D	D	D	D
5	.	.	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D
6	.	.	.	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
7	.	.	.	.	DU	DU	DU	DU	DU	DU	DU	DU	DU
8	.	.	.	.	.	DU	DU	DU	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., 2 subjects experience DLT before the third subject enrolls.

Table 19 Operating Characteristics of mTPI-2 Design Based on 10000 Simulations

	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Number of Patients	% Early Stopping
Scenario1							
True DLT rate	0.2	0.35	0.43	0.48	0.54		
Selection %	76.32	12.23	0.96	0.13	0		10.36
# Pts treated	14	5.57	0.65	0.04	0	20.3	
Scenario2							
True DLT rate	0.07	0.2	0.35	0.46	0.57		
Selection %	23.78	59.72	15.07	1.07	0.03		0.33
# Pts treated	10.34	12.19	4.38	0.44	0.01	27.4	
Scenario3							
True DLT rate	0.01	0.04	0.08	0.2	0.35		
Selection %	0.08	2.48	31.41	53.52	12.51		0
# Pts treated	5.36	6.56	8.55	7.34	2.01	29.8	
Scenario4							
True DLT rate	0.05	0.1	0.2	0.4	0.55		
Selection %	4.2	29.52	56.36	9.54	0.26		0.12
# Pts treated	7.18	9.95	8.94	2.6	0.13	28.8	

9.1.2 Dose Expansion

For Part A dose expansion cohort, the goal is to enroll approximately 20 previously untreated HR-MDS subjects treated at the potential RP2D in dose escalation and dose expansion. For Part B dose expansion cohort, the goal is to enroll approximately 20 previously untreated AML subjects treated at the potential RP2D in dose expansion or safety run-in. For the Part C dose expansion cohort, the goal is to enroll approximately 20 subjects with TP53 mutated or deleted AML treated at the potential RP2D of SL-172154 and azacitidine in dose expansion. The sample size of 20 is primarily chosen to obtain a preliminary assessment of the anti-tumor activity with a certain degree of precision. Table 20 provides the 90% confidence interval (CI) based on exact probability method for a range of possible responses out of 20 subjects.

Table 20 Response Rate and 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 Part D dose expansion cohort, 60 previously untreated subjects with higher-risk (intermediate, high, or very high per IPSS-R) MDS will be randomized 1:1:1 to three arms: 3.0 mg/kg of SL-172154 in combination with azacitidine (n=20), 1.0 mg/kg of SL-172154 in combination with azacitidine (n=20), or azacitidine monotherapy (n=20). Subjects will be stratified based on TP53 mutation status and baseline bone marrow blast (<5% vs ≥5%) to have similar distribution for these 2 stratification factors across treatment arms. The sample size calculation was performed using nQuery version 9.3.1. A sample size of 20 in each arm provides 71% power to detect difference in CR rate between SL-172154 in combination with azacitidine (either 3mg/kg or 1mg/kg) and azacitidine monotherapy based on the following assumptions:

- CR is 22% for azacitidine monotherapy
- CR rate is 55% for SL-172154 in combination with azacitidine (either SL-172154 3.0 mg/kg or 1.0 mg/kg)
- One-sided type one error is 0.1

Each dose expansion cohort will allow further characterization of the safety profile of SL-172154 in combination with azacitidine or azacitidine and venetoclax, with particular emphasis on toxicities leading to discontinuation of SL-172154 and the combination agents, SAEs and Grade ≥3 AEs. The SMC will meet monthly during dose escalation, provided that subjects have been enrolled and data are available, to review and discuss safety data and communicate results of ongoing analyses throughout the conduct of dose expansion. Continuous toxicity monitoring based on the Pocock-type stopping boundary [Ivanova, 2005] will be used for the rate of AEs leading to treatment discontinuation (e.g., prolonged neutropenia lasting past cycle day 42 in the absence of AML or MDS, high-grade non-hematologic adverse events, treatment-related deaths) within the dose expansion cohorts for the SL-172154 and azacitidine combination regimen (Part A or C) or

SL-172154, azacitidine and venetoclax combination regimen (Part B). The discontinuation rate owing to AEs with azacitidine and venetoclax or azacitidine was 24% and 20% respectively [DiNardo, 2020b], thus a 20% rate of subjects with AEs leading to treatment discontinuation was selected for the combination regimen. Accrual will be temporarily stopped if an excessive number of subjects who experience AEs leading to SL-172154 and the combination agent(s) discontinuation; that is, if the number of subjects who experience AEs leading to SL-172154 and the combination agent 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 stop when the true rate of subjects with AEs leading to treatment discontinuation is 30%.

Number of Patients, 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	2	2	3	3	3	4	4	4	4	5	5	5	5	6	6	6	6	6

9.1.3 Sample Size Determination

The planned sample size is approximately 160 to 177 subjects, depending on the number of dose levels evaluated in dose escalation for each of the regimens. Twenty to 26 subjects will be enrolled in a SL-172154 monotherapy dose escalation cohort. For the SL-172154 and azacitidine combination regimen, approximately 20 to 26 subjects will be enrolled in dose escalation cohorts, approximately 20 subjects will be enrolled in the dose expansion cohort (Part A) and approximately 20 subjects will be enrolled in the AML TP53 dose expansion cohort (Part C); for the SL-172154, azacitidine and venetoclax combination regimen, approximately 8-13 subjects will be enrolled in the safety run-in cohort and approximately 12 additional subjects will be enrolled in the dose expansion cohort (Part B). For Part D, approximately 60 subjects will be enrolled with approximately 20 subjects in each arm.

NOTE: The planned sample sizes may be revised 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 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 decisions. The Sponsor, in consultation with the SMC, may also elect to add subjects to the monotherapy cohort or combination dose escalation or safety run-in cohort if additional data is needed to select the dose level for the dose expansion cohorts.

9.2 Statistical Analyses

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

When determining the RP2D, the totality of the safety, tolerability, PK, PD and efficacy data is taken into consideration.

9.2.1 Analysis Populations

The populations defined for analysis will include the following:

- Enrolled population: all subjects who have signed the main study informed consent.
- Screen failures: all subjects who have signed the main study informed consent but have not received any dose of study treatment.
- All Treated Population: all subjects who receive at least one dose of any study drug(s). Safety data will be evaluated based on this population.
- Intent-to-treat (ITT) population for Part D cohort of dose expansion: all randomized subjects regardless of whether or not treatment was administered. This population will be based on the treatment to which the subject was randomized. Any subject who receives a treatment randomization number will be considered to have been randomized.
- DLT-Evaluable Population: all subjects enrolled in the dose escalation cohorts (SL-172154 monotherapy, or SL-172154 and azacitidine combination) or in the safety run-in cohort (SL-172154, azacitidine and venetoclax) who receive at least 2 of 4 scheduled doses of SL-172154 and at least 50% of the scheduled doses of the combination agent (azacitidine or venetoclax) 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.
- Pharmacokinetic Population: subjects in the All Treated Population from whom at least one PK sample is obtained and analyzed.
- Response-Evaluable Population: subjects in the All Treated Population who have at least one post-baseline disease assessment or who have progressed or died before the first post-baseline disease assessment.
- ADA Analysis Population: subjects in the All Treated Population for whom at least one ADA sample is obtained and analyzed.
- Pharmacodynamic Population: subjects in the All Treated Population for whom at least one PD sample is obtained and analyzed.

9.2.2 Data Analysis During Dose Escalation and Safety Run-In

During the dose escalation and safety run-in, the number of subjects with DLTs will be determined after each cohort of approximately 5 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. Selected AE summary tables and listings may be provided during dose escalation to support dose escalation decisions.

9.2.3 General Data Analysis and Consideration

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

As it is anticipated that accrual will be spread across centers and summaries of data by center would be unlikely to provide valuable information, data from all participating centers will be pooled prior to analysis. All data up to the time of study completion/withdrawal from study will be included in the analysis for each subject, regardless of duration of treatment.

9.2.4 Safety Analyses

The safety evaluation will be based on the All Treated Population and the DLT evaluation will be based on the DLT-evaluable population.

DLTs will be summarized by dose level/regimen for combination dose escalation cohorts and by dose level for the monotherapy cohort. Frequency tables by dose levels will be used to describe safety and tolerability parameters such as: AEs, SAEs, fatal AEs AEs leading to dose reduction of SL-172154, and AEs leading to discontinuation of SL-172154, azacitidine and venetoclax. 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. AEs will be graded according to the NCI CTCTAE v5.0. CRS will be graded per the ASTCT Consensus Grading Criteria for CRS. Concomitant medications will be coded using the WHO Drug Dictionary.

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 20% among all dose with the isotonic estimate of DLT rate ≥15%. If two or more doses tie for the smallest difference, the following rules will be performed:

- If the estimated DLT rate < 20% 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 < 20% and > 20% for all doses, then select the higher dose among the tied doses;
- If the estimated DLT rate > 20% for all doses, then select the lower dose among the tied doses;

An MAD will be reported if the isotonic estimate of DLT rate is less than 15% for all dose levels. Otherwise, an MTD will be reported.

9.2.5 Efficacy Analyses

For dose escalation and Parts A, B and C of dose expansion, efficacy analysis will be based on the All Treated population and Response-Evaluable populations. All efficacy data will be summarized by treatment regimen, dose level, prior treatment status (treatment naïve or relapsed/refractory

disease), TP53 mutation or deletion (Yes or No for subjects with AML), and overall for MDS and AML, respectively.

For Part D of dose expansion, efficacy analysis will be based on the ITT, All Treated and response evaluable population. All efficacy data will be summarized by the treatment arm. The CR rate and 95% CI in each arm will be calculated and CR rate will be compared between SL-172154 1 mg/kg or 3mg/kg in combination with azacitidine and azacitidine monotherapy using Fisher's exact test, 95% CIs for the difference in CR rate will be calculated. If data warrant, the CR rate will be compared using Cochran-Mantel-Haenzszel (CMH) test stratified by stratification factors used in randomization. There is no adjustment for multiple comparisons. The primary efficacy analysis will include the following outcome measures:

- CR is defined as the proportion of subjects who reach CR prior to the initiation of any new therapy for AML or MDS.
- Duration of CR is measured from the date when the CR criteria are first met to the date of relapse or death, whichever occurs first.
- Time to CR is defined as the time from the first dose of study treatment to the date of CR criteria are first met.
- CR/CRh is defined as the proportion of subjects who reach CR or CRh prior to the initiation of any new therapy for AML.
- Duration of CR/CRh is measured from the date when the CR or CRh criteria are first met to the date of relapse or death, whichever occurs first.
- ORR is defined as the proportion of subjects who reach objective response prior to the initiation of any new therapy for AML or MDS. The objective response is defined as CR, PR, marrow CR, or HI based on IWG criteria for MDS, and CR, CRi, PR, or (MLFS based on ELN criteria for AML.
- Duration of response (DOR) is measured from the date when the objective response criteria are first met to the date of relapse, disease progression or death, whichever occurs first.
- Time to objective response is defined as the time from the first dose of study treatment to the date of objective response criteria are first met.
- Composite CR rate is the proportion of subjects who reach composite CR prior to initiation of any new therapy for AML. The composite CR includes CR and CRi per ELN for AML.
- Duration of composite CR is measured from the date when the composite CR criteria are first met to the date of relapse or death, whichever occurs first.
- Time to composite CR is defined as the time from the first dose of study treatment to the date of composite CR criteria are first met.
- Progression free survival (PFS) is defined as the time from the first dose of study treatment to the date of documented disease progression, relapse, or death from any cause, whichever occurs first.
- Event free survival (EFS) is defined as the time from the first dose of study treatment to the date of documented treatment failure, disease progression, relapse, or death from any cause, whichever occurs first.

- RBC transfusion independence rate is the proportion of subjects who have a 56-day or longer period with no RBC transfusions.
- Duration of RBC transfusion independence: the duration of RBC transfusion independence is measured from the date on which measurement criteria are first met for RBC transfusion independence to the first date of RBC transfusion prior to initiation of any new therapy for AML or MDS.
- Platelet transfusion independence rate is the proportion of subjects who have a 56-day or longer period with no platelet transfusions.
- Duration of platelet transfusion independence: the duration of platelet transfusion independence is measured from the date on which measurement criteria are first met for platelet transfusion independence to the first date of platelet transfusion prior to initiation of any new therapy for AML or MDS.
- MRD-negative response rate is defined as the proportion of subjects who achieve MRD negativity and CR, CRi, or MLFS (subjects with AML) or CR or marrow CR (subjects with MDS). Subjects who have no MRD assessment will be considered as non-responder for the calculation of MRD-negative response rate.
- Overall survival (OS) is defined as the time from the first dose of study treatment to the date of death from any cause.

The ORR, CR, composite CR, CR/CRh, RBC and platelet transfusion independence rate, and MRD-negative response rate will be estimated along with a 95% confidence interval using the exact probability method. DOR and time to response will be evaluated, using the Kaplan-Meier method, for the subgroup of subjects with a CR, composite CR, CR/CRh, and ORR, respectively. Duration of RBC and platelet transfusion independence will be evaluated, using the Kaplan-Meier method, for the subgroup of subjects with transfusion independence. The Kaplan-Meier method will be used to estimate the PFS/EFS/OS curve and PFS/EFS/OS rate at time of point of interest.

Supplementary analysis may be conducted by applying the IWG 2023 MDS response criteria to understand preliminary efficacy further [Zeidan, 2023].

9.2.6 Pharmacokinetics

Plasma concentrations for SL-172154 will be summarized using tabular and graphical format. SL-172154 PK parameters (Table 21) 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 outcome measures may be explored using appropriate graphical and statistical methods.

Table 21 Serum SL-172154 PK Parameters

Cmax	Maximum observed concentration
Clast	Last quantifiable concentration
Tmax	Time of maximum observed concentration
AUC0-last	The area under the serum concentration-time curve, from time 0 to the last quantifiable concentration, calculated by a combination of linear and logarithmic trapezoidal methods (Linear up/log down method).
AUC0-t	The area under the serum concentration-time curve, from time 0 to time=t, calculated by a combination of linear and logarithmic trapezoidal methods (Linear up/log down method).
AUC0-inf	Area under the serum concentration-time curve from time 0 extrapolated to infinity, calculated as AUC0-last + Clast/terminal elimination rate constant (λz). Reliability of AUC0-inf values is contingent on the percent of the total area obtained by extrapolation: AUC0-inf values with <20% of the total area coming from Clast/λz are considered acceptable. Any exceptions to the above procedures will be clearly documented/justified in the PK report.
AUCtau	The area under the serum concentration-time curve, over the dosing interval following doses > first dose, calculated by a combination of linear and logarithmic trapezoidal methods (Linear up/log down method)
%AUCext	Percentage of AUC0-inf due to extrapolation from Tlast to infinity
t½	Terminal elimination half-life, estimated using the equation [ln(2)/λz]
CL	Clearance; calculated as Dose/AUC0-inf
Vz	Volume of distribution; calculated as Dose/(λz * AUC0-inf)
Vss	Volume of distribution at steady state

PK parameters based on the elimination phase (e.g., AUC0-inf, t1/2, CL, Vz) will be calculated and reported as data allow.

9.2.7 Immunogenicity Analysis

The immunogenic potential of SL-172154 will be assessed by summarizing the number/proportion of subjects with positive and negative post-dose 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.

9.2.8 Pharmacodynamics Analyses

The PD data analysis will be based on the PD population. PD biomarkers values will be summarized descriptively by planned visit, treatment regimen, dose level, cancer type (MDS or AML) and/or overall for all subjects.

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 participants in this study. The clinical trial 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 International Council for Harmonisation (ICH) E6 and consistent with the consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002), or ethical policy statement specific to the country, whichever provides the most protection to human subjects.

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

13.4 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating Investigators, their staff, and the Sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, study documentation, data, and all other study-related information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

The study monitor, auditors, other authorized representatives of the Sponsor including the contract research organization (CRO), if applicable, representatives of the IRB/IEC or the Sponsor supplying study product, the Federal government or its designee and applicable regulatory authorities will be granted direct access to the study participants' original medical records (including but not limited to office, clinic, hospital, or pharmacy records), all documents required to be maintained by the Investigator, for verification of clinical trial procedures and/or data, without violating the confidentiality of the participants, to the extent permitted by the law and regulations.

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

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

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

- Intended Use: Samples and data collected under this protocol may be used to study the effects of the investigational drug on how one's immune system reacts and how the body responds to this type of treatment in treating different types of cancers.
- Storage: Access to stored samples will be limited to specified study personnel/vendor personnel. Samples will be identified by unique subject identification codes. Samples and data will be stored using subject ID assigned by the Sponsor and Investigators. 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 treatment with SL-172154, SMC meetings will be held to review relevant data with the Investigators or designees. These meetings will be held once a month (or more frequently if required) to share safety data and communicate results of ongoing analyses. All available safety, PK, 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 and the process for safety review.

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

14.2 Data Collection and Management Responsibilities

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

14.3 Study Record Retention

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

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

No study records should be destroyed without prior 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 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 Revised International Prognostic Scoring System (IPSS-R) for MDS

IPSS-R Risk Category	Overall Risk Score
Very low	≤ 1.5
Low	>1.5 – 3.0
Intermediate	>3.0 – 4.5
High	>4.5 – 6.0
Very high	>6.0

	IPSS-R Prognostic Score Value						
Prognostic Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	na	Good	na	Intermediate	Poor	Very Poor
Marrow blasts (%)	≤ 2	na	>2 but <5	na	≥5 but ≤ 10	> 10	na
Hemoglobin (g/dL)	≥ 10	na	≥8 but <10	< 8	na	na	na
Platelets (10^9/L)	≥ 100	≥50 but <100	< 50	na	na	na	na
ANC (10^9/L)	≥ 0.8	< 0.8	na	na	na	na	na

Abbreviations: ANC = absolute neutrophil count; na = not applicable

Source: [Greenberg, 2012]

16.2 2017 ELN Risk Stratification by Genetics (AML)

Risk Category*	Genetic Abnormality
Favorable	t(8;21)(q22;q22.1); RUNX1-RUNX1T1
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
	Mutated NPM1 without FLT3-ITD or with FLT3-ITD^{low}†
	Biallelic mutated CEBPA
Intermediate	Mutated NPM1 and FLT3-ITD^{high}†
	Wild-type NPM1 without FLT3-ITD or with FLT3-ITD^{low}† (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); MLLT3-KMT2A‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse / Poor	t(6;9)(p23;q34.1); DEK-NUP214
	t(v;11q23.3); KMT2A rearranged
	t(9;22)(q34.1;q11.2); BCR-ABL1
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM(EVI1)
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype§, monosomal karyotype//
	Wild-type NPM1 and FLT3-ITD^{high}†
	Mutated RUNX1¶
	Mutated ASXL1¶
	Mutated TP53#

*Prognostic impact of a marker is treatment-dependent and may change with new therapies.

†Low, low allelic ratio (<0.5); high, high allelic ratio (≥0.5); semiquantitative assessment of FLT3-ITD allelic ratio (using DNA fragment analysis) is determined as ratio of the area under the curve "FLT3-ITD" divided by area under the curve "FLT3-wild-type"; recent studies indicate that AML with NPM1 mutation and FLT3-ITD low allelic ratio may also have a more favorable prognosis and patients should not routinely be assigned to allogeneic-HCT.

‡The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.

§Three or more unrelated chromosome abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with BCR-ABL1.

//Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality (excluding core-binding factor AML).

¶These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.

#TP53 mutations are significantly associated with AML with complex and monosomal karyotype

Source: [Döhner, 2017]

16.3 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 post-menopausal for at least 12 consecutive months.

Definition of Female of Non-Reproductive Potential

Female subjects will be considered of non-reproductive potential if they:

1. Are post-menopausal if defined as 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 post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 consecutive months of amenorrhea, a single FSH measurement is insufficient.

   OR

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

   OR

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

Definition of Male of Non-Reproductive Potential

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

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

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) a highly effective contraception during heterosexual activity.

Highly effective 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
  - Male subjects: the following contraception methods may be used by female partners and requires use of a male condom for the male subject:
    - diaphragm with spermicide
    - cervical cap with spermicide (nulliparous women only)
    - contraceptive sponge (nulliparous women only)
    - hormonal contraceptives including oral contraceptive pill (estrogen/progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is: (1) consistently employed during the entire period of risk associated with the study drug; (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, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. To participate in the study, female subjects of childbearing potential must use a highly effective method of contraception (i.e., <1% failure rate), as described above, at least 14 days prior to initiation of study treatment, and continue use during treatment and for 30 days (which exceeds 5 half-lives) after the last dose of SL-172154, or for the duration required by local prescribing information after the last dose of azacitidine (i.e., for sites in UK at least 6 months after the last dose of azacitidine in either combination regimen).

Male subjects with female partners of childbearing potential must have azoospermia from a prior vasectomy, an underlying medical condition, or agree to use a highly effective method of contraception (i.e., <1% failure rate), as described above, during treatment and for 30 days (which exceeds 5 half-lives) after the last dose of SL-172154, or for the duration required by local prescribing information after the last dose of azacitidine (i.e., for sites in UK at least 3 months; for sites in Canada, at least 6 months).

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

16.4 Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (TLS)

Management and procedures for TLS should be implemented as per regional guidelines or institutional standards.

The following recommendations may be followed where applicable.

Abnormality	Management Recommendations
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	• Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If further ≥0.2 mmol/L increase in potassium, but still < upper limit of normal (ULN), manage per potassium ≥ULN. Otherwise recheck in 1 hour. • Resume per protocol testing if change in potassium <0.2 mmol/L, and potassium <ULN, and no other evidence of tumor lysis. • At discretion of Investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the Investigator. Potassium, phosphorus, uric acid, calcium and creatinine must be rechecked within 24 hours.
Potassium > ULN	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) notification with consideration of initiating dialysis. • Administer sodium polystyrene sulfonate (e.g. Kayexalate or Resonium A 60 g). • Administer diuretics (e.g. furosemide 20 mg IV x 1) • Administer calcium gluconate if there is ECG/telemetry evidence of life-threatening arrhythmias. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If potassium <ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine, 1, 2, and 4 hours, if no other evidence of tumor lysis.
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g., muscle cramps, weakness, paresthesia, nausea, vomiting, diarrhea)	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) assessment with consideration of initiating dialysis. • Administer sodium polystyrene sulfonate (e.g. Kayexalate or Resonium A 60 g) • Administer diuretics (e.g. furosemide 20 mg IV x 1) • Administer rapid-acting insulin (e.g. insulin 0.1 Units/kg) and glucose infusion (25% dextrose 2 ml/kg) • Administer sodium bicarbonate 1-2 mEq/kg IV push ○ If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation.

Abnormality	Management Recommendations
	• Administer calcium gluconate if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in the same IV line as sodium bicarbonate. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine every hour STAT.
Hyperuricemia	
Uric acid ≥8.0 mg/dL (476 µmol/L)	• Consider rasburicase (prior to rasburicase administration please refer to local label for tests to be performed, contraindications and precautions. Dosing per institutional guidelines). ○ If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT.
Uric acid ≥ 10 mg/dL (595 µmol/L) OR Uric acid ≥ 8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.026 mmol/L) from predose level	• Administer rasburicase (prior rasburicase administration please refer to local label for tests to be performed, contraindications and precautions. Dosing per institutional guidelines). ○ If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Notify nephrology (or other acute dialysis service). • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If uric acid <8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later if no other evidence of tumor lysis.
Hypocalcemia	
Calcium ≤ 7.0 mg/dL (1.75 mmol/L) AND Patient symptomatic e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias)	• Administer calcium gluconate with ECG monitoring. • Telemetry. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later if no other evidence of tumor lysis. • Calculate corrected calcium and check ionized calcium if albumin low.
Hyperphosphatemia	
Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase	• Administer a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology (or other acute dialysis service) notification (dialysis required for phosphorus ≥ 10 mg/dL • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT.

	• If phosphorus < 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later if no other evidence of tumor lysis.
Creatinine	
Increase ≥ 25% from baseline	• Start or increase rate of IV fluids. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 – 2 hours STAT.

Abbreviation: STAT(statim): urgent order.
Source: [Coiffier, 2008; DiNardo, 2019]

16.5 Recommendation for Toxicity Management of Cytopenias for Azacitidine Combination Regimen

Recommendations are provided in the following table. If the country-specific prescribing information is different, the current local guidelines should be used.

Beginning with Cycle 2, if the start of a subsequent cycle (e.g., Day 1) is delayed due to azacitidine-related toxicities (e.g., cytopenia), SL-172154 dose should also be delayed. Consequently, the current cycle length is extended (i.e., the cycle lasts longer than 28 days).

For subjects with baseline (start of treatment) WBC $\geq$ 3. 0 x10^9/L, ANC $\geq$ 1.5 x10^9/L, and platelets $\geq$ 75 x10^9/L, adjust the azacitidine dose as follows, based on nadir counts for any given cycle:

Nadir Counts		% Dose in the Next Course
ANC (x10^9/L)	Platelets (x10^9/L)	
<0.5	<25	50%
0.5 – 1.5	25-50	67%
>1.5	>50	100%

Source: [VIDAZA-USPI, 2020]

For subjects whose baseline counts are WBC < 3.0 x10^9/L, ANC < 1.5 x10^9/L, and platelets <75 x10^9/L, base dose adjustments on nadir counts and bone marrow biopsy cellularity at the time of the nadir as noted below, unless there is clear improvement in differentiation (percentage of mature granulocytes is higher and ANC is higher than at onset of that course) at the time of the next cycle, in which case continue the current dose.

WBC or platelet nadir % decrease in counts from baseline	Bone Marrow Biopsy Cellularity at Time of Nadir (%)		
	30-60	15-30	<15
	% Dose in the Next Course		
50 – 75	100	50	33
>75	75	50	33

If a nadir as defined in the table above has occurred, give the next course 28 days after the start of the preceding course, provided that both the WBC and the platelet counts are greater than 25% above the nadir and rising. If a greater than 25% increase above the nadir is not seen by Day 28, reassess counts every 7 days. If a 25% increase is not seen by Day 42, reduce the scheduled dose by 50%.

16.6 Recommendation for Toxicity Management of Cytopenias for Venetoclax and Azacitidine Combination Regimen

Recommendations are provided in the following table. If the country-specific prescribing information is different, the current local guidelines should be used.

Beginning with Cycle 2, if the start of a subsequent cycle (e.g., Day 1) is delayed due to venetoclax-related toxicities (e.g., cytopenia), SL-172154 dose should also be delayed. Consequently, the current cycle length is extended (i.e., the cycle lasts longer than 28 days).

Adverse Reaction	Occurrence	Recommended Action
Grade 4 neutropenia with or without fever or infection; **OR** Grade 4 thrombocytopenia	Prior to achieving remission[a]	In most instances, do not interrupt venetoclax in combination with azacitidine due to cytopenias prior to achieving remission
	First occurrence after achieving remission and lasting at least 7 days	Delay subsequent cycle of venetoclax in combination with azacitidine and monitor blood counts. Upon resolution to Grade 1 or 2, resume venetoclax at the same dose in combination with azacitidine. *Note: venetoclax and azacitidine will resume on the same day after the interruption to allow for count recovery.*
	Subsequent occurrences in cycles after achieving remission and lasting 7 days or longer	Delay subsequent cycle of venetoclax in combination with azacitidine and monitor blood counts. Upon resolution to Grade 1 or 2, resume venetoclax at the same dose in combination with azacitidine and reduce venetoclax duration by 7 days during each of the subsequent cycles, such as 21 days instead of 28 days. *Note: venetoclax and azacitidine will resume on the same day after the interruption to allow for count recovery.*

[a] Recommend bone marrow evaluation.
Source: [VENCLEXTA-USPI, 2020]

If cytopenia occurs in cycles with reduced venetoclax duration, delay subsequent cycle of venetoclax in combination with azacitidine and monitor blood counts. If a 25% increase in nadir (mid-cycle) has not been achieved within 21 days, consider azacitidine dose adjustment on next cycle based on bone marrow cellularity using the most recent value.

16.7 Recommendation for the Management of Potential Venetoclax Interactions with CYP3A and P-gp Inhibitors

Recommendations from the venetoclax USPI [VENCLEXTA-USPI, 2020] is provided as an example in the following table. If the country-specific prescribing information is different, the current local guidelines should be used. Please see the country's current prescribing information (e.g., SmPC, or Product Monograph) for additional information.

Co-administered Drug	Initiation and Ramp-up Phase	Steady Daily Dose (After Ramp-up Phase)
Posaconazole	Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 70 mg	Reduce venetoclax dose to 70 mg
Other strong CYP3A inhibitor	Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 100 mg	Reduce venetoclax dose to 100 mg
Moderate CYP3A inhibitor	Reduce venetoclax dose by at least 50%	
P-gp inhibitor		

Source:[VENCLEXTA-USPI, 2020]

16.8 ECOG Performance Status Criteria

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Source: [Oken, 1982]

16.9 Cockcroft-Gault Formula for Creatinine Clearance

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

Q = 0.85 for females
Q = 1.0 for males

OR

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

K = 1.0 for females
K = 1.23 for males

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

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

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

Example:

Male, actual body weight = 90.0 kg; height = 68 inches; IBW = 50 + (2.3) (68 – 60) = 68.4 kg

This subject's actual body weight is >30% over IBW. Therefore, in this case, the subject's IBW of 68.4 kg should be used in calculating the estimated creatinine clearance

References:

[McCarron, 1974; Levey, 2006; Levey, 2009]

16.10 Summary of Changes for Protocol Amendment 01

This amendment applies to all Investigator sites participating in this study. Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 1.

Minor editorial changes (including protocol version number and approval date, table of contents) as well as minor clarification edits to text are incorporated in this amendment.

This protocol was amended to include the following:

1. The study design has been revised as follows:

   - Monotherapy dose escalation has been incorporated. The option to add azacitidine beginning in Cycle 2 for subjects in monotherapy dose escalation cohort has been removed.
     - Study Schema
     - Section 1.7, Study Rationale
     - Section 3.0, Study Design
     - Section 3.1.1, SL-172154 Monotherapy Dose Escalation

Deleted text in these sections: ~~For those subjects who do not achieve a response (e.g., CR, Cri or MLFS in subjects with AML or CR, PR or marrow CR in subjects with MDS) at the end of Cycle 1, and at the discretion of the investigator, SL 172154 monotherapy may be continued or azacitidine may be administered with SL 172154 beginning in Cycle 2 and continued for the duration of the treatment period in this study. Subjects who have azacitidine added must follow the schedule for SL 172154 dosing and all assessments per the SOA for the SL 172154 and azacitidine regimen as described in Section 3.2.1 and Section 6.2.~~

~~If azacitidine was added to SL 172154 for any subject in the monotherapy cohort, safety data from Cycle 1 (SL-172154 monotherapy) as well as from Cycle 2 (first cycle with SL-172154 administered with azacitidine) will be reviewed by the study's SMC and considered in the determination of the SL 172154 starting dose for each of the combination regimen dose escalation cohorts (see Section 7.8). Enrolment to the dose escalation combination regimen cohorts will not begin until the SMC review and decision is documented~~.

   - Starting dose (1.0 mg/kg) rationale has been updated to indicate that the 3.0 mg/kg dose has cleared the DLT evaluation period without a DLT reported in the SL-172154 monotherapy dose escalation in subjects with ovarian cancer in the ongoing Study SL03-OHD-104.

     Sec 1.6, Summary of Clinical Data
     Sec 3.0, Description of Study Design

     New text (italics): *Of note, following the safety data cut-off date, a third subject initiated treatment with SL-172154 at 3 mg/kg and has completed the DLT evaluation period with no DLT reported. The next planned dose level in study SL03-OHD-101 is 10 mg/kg*.

   - Proposed dose levels have been modified from half-log increments to the following SL-172154 doses: 1 mg/kg, 3 mg/kg, 6 mg/kg, and 10 mg/kg. Should it be needed to better define the SL-172154 MTD or maximum administered dose (MAD), dose exploration

beyond 10 mg/kg will proceed as a protocol amendment. Previous protocol language regarding investigation of additional dose levels or schedules have been removed; any such investigation will be done via protocol amendment.

- Study Schema
- Section 3.0, Study Design
- Section 3.1.1, SL-172154 Monotherapy Dose Escalation
- Section 3.2.1, SL-172154 Administered with Azacitidine (Combination Dose Escalation Cohort)
- Section 3.2.2, SL-172154 Administered with Azacitidine and Venetoclax (safety run-in cohort)
- Section 3.5, Evaluation of a Less Frequent Dosing Schedule

Deleted text:

~~**DOSE LEVEL**~~	~~**IV Dose of SL-172154 (mg/kg)** [a,b]~~	~~**Duration of Infusion**~~
~~DL 1 (starting dose)~~	~~1.0~~	~~30 minutes (+/- 10 minutes)~~
~~DL -1[e]~~	~~0.3~~	~~30 minutes (+/- 10 minutes)~~

New Text:

DOSE LEVEL	***IV Dose of SL-172154 (mg/kg)*** [a,b]	***Duration of Infusion***
DL -1[c]	*0.3*	*30 minutes (+/- 10 minutes)*
DL 1 (starting dose)	*1.0*	*30 minutes (+/- 10 minutes)*
DL 2	*3.0*	*60 minutes (+/- 10 minutes)*
DL 3	*6.0*	*60 minutes (+/- 10 minutes)*
DL 4	*10*	*60 minutes (+/- 10 minutes)*

- Section 3.2.1, SL-172154 administered with azacitidine (combination dose escalation cohort) – new text in *italics*

DOSE LEVEL (DL)	**SL-172154 DOSE[a,b] [D2, 9, 16, 23 in each 28d cycle]**	**Combination Regimen 1**
DL -1a[c]	0.3 mg/kg	Azacitidine (75 mg/m^2) SC or IV on days 1-7 or use 5-2-2 schedule in each 28-day cycle. On days when both are administered, azacitidine administration should be completed at least 30 minutes prior to the start of the SL-172154 infusion.
DL 1a	1.0 mg/kg	
DL 2a	3.0 mg/kg	
DL 3a	*6.0 mg/kg*	
DL ~~3~~*4a*	10 mg/kg	

Deleted text: ~~The planned dose escalation of SL-172154 will not exceed half-log increments as outlined in Table 2; additional doses and/or schedules or intermediate doses may be explored based on emerging safety, PK and PD data~~.

New text (italics): If safety and pharmacodynamic data support exploration of a less intensive dosing schedule, then subsequent cohort enrollment on an alternative less frequent schedule may be instituted in lieu of the weekly schedule for SL-172154 dosing…. *Any such evaluation of alternative dosing schedule(s) will be done by protocol amendment*.

- A staggered parallel design has been incorporated to explore the combination of SL-172154 and azacitidine in parallel with the monotherapy dose escalation. The starting dose of this combination regimen dose escalation cohort will be one dose level lower than tested in the monotherapy dose escalation arm of the study.
    - Study Schema
    - Section 3.2.1, SL-172154 Administered with Azacitidine (Dose Escalation)
- Subjects with relapsed/refractory disease (AML or higher-risk MDS) with no more than 4 (revised from 2) prior therapies for their disease will be enrolled in monotherapy and SL-172154 + azacitidine Dose Escalation cohorts. Treatment-naïve subjects will not be eligible to enroll in these cohorts, with the exception of subjects with subtypes of AML that respond very poorly to conventional drugs, such as those with high-risk genetic abnormalities (per FDA Guidance, AML: Developing Drugs and Biological Products for Treatment).
    - Section 1.7, Study Rationale
    - Section 3.0, Description of Study Design
    - Section 3.1.1, SL-172154 Monotherapy Dose Escalation
    - Section 3.2.1, SL-172154 Administered with Azacitidine (Dose Escalation)
    - Section 4.1, Inclusion Criteria 5 and 6
- A recommended dose of SL-172154 administered with azacitidine will be identified prior to initiation of enrollment to a safety run-in cohort to explore the SL-172154, azacitidine and venetoclax combination regimen. Subjects with AML not previously treated will be enrolled to this cohort.
    - Section 3.0, Description of Study Design
    - Section 3.2.2, SL-172154 Administered with Azacitidine and Venetoclax (Safety run-in)
    - Section 3.3.2, SL-172154 Administered with Azacitidine and Venetoclax in Subjects with AML (Dose Expansion)
- Once a recommended dose of SL-172154 administered with azacitidine is identified in dose escalation, enrollment to expansion cohorts of either (1) subjects with higher-risk MDS, or (2) AML subjects with at least one TP53 mutation or deletion. Subjects in these expansion cohorts will not have previously received treatment for their disease.
    - Section 3.3.1, SL-172154 Administered With Azacitidine in Subjects with Higher-risk MDS

  - Section 3.3.3, SL-172154 Administered with Azacitidine in AML Subjects with TP53 gene mutation/deletion

- The projected planned sample size, enrollment duration, and study duration has been revised based on the revised study design.
  - Synopsis
  - Section 3.1.1, SL-172154 Monotherapy Dose Escalation
  - Section 3.2.1, SL-172154 Administered with Azacitidine (Dose Escalation)
  - Section 3.2.2, SL-172154 Administered with Azacitidine and Venetoclax (Safety run-in)
  - Section 9.1.3, Sample Size Determination

2. SL-172154 administration
   - Observation of subjects for 4 hours after each SL-172154 administration has been added. Longer periods of observation for subjects experiencing IRR or CRS remains as previously described in the recommended toxicity management guidelines for each.
     - Section 5.1.4, Monitoring Dose Administration
     - Section 6.1 (footnote k), Schedule of Assessments: SL-172154 Monotherapy Dose Escalation Cohorts Only
     - Section 6.2 (footnote k), Schedule of Assessments: SL-172154 Combination Cohorts, Dose Escalation or Dose Expansion (SL-172154 with azacitidine or azacitidine and venetoclax)

   - Premedication for primary prophylaxis of IRR with SL-172154 administration is already defined in Section 5.1. For further clarification, this information is detailed elsewhere in the protocol with this amendment.
     - Synopsis
     - Section 3, Description of Study Design
     - Section 3.1.1, SL-172154 Monotherapy Dose Escalation
     - Section 3.2.1, SL-172154 Administered with Azacitidine (Dose Escalation)
     - Section 3.2.2, SL-172154 Administered with Azacitidine and Venetoclax (Safety run-in)
     - Section 3.3.1, SL-172154 Administered With Azacitidine in Subjects with Higher-risk MDS
     - Section 3.3.2, SL-172154 Administered with Azacitidine and Venetoclax in Subjects with AML (Dose Expansion)
     - Section 3.3.3, SL-172154 Administered with Azacitidine in AML Subjects with TP53 gene mutation/deletion (Dose Expansion)

   - Recommendation to have 2 doses of tocilizumab available at the time of SL-172154 has been added in case of CRS. Provisional plan for alternative management of CRS when tocilizumab is not available has been included.

     New text (italics): *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 3.8.2 for toxicity management recommendations). When tocilizumab is not available, consider*

using drug with similar mechanism of actions such as anti-IL-6 receptor mAbs (e.g. sarilumab) or anti-IL-6 mAbs (e.g., siltuximab).

- Section 5.1.4, Monitoring Dose Administration
- Section 3.8.2, Recommendation for Management of Cytokine Release Syndrome

3. DLT criteria have been modified in Section 3.6 as follows (new text, italics):

Protocol-defined dose limiting toxicity (DLT) criteria are applicable to the Dose Escalation portion of the study. The determinant period for DLT is the first 28 days of treatment (i.e., Cycle 1) ~~except for the 42-day period described for prolonged myelosuppression~~. However, there is provision in the criteria below for AEs that occur beyond this period to be considered in the determination of DLTs and RP2D. *All* toxicities *except for CRS* will be graded as per NCI CTCAE v5. *CRS will be graded per the ASTCT Consensus Grading Criteria for CRS (Section 3.8.2).* AEs clearly related to disease progression, intercurrent illness, or concomitant medications are not considered DLTs. *Infection, bleeding, or other expected direct complication of cytopenias due to active underlying MDS or AML will not be considered a DLT.* A DLT is defined as an event considered related *or possibly related* to SL-172154 and meets one of the following criteria:

- ~~Prolonged myelosuppression, as defined by the National Cancer Institute (NCI) criteria specific for leukemia, i.e., marrow cellularity <5% on day 42 (6 weeks) or later from start of therapy without evidence of leukemia (may occur outside of the 28-day DLT window)~~
- *SL-172154 monotherapy cohort: Grade 4 neutropenia or thrombocytopenia lasting ≥14 days from the start of the cycle in the absence of evidence of active AML or MDS*
- *SL-172154 in combination with azacitidine or azacitidine and venetoclax: Grade 4 neutropenia or thrombocytopenia lasting ≥ 28 days from the start of the cycle in the absence of active AML or MDS*
- Any death not clearly related to underlying disease or intercurrent illness
- *Any Grade 3* elevations ~~in liver transaminases (~~aspartate aminotransferase [AST], alanine aminotransferase [ALT]~~)~~ and/or total bilirubin:

o ~~An isolated indirect/unconjugated hyperbilirubinemia without significant clinical consequences would not be considered a DLT.~~

O ~~In subjects who enroll with AST/ALT/total bilirubin ≤ upper limit of normal (ULN); AST or ALT elevation of >8 x ULN or total bilirubin > 5 x ULN~~

~~o In subjects who enroll with AST/ALT/total bilirubin > ULN; AST or ALT elevation of >8 x baseline or total bilirubin > 5 x baseline~~

o Evidence of Hy's Law (AST or ALT ~~≥~~ 3 x ULN ~~[or baseline*]~~ ~~with concurrent increase in~~ in the setting of total bilirubin ~~≥~~ 2 x ULN ~~[or baseline*]~~ without evidence of cholestasis and no other reason can be found to explain the combination of increased aminotransferases and total bilirubin, ~~or alternative explanation~~ such as viral hepatitis A, B or C, preexisting or acute liver disease, or another drug capable of causing the observed injury) ~~disease progression or viral hepatitis~~

~~*ULN or baseline dependent on value at enrollment as described above~~

- Grade 3 or greater non-hematologic AE that requires permanent discontinuation of SL-172154
- Any Grade 3 or greater non-hematologic AE except for those listed below:

o Grade 3 fatigue lasting ≤ 7 days

o *Grade 3 anorexia, nausea, vomiting or diarrhea provided that it does not require tube feeding, total parenteral nutrition, or require or prolong hospitalization*.

O ~~Grade 3 electrolyte abnormalities that are not associated with clinical signs/symptoms and are reversed with appropriate medical intervention~~

o *Grade 3 laboratory abnormalities which resolve to Grade 1 or baseline within 72 hours with or without intervention* ~~that are not deemed clinically significant by the Safety Monitoring Committee (SMC)~~.

O ~~Indirect/unconjugated hyperbilirubinemia without significant clinical consequences~~

o Grade 3 ~~amylase and/or lipase~~ *laboratory abnormalities which resolve to Grade 1 or baseline within 72 hours with or without intervention* ~~that are not associated with clinical signs/symptoms or finding on imaging consistent with pancreatitis~~

o ~~Grade 3 vomiting and/or Grade 3 nausea that resolves within 72 hours with appropriate clinical management~~

o Grade 3 hypertension that can be controlled (ie, systolic BP < 140 mmHg and diastolic BP < 90 mmHg) with medical therapy.

O ~~Grade 3 diarrhea with no evidence of colitis that resolves within 72 hours with appropriate clinical management~~

o Vitiligo or alopecia of any grade

4. Concomitant medications section has been modified to reflect additional details regarding venetoclax (based on US prescribing information, 2020)
    - Section 3.7.1, Prohibited Medications or Treatments
        - New text (italics):

          • *For venetoclax cohorts: Use of P-gp substrates concomitantly with venetoclax. When azole antifungals that are P-gp inhibitors must be used, they are permitted. ;I if concomitant use of P-gp substrate is unavoidable, separate dosing of P-gp substrate by at least 6 hours before venetoclax administration. If concomitant use of P-gp inhibitor is unavoidable, venetoclax dose should be reduced per the prescribing information described in Section 16.6.*

          • *For venetoclax cohorts: Concomitant use of strong or moderate CYP3A4 inducers at least 14 days or 5 half-lives (whichever is longer) prior to first dose of study treatment and throughout the study treatment period. When azole antifungals that strong and moderate CYP3A4 inhibitors must be used, they are permitted. If strong or moderate CYP3A4 inhibitors must be used, the venetoclax dose should be reduced per the prescribing information described in Section 16.6*
    - Section 3.7.2, Medications to be Used with Caution
        - New text (italics): For subjects receiving venetoclax, concomitant use with a P-gp inhibitor or a strong or moderate CYP3A inhibitor should be avoided and alternative medications should be considered. *In the presence of unavoidable*

strong and moderate CYP3A4 inhibitors or P-gp inhibitor, the venetoclax dose should be reduced per the prescribing information described in Section 16.6.

5. Recommendations for management of IRR has been updated as follows (Section 3.8.1):
    - Recommendation for additional monitoring of vital signs with any grade of IRR (also included for any grade of CRS in Section 3.8.2), new text (italics):
      Vital signs should be measured every 15 minutes for the first hour of SL-172154 infusion and then every 30 minutes for the second hour and through 1 hour after the end of the SL-172154 infusion (NOTE: this timing allows for variable durations of SL-172154 infusions).
        - Also included in Schedule of Assessments (footnote d), Section 6.1 and Section 6.2
    - Reference to CRS management has been removed from Section 3.8.1 and is now included as a separate toxicity management table in Section 3.8.2.

6. Recommendations for management of CRS has been added
    - Section 3.8.2, new section in Protocol Amendment 1
    - Section 3.1, new text (italics) added to allow for reduced increments of SL-172154 dose escalation in the event that Grade 2 or 3 event of CRS is reported in the study: *During dose escalation, the following guideline should be followed if an event of CRS occurs on Cycle 1 Day 8 or later:*
        - *Grade 2 CRS: SL-172154 dose should not be escalated by more than 50% between subsequent dose levels*
        - *Grade 3 CRS: SL-172154 dose should not be escalated by more than 25% between subsequent dose levels*
    - Section 5.1.1, new text (italics)
        - *Premedication with corticosteroid will be given to all subsequent subjects following the first case of grade ≥Grade 2 CRS*

7. Recommendations for management of hepatotoxicity has been modified (Section 3.8.3)
    - Definition of Hy's Law has been revised; in addition, the requirement for Grade 3 elevations to be evaluated for potential DLT has been included and reflects the updates to the DLT criteria [new text (italics)]: Discontinue SL-172154 for Hy's Law as follows: ~~in subjects who enroll with AST/ALT/total bilirubin≤ ULN who experience concomitant AST or ALT > 3 x ULN and total bilirubin > 2 x ULN; or in subjects who enroll with AST/ALT/total bilirubin > ULN who experience concomitant AST or ALT > 3 x baseline and total bilirubin > 2 x baseline~~ *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*.
    - Modification made to recommendation for Grade 2 events (new text in italics):
        - ~~Hold SL-172154~~ *Dose reduce SL-172154 by one dose level*

- ~~Assessments as above,~~ Monitor liver function ~every 3 days. *If persistent or rising liver chemistries or significant clinical symptoms, interrupt SL-172154*.
- Consider hepatology consult and liver biopsy is optional.
- ~~If persistent or rising liver chemistries or significant clinical symptoms and~~ *If* an immune etiology is suspected, start oral prednisone 0.5-1.0 mg/kg/day (or equivalent of methylprednisolone) with 4-week taper.
- Resume SL-172154 when toxicity ≤ G1 and corticosteroid taper to ≤ 10 mg/day prednisone or equivalent

8. Recommended dose modification of SL-172154 has been added
   - Section 3.8.4, Management of Non-hematologic and Hematologic AEs Not Specified
     - New table describing SL-172154 dose reduction recommendations
     - Deleted text: ~~No SL-17215 dose modification (dose reduction) will be permitted. Dose delay is recommended as the only method or managing SL-172154 related toxicities~~.
   - Section 3.8, Toxicity Management for SL-172154
     - New text (italics): *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 SL-172154. Only one level dose reduction is permitted for AE management and then SL-172154 administration should be interrupted. 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 adverse event 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 5 SL-172154 Dose Reduction for Management of Toxicities

STARTING DOSE LEVEL (mg/kg)	***DOSE LEVEL REDUCTION (mg/kg)***
0.3	*Interrupt SL-172154 until toxicity resolves to </= grade 1 or baseline and then restart at same dose level.*
1.0	*0.3*
3.0	*1.0*
6.0	*3.0*
10	*6.0*

9. A sample for SL-172154 PK has been added at 0.5h after the end of SL-172154 infusion on Cycle 1 Day 1
   - Section 6.1.1, PK, ADA, and Cytokines Sampling Schedule – Peripheral Blood (SL-172154 Monotherapy Dose Escalation Cohorts Only)
   - Section 6.1.2, PK, ADA, and Cytokines Sampling Schedule – Peripheral Blood (SL-172154 Combination Dose Escalation or Dose Expansion Cohorts)

10. Additional safety monitoring for subjects receiving venetoclax, based on US Prescribing Information (2020), has been included (new text, italics):
    For subjects receiving venetoclax, the following additional laboratory assessments should be performed:
    - *chemistry tests to monitor for TLS should be drawn (calcium, inorganic phosphorus, potassium, uric acid and creatinine) on the first, second and third day of venetoclax dosing at predose (within 4 hours prior to dosing) and 6 – 8 hours post-dose during ramp-up, and 24 hours after reaching final dose*
    - *INR should be monitored more frequently in subjects using warfarin concomitantly with venetoclax*

    Section 6.4.7, Local and Central Laboratory Assessments

    Section 6.2, Schedule of Assessments: SL-172154 Combination Cohorts, Dose Escalation or Dose Expansion (SL-172154 with azacitidine or azacitidine and venetoclax)

11. Clarification that the collection timepoints of bone marrow aspirates to send to central laboratory for research purposes is at select timepoints and not with every bone marrow performed for disease assessment during this study.
    - Section 6.8, Bone Marrow Assessments
    - Section 6.1 and Section 6.2, Schedule of Assessments (footnote n)

A sufficient bone marrow aspirate must be collected for clinical disease assessment and biomarker assessments ~~Bone marrow aspirate samples must be collected for all subjects~~ *from the bone marrow performed at the following timepoints:*

- *Screening (baseline)*
- *End of Cycle 1.*
- *End of Cycle 4*
- *End of Cycle 13*

If a bone marrow is performed for subjects with a CR, marrow CR, or MLFS at any unscheduled timepoint prior to the end of Cycle 13, a portion of the bone marrow aspirate should also be sent to the central laboratory for exploratory research.

12. Allowance to monitor either blood urea nitrogen or urea as well as either bicarbonate or CO_2 has been added to allow flexibility of standard analytes as local laboratories.
    - Section 6.4.7 (Clinical Chemistry in Local Clinical Labs table; new text in *italics*)
        - Blood urea nitrogen *or Urea*
        - Bicarbonate *or* CO_2

13. ELN response criteria for AML table was modified to incorporate description of relapse (hematologic and molecular relapse); language was previously included as text following the table.
    - Section 8.1.1

14. IWG response criteria for MDS table has been modified to include relapse after CR or PR category, transfusion dependence as measure of disease progression by bone marrow, and edit the ANC and platelet units to SI units.
    - Section 8.1.2

15. The target DLT rate for MTD in dose escalation has been adjusted from 33% to 20%. This change required an increase in cohort size from approximately 3 to 5 subjects.
    - Section 9.1.1, Monotherapy and Combination Dose Escalation Cohorts
    - Section 9.1.2, Dose Expansion

16. Recommendations for management of cytopenias (azacitidine + venetoclax cohort) has been revised to reflect the US Prescribing Information (2020 for each agent)
    - Appendix 16.5
        - Deleted text:
            - ~~bone marrow cellularity 15-50%: administer 50% azacitidine dose~~
            - ~~bone marrow cellularity <15%: administer 33% azacitidine dose~~
        - New text (italics): *For subjects with baseline (start of treatment) WBC ≥ 3.0x10^9/L, ANC ≥ 1.5 x10^9/L, and platelets ≥ 75x10^9/L, adjust the azacitidine dose as follows, based on nadir counts for any given cycle*:

Nadir Counts		*% Dose in the Next Course*
ANC (x10^9/L)	*Platelets (x10^9/L)*	
<0.5	*<25*	*50%*
0.5 – 1.5	*25-50*	*67%*
>1.5	*>50*	*100%*

For subjects whose baseline counts are WBC < 3.0x10^9/L, ANC < 1.5 x10^9/L, and platelets < 75x10^9/L, base dose adjustments on nadir counts and bone marrow biopsy cellularity at the time of the nadir as noted below, unless there is clear improvement in differentiation (percentage of mature granulocytes is higher and ANC is higher than at onset of that course) at the time of the next cycle, in which case continue the current dose.

WBC or platelet nadir % decrease in counts from baseline	*Bone Marrow Biopsy Cellularity at Time of Nadir (%)*		
	30-60	*15-30*	*<15*
	% Dose in the Next Course		
50 – 75	*100*	*50*	*33*
>75	*75*	*50*	*33*

If a nadir as defined in the table above has occurred, give the next course 28 days after the start of the preceding course, provided that both the WBC and the platelet counts are greater than 25% above the nadir and rising. If a greater than 25% increase above the nadir is not seen by day 28, reassess counts every

7 days. If a 25% increase is not seen by day 42, reduce the scheduled dose by 50%.

17. Recommendation for management of potential venetoclax interactions with CYP3A and P-gp inhibitors has been added as Appendix 16.6 (new section); reflects US Prescribing Information (2020).

16.11 Summary of Changes for Protocol Amendment 02

This amendment applies to all Investigator sites participating in this study. Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 2.

Minor editorial changes (including protocol version number and approval date, table of contents) as well as minor clarification edits to text are incorporated in this amendment.

This protocol was amended to include the following:

1) Reference to stem cell transplantation (SCT) has been revised to hematopoietic cell transplantation (HCT) throughout the document. Hematopoietic cell transplantation (HCT), hematopoietic stem cell transplantation (HSCT), or stem cell transplantation (SCT) have been interchangeably used to refer to the same therapeutic modality. The Center for International Blood and Marrow Transplant Research (CIBMTR) and the American Society for Transplantation and Cellular Therapy (ASTCT) has recently started to standardize the wording to HCT. Thus, the protocol will follow the standardized word.
2) Rationale for exploring novel agent in combination with azacitidine for AML subjects with TP53m has been included.
    - Sec 1.3

New text: *Nonetheless, the benefit of improved median OS from the combination of azacitidine and venetoclax has not been observed in TP53-mutated AML patients. No benefit in OS was observed in this poor prognostic subgroup although an increase in ORR was observed (55% vs. 0% in patients treated by the combination of azacitidine and venetoclax vs. the combination of azacitidine and placebo, respectively) [DiNardo, 2020a; Cluzeau, 2021]. This is in line with other retrospective cohorts of TP53-mutant AML patients treated with decitabine, another hypomethylating agent, and venetoclax. Despite use of extended decitabine courses, these cohorts demonstrated a median OS of approximately 6 months regardless of venetoclax receipt [Maiti, 2019; DiNardo, 2020a; Venugopal, 2021]. These clinical findings are supported by recent mechanistic observations identifying TP53 mutation to be a direct driver of venetoclax resistance [Nechiporuk, 2019; DiNardo, 2020b]. In total, these data demonstrate that the addition of venetoclax to azacitidine has not provided a significant improvement for AML patients with TP53 mutation, and thus the investigation of novel agents in combination with azacitidine is warranted.*

3) Summary of study design description that was available in other sections of the protocol in Amendment 1 has also been added to the Study Rationale (Sec 7.1)

Study SL03-OHD-104 will initially enroll approximately 5 subjects with relapsed or refractory disease (MDS or AML) to SL-172154 monotherapy dose escalation cohort at the starting dose of 1 mg/kg SL-172154. Subjects will be enrolled into sequential dose levels of SL-172154 and assessed for DLT during the first 28 days. This will inform the safety, tolerability, efficacy, PK, PD, and preliminary anti-tumor activity profile of SL-172154 monotherapy by dose level.

While clinical response is possible with SL-172154 monotherapy, limited clinical responses have been observed with other investigational agents targeting CD47 and CD40 administered as monotherapy [Vonderheide, 2007; Vyas, 2018; Sallman, 2019a; Sikic, 2019]. The mechanism of

action of SL-172154 suggests that combination therapy is likely to provide greater benefit. In addition, subjects with higher-risk MDS or AML often have rapidly progressing disease.

Upon completing the DLT evaluation period of the 3.0 mg/kg SL-172154 cohort in monotherapy dose escalation and the decision to escalate to the next dose level is confirmed, enrollment may begin in parallel to the dose escalation cohorts investigating SL-172154 (starting dose 1 mg/kg) administered with azacitidine to maximize the potential for clinical benefit to participating subjects. Once the selected dose of SL-172154 administered with azacitidine is identified in dose escalation, enrollment of treatment-naïve subjects with AML to a safety run-in cohort (n=8) of SL-172154 administered with azacitidine and venetoclax will commence using the same SL-172154 dose. ~~*In addition, after evaluating and confirming the safety of SL-172154 in the monotherapy cohort, further dose escalation of SL-172154 will occur in combination with standard of care doses and schedules of azacitidine to maximize the potential for clinical benefit to participating subjects*~~.

4) The outcome measures (endpoints) for a secondary objective have been modified for clarity.
   - Synopsis
   - Sec 2
   - Sec 9.2.5

Secondary Objectives	
To assess preliminary evidence of anti-tumor efficacy of SL-172154 administered alone or with azacitidine OR azacitidine + venetoclax in subjects with higher-risk MDS or AML	• Investigator assessed disease response according to IWG 2006 criteria (MDS) (Cheson, 2006) [Cheson, 2006]or ELN 2017 criteria (AML) (Dohner, 2017) ○ CR ~~based on Investigator assessed IWG criteria (MDS) or ELN 2017 criteria (AML)~~ ○ ORR *defined as CR, partial remission (PR), marrow CR, or hematologic improvement (HI) for MDS, or CR, CR with incomplete hematologic improvement (CRi), PR, or morphologic leukemia-free state (MLFS) for AML* ~~based on Investigator assessed IWG criteria (MDS) or ELN 2017 criteria (AML)~~ ○ Composite CR rate *(CR and CRi) for AML* ~~based on Investigator assessed IWG criteria (MDS) or ELN 2017 criteria (AML)~~ ○ *CR/CR with partial hematological recovery (CRh) for AML* • Time to response • Duration of response • Progression free survival (PFS) • Event free survival (EFS) • MRD-negative response rate

	• *Proportion of subject with MDS with hematologic improvement*

5) Assessment of platelet transfusion-independence has been added to the objectives and endpoints.
   - Synopsis
   - Sec. 2
   - Sec 9.2.5

Exploratory Objectives	
To assess the rate and duration of RBC *and platelet* transfusion independence in subjects with higher-risk MDS or AML receiving SL-172154 alone or with azacitidine OR azacitidine + venetoclax	• Proportion of participants who have a 56-day or longer period with no RBC transfusions • Duration of RBC transfusion independence • *Proportion of participants who have a 56-day or longer period with no platelet transfusions* • *Duration of platelet transfusion independence*

6) Previously untreated subjects with MDS with at least one TP53 gene mutation/deletion have been included in the definition of subjects eligible for the dose escalation cohort of SL-172154 plus azacitidine. TP53 mutation is an unfavorable prognostic marker in subjects with MDS and is associated with poor overall survival. In addition, azacitidine single agent therapy has been reported to provide unsatisfactory disease control in MDS with TP53 mutation. Thus, there is a high unmet need for patients with MDS with TP53 mutation.
   - Study Schema
   - Sec 3
   - Sec 3.2.1
   - Sec 4.1 (inclusion criterion 6)

   Upon completing the DLT evaluation period of the 3.0 mg/kg SL-172154 cohort in monotherapy dose escalation and the decision to escalate to the next dose level is confirmed, enrollment may begin in parallel to the dose escalation cohort investigating SL-172154 administered with azacitidine using a starting dose of 1.0 mg/kg SL-172154. Subjects with *relapsed/refractory* AML or higher-risk MDS *being treated in the relapsed/refractory setting* will be enrolled in this dose escalation cohort; previously untreated subjects with AML and known adverse cytogenetics (e.g., ELN adverse risk group) *as well as previously untreated subjects with MDS with at least one TP53 gene mutation/deletion* may also be considered for enrollment in this cohort.

   Inclusion Criterion 6:

   [*Dose Escalation Cohort – SL-172154 Administered with Azacitidine*] AML and MDS subjects ~~must have~~ *with* relapsed/refractory disease (as defined in Inclusion criterion 5) following at least 1 prior line of therapy but no more than 4 prior lines of therapy.

   a. Treatment for MDS preceding secondary AML will not be considered as a prior line of therapy for secondary AML.

b. Prior hydroxyurea or other supportive care in the form of transfusions or growth factors will not be considered prior therapy.

c. Subjects who have undergone allo-~~SCT~~ *HCT* are eligible if they are at least 6 months post-~~SCT~~ *HCT*, have relapsed AML or MDS as defined above, are not on treatment or prophylaxis for GVHD for at least 6 weeks before ~~administration~~ *the first dose* of study treatment, and have no active GVHD.

*In addition, previously untreated subjects are eligible for this cohort when the following criteria are m*et:

a. Previously untreated subjects with AML with known adverse cytogenetics who fall into the adverse ELN risk group and who are unlikely to benefit from standard intensive induction therapy or refuse intensive induction therapy at time of enrollment are also eligible.

b. Previously untreated subjects with MDS with documentation of at least one TP53 gene mutation or deletion based on local test. Prior lenalidomide or other supportive care in the form of transfusions or growth factors is allowed.

7) Language has been added regarding administration of COVID-19 vaccinations.
   - Sec 3.7.1 Prohibited Medications or Treatments
   - Sec 4.2 (exclusion criterion 7)

   (Prohibited Medications or Treatments) Live attenuated vaccines during the study through 30 days after the last dose of SL-172154, *the exception is that vaccines for COVID-19 are permitted*.

8) Language has been added to allow potential for continuation of study treatment with equivocal disease progression.
   - Sec 3.12 (new text)

   A subject meeting the response criteria of relapsed or progressive disease, or determination of clinical progression is considered a sufficient reason to discontinue study drug treatment. However, if the determination of progression is equivocal, the Investigator may continue study drug treatment until it is considered to be no longer beneficial to the subject.

9) Collection of transplant information has been added for subjects that discontinue study treatment when (s)he becomes eligible for and agrees to transplant.
   - Sec 3.13
   - Sec 6.1 (footnotes m, o)
   - Sec 6.2 (footnotes m, o)
   - Sec 6.11

   (Sec 3.13) New text

   In addition, for subjects that proceed to hematopoietic cell transplantation (HCT), HCT-relevant information, will be collected and entered in the EDC.

   (Sec 6.11) New Section

   In addition to the assessments noted in the Schedule of Assessment table (Section 6.1 or Section 6.2) to be performed at the Post Treatment Visit, additional information should be collected

regarding the subject. Beginning at the Post Treatment Visit and during Survival Follow-up, the start date and agent name of subsequent anticancer therapy(ies) for AML or MDS will be collected and entered in the EDC.

In addition, for subjects that proceed to HCT, HCT-relevant information (e.g., type of transplant, GVHD and transplant-related complications) may also be collected and entered in the EDC. Should the subject be followed by another physician, the study Investigator should contact the subject's hematologist/oncologist/transplant physician to obtain this information.

10) To address patient safety as well as the integrity of the study data in clinical trials performed during the COVID-19 pandemic, Shattuck Labs has developed a COVID-19 Risk Assessment Policy. This policy is a separate, living document outside of individual clinical study protocols.

- Sec 3.15 (New Section: COVID-19 Risk Assessment)

Shattuck Labs has developed a separate COVID-19 risk assessment policy to address conduct of clinical trials during the Coronavirus Disease 2019 (COVID-19) pandemic to ensure patient safety as well as management of potential implications to data integrity. A copy of this document can be made available upon request.

11) Therapies not considered a prior line of therapy for the previously untreated subjects with MDS enrolled to the SL-172154 + azacitidine dose escalation cohort has been revised. Hydroxyurea is typically used for myeloproliferative disorders (MDS/MPN) and high blast count and not generally used in patients with MDS. As patients who have developed MDS as a result of MPN are excluded in this study, it would be appropriate to remove the allowance for prior hydroxyurea in relation to MDS.

- Synopsis (inclusion criterion 7)
- Sec 4.2 (inclusion criterion 7)

[Dose Expansion Cohort Part A: SL-172154 Administered With Azacitidine]: Subjects diagnosed with MDS must be previously untreated. *Prior MDS therapy with lenalidomide*, ~~hydroxyurea~~ or other supportive care in the form of transfusions or growth factors *is allowed* ~~will not be considered prior therapy~~. *Up to 1 cycle of prior therapy with a hypomethylating agent is permitted*. Subjects with newly diagnosed treatment-related MDS are *also* eligible for enrollment

12) Blood sample that was planned for exploratory MRD analysis is now being collected for exploratory assessment of T cell repertoire. Although there is a scientific interest as to how MRD detection differs between using bone marrow and peripheral blood samples, this study will assess MRD only in bone aspirate. TCR analysis will provide how T cell repertoire changes and T cells clonally expand during SL-172154-based treatment, which may provide the relevant information relating to the MOA of SL-172154.

- Synopsis
- Sec. 2
- Sec 6.1
- Sec 6.2
- Sec 6.4.7

Exploratory Objectives	
To assess minimal residual disease (MRD) in subjects with higher-risk MDS or AML receiving SL-172154 alone or with azacitidine OR azacitidine + venetoclax	• MRD assessed in ~~peripheral blood or~~ bone marrow aspirate by NGS and/or flow cytometry

Blood sample *being sent* for *TCR* ~~exploratory~~ ~~research~~ ~~(MRD)~~ is to be collected ~~on the same day that a bone marrow aspirate is collected at baseline and end of Cycle 4 only~~ and sent for exploratory research.

Collection timepoints (on the same day bone marrow aspirate is collected) include baseline, end of Cycle 1, end of Cycle 4, end of Cycle 13, and then every 6 months (e.g., 6 cycles) thereafter. If a bone marrow assessment is performed when a subject discontinues study treatment as (s)he become eligible for and agrees to proceed to HCT, a sample of the aspirate as well as blood sample for TCR analysis should also be sent for exploratory research.

13) Additional hematology assessments on Day 15 of Cycles 2, 3, 4, 5, and 6 have been included to allow evaluation of changes in hematologic counts in the first 6 cycles of treatment in this study.

- Sec 6.1
- Sec 6.2

14) Assessment of hematologic improvement at the beginning of each cycle beginning in Cycle 2 for subjects with MDS has been added. The frequency of bone marrow tests will be reduced to every 6 cycles beyond Cycle 13, therefore disease response (e.g., CR, PR) will be assessed approximately every 6 months beyond Cycle 13. Meanwhile, hematologic improvement can be evaluated every cycle with peripheral blood results and red blood cell transfusion record, which will provide scientifically meaningful information.

- Sec 6.1
- Sec 6.2
- Sec 8.1.2

All subjects who completed at least one cycle of study treatment will be assessed by the Investigators using the IWG 2006 MDS response criteria as described below. *Bone marrow* assessments ~~will~~ *should* be performed *to assess disease response as described in Section 6.8* ~~at the end of Cycle 1 and every 3 cycles thereafter for response assessment. For subjects with resistant disease at end of Cycle 1, a repeat bone marrow will be performed at the end of Cycle 2~~. *Response assessment for hematologic improvement will be performed at each cycle beginning in Cycle 2 regardless of whether a bone marrow test is performed.*

15) Based on emerging data from the ongoing Study SL03-OHD-101 Phase 1, collection of blood sample for cytokine analysis has been modified to remove samples at D15 (monotherapy) or D16 (combination regimens) in Cycle 1.

- Sec 6.1 and 6.1.1

- Sec 6.2 and 6.2.1

16) As confirmation of TP53 gene mutation/deletion for subjects enrolled in Dose Escalation (SL-172154 + azacitidine) or Dose Expansion (Part C) is performed by the Investigator using historical information and not a study-specific procedure, it has been removed from the Schedule of Assessment table in Section 6.2.

    Additionally, clarification regarding local confirmation of TP53m has been added in Section 6.8.1:

    Documentation of TP53 gene mutation/deletion by local testing will serve as entry criterion for subject *with previously untreated MDS with TP53m enrolled in the Dose Escalation Cohort of SL-172154 administered with azacitidine* and for subjects with AML enrolled in Part C Cohort of Dose Expansion.

17) The collection of a subject's transfusion history prior to enrollment on this study has been modified to better reflect the AML or MDS populations.
    - Sec 6.1
    - Sec 6.2
    - Sec 6.10

    From 8 weeks *(subjects with MDS) or from 4 weeks (subjects with AML)* prior to the first dose throughout end of treatment date.

18) The protocol-specified schedule of bone marrow for disease assessments has been modified to allow less frequent procedures for subjects that continue on study treatment for longer than approximately 1 year as these subjects are anticipated to have better disease control. Although bone marrow aspirate (or biopsy) is essential to evaluate disease assessment, the procedure is invasive and painful for patients. Thus, flexibility of mandatory bone marrow examination to accommodate institutional/regional standard practice has been added.
    - Sec 6.8
    - Sec 6.1
    - Sec 6.2

Bone marrow *for disease* assessments should be performed at the following timepoints:

- Screening (baseline)
- End of Cycle 1 (performed -7 days of Cycle 2 Day 1 ~~and resulted prior to the administration of treatment for Cycle 2~~)
    - For *AML* subjects with resistant disease at end of Cycle 1, a repeat bone marrow must be performed at the end of Cycle 2 (performed ±7 days of Cycle 3 Day 1) ~~based on the hematologic recovery to confirm response~~
- End of every 3 Cycles ~~thereafter~~ until Cycle 13 (e.g., End of Cycle 4, Cycle 7, ~~etc.~~ Cycle 10, Cycle 13)
- *End of every 6 Cycles beyond Cycle 13 (e.g., End of Cycle 19, Cycle 25, etc.)*
- At time of relapse/progression: if clinically feasible

- *A bone marrow assessment is strongly encouraged when a subject discontinues study treatment as (s)he becomes eligible for and is planned to proceed to HCT.*
- *In the event that a subject experiences prolonged response or stable disease beyond Cycle 7, less frequent bone marrow assessment is permitted after consultation with the Sponsor Medical Monitor*.

19) The protocol-specified schedule of collection of bone marrow aspirate for exploratory research has been modified. Submission requirements of bone marrow specimen has been changed to add timepoints at the end of Cycle 2 (select AML subjects only), end of Cycle 7, end of Cycle 10, and every 6 cycles (e.g., 6 months) beyond Cycle 13, which is the second year of the study treatment. Assessing minimal residual disease (MRD) is clinically meaningful in the patients who are experiencing "good" disease control such as CR because these patients may have deeper response typically represented by negative MRD.

- Sec 6.8
- Sec 6.1
- Sec 6.2

Submission of a sufficient bone marrow aspirate *for central laboratory analysis* ~~must~~ *should* be collected ~~for clinical disease assessment and *exploratory research* biomarker assessments from the bone marrow performed~~ at the following timepoints *(each with a 7 day window)*:

- Screening (baseline)
- End of Cycle 1 *(e.g., performed -7 days of Cycle 2 Day 1)*
  - *End of Cycle 2 for AML subjects with resistant disease at end of Cycle 1 (performed ±7 days of Cycle 3 Day 1)*
- End of Cycle 4
- *End of Cycle 7*
- *End of Cycle 10*
- End of Cycle 13
- *Every 6 cycles (e.g. 6 months) thereafter*
- *When a subject discontinues study treatment as (s)he becomes eligible for and is planned to proceed to HCT if a bone marrow assessment is performed*

If a bone marrow is performed *at any unscheduled timepoint prior to the end of Cycle 13* for subjects with *AML who achieve* CR, ~~marrow CR~~ *Cri*, or MLFS, *or for subjects with MDS who achieve CR or marrow CR* ~~at any unscheduled timepoint prior to the end of Cycle 13~~, a portion of the bone marrow aspirate should also be sent to the central laboratory for exploratory research.

20) Assessment of cyotogenetic CR per 2003 IWG AML response criteria has been added for the response evaluation of subjects with AML. Cytogenetic CR was included as a part of 2003 IWG AML response criteria. Due to the nature of a phase 1 study, the locally assessed cytogenetic information will help to obtain insight of efficacy signal from SL-172154 or its combination with azacitidine OR azacitidine + venetoclax.

Sec 8.1.1
All subjects who completed at least one cycle of study treatment will be assessed by the Investigators using the 2017 ELN Response Criteria for AML as described below. Assessments will be performed ~~at the end of Cycle 1 and every 3 cycles thereafter~~ for response assessment *as described in Section 6.8*. ~~For subjects with resistant disease at end of Cycle 1, a repeat bone marrow will be performed at the end of Cycle 2~~. *Additionally, for subjects with cytogenetic abnormalities at the baseline bone marrow test, cytogenetic CR should be reported per 2003 IWG AML response criteria [Cheson, 2003] when the result is available. Cytogenetic CR is defined as reversion to a normal karyotype at CR.*

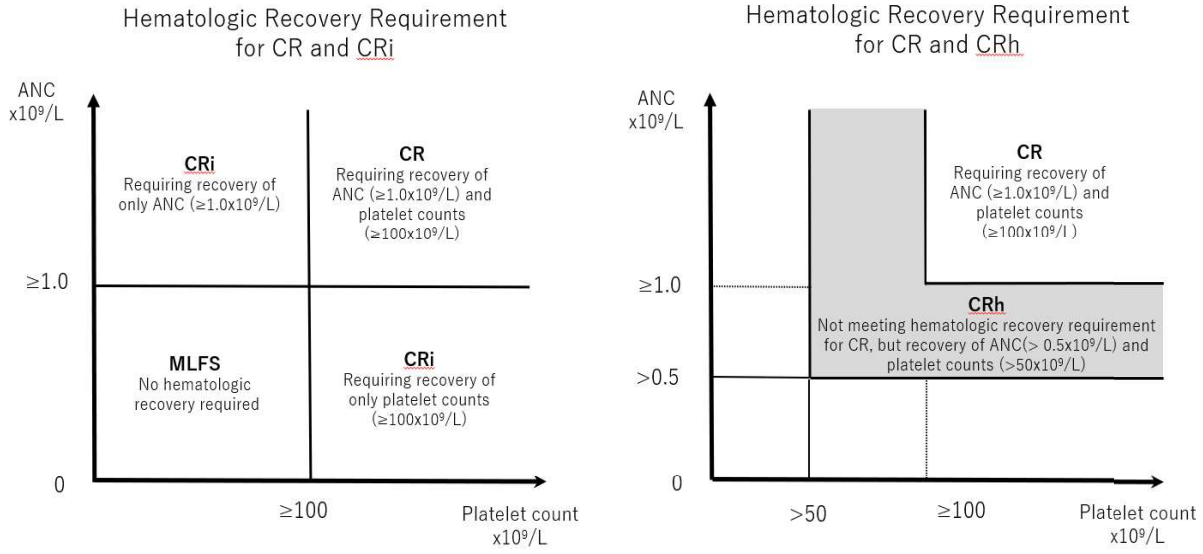
Sec 8.1.2
Cytogenetic CR has been included in the IWG response criteria table

Cytogenetic CR	• Disappearance of the chromosomal abnormality without appearance of new ones in subjects who achieve CR

21) Assessment of CRh (complete remission with partial hematologic recovery) has been added for the response evaluation of subjects with AML Some patients who achieved less than CR derive benefit from particular types of AML therapy. CRh (complete remission with partial hematologic recovery) is an emerging concept in the management of AML.

Sec 8.1.1 (new text)
Additionally, CRh (complete remission with partial hematologic recovery) will be evaluated separately from the ELN response criteria. CRh is defined as all CR criteria except for partial hematological recovery of peripheral blood counts (e.g., platelets >50 x 10^9/L and ANC >0.5 x 10^9/L), as described in Figure 2.

Figure 2 Hematologic Recovery Requirements for CR, CRh, and Cri



ANC: absolute neutrophil count; CR: complete remission; Cri: complete remission with incomplete hematologic recovery; MLFS: morphologic leukemia-free state; CRh: complete remission with partial hematologic recovery

To determine transfusion dependence or independence, RBC transfusion history should be collected for 4 weeks prior to initiating study treatment for AML subjects regardless of hemoglobin level.

22) Based on the revisions described in Amendment 2 that are related to efficacy assessment, the following changes have been made to the efficacy analyses descriptions in the statistical analysis section of the protocol.

- Section 9.2.5

The primary efficacy analysis will include the following endpoints:

- CR is defined as the proportion of subjects who reach CR prior to the initiation of any new therapy *for AML or MDS*.
- Duration of CR is measured from the date when the CR criteria are first met to the date of relapse *or death, whichever occurs first*.
- Time to CR is defined as the time from the first dose of study treatment to the date of CR criteria are first met.
- *CR/CRh is defined as the proportion of subjects who reach CR or CRh prior to the initiation of any new therapy for AML.*
- *Duration of CR/CRh is measured from the date when the CR or CRh criteria are first met to the date of relapse or death, whichever occurs first*.
- ORR is defined as the proportion of subjects who reach objective response prior to the initiation of any new therapy *for AML or MDS*. The objective response is defined as CR, Partial Remission (PR), marrow CR, or hematologic improvement based on IWG criteria for MDS, and CR, CR with incomplete hematologic recovery (CRi), PR, or morphologic leukemia-free state (MLFS) based on ELN criteria for AML.
- Duration of Response (DOR) is measured from the date when the objective response criteria are first met to the date of relapse, *disease progression or death, whichever occurs first*.
- Time to objective response is defined as the time from the first dose of study treatment to the date of objective response criteria are first met.
- Composite CR rate is the proportion of subjects who reach composite CR prior to initiation of any new therapy *for AML*. The composite CR includes ~~CR and marrow CR per IWG for MDS and~~ CR and CRi per ELN for AML. ~~Partial remission rate is the proportion of subjects who achieve a PR as the best response prior to initiation of any new therapy.~~
- Duration of composite CR is measured from the date when the composite CR criteria are first met to the date of relapse *or death, whichever occurs first*.
- Time to composite CR is defined as the time from the first dose of study treatment to the date of composite CR criteria are first met.
- Progression Free Survival (PFS) is defined as the time from the first dose of study treatment to the date of documented disease progression, relapse, or death from any cause, whichever occurs first.

- EFS is defined as the time from the first dose of study treatment to the date of documented treatment failure, disease progression, relapse, or death from any cause, whichever occurs first.
- RBC transfusion independence rate is the proportion of subjects who have a 56-day or longer period with no RBC transfusions.
- Duration of RBC transfusion independence: the duration of RBC transfusion independence is measured from the date on which measurement criteria are first met for RBC transfusion independence to the first date of RBC transfusion prior to initiation of any new therapy *for AML or MDS*.
- *Platelet transfusion independence rate is the proportion of subjects who have a 56-day or longer period with no platelet transfusions.*
- *Duration of platelet transfusion independence: the duration of platelet transfusion independence is measured from the date on which measurement criteria are first met for platelet transfusion independence to the first date of platelet transfusion prior to initiation of any new therapy for AML or MDS.*
- MRD Negative response rate is defined as the proportion of subjects who achieve MRD negativity and ~~composite~~ CR, *CRi, or MLFS (subjects with AML) or CR or marrow CR (subjects with MDS)*. Subjects who have no MRD assessment will be considered as non-responder for the calculation of MRD negative response rate.
- Overall Survival (OS) is defined as the time from the first dose of study treatment to the date of death from any cause.

The ORR, CR, composite CR, *CR/CRh*, RBC *and platelet* transfusion independence rate, and MRD negative response rate 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 CR, composite CR, *CR/CRh*, and ORR, respectively. Duration of RBC *and platelet* transfusion independence will be evaluated, using the Kaplan-Meier method, for the subgroup of subjects with transfusion independence. The Kaplan-Meier method will be used to estimate the PFS/EFS/OS curve and PFS/EFS/OS rate at time of point of interest.

16.12 Summary of Changes for Protocol Amendment 03

This amendment applies to all Investigator sites participating in this study. Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 03.

Minor editorial changes (including protocol version number and approval date, table of contents) as well as minor clarification edits to text are incorporated in this amendment.

This protocol was amended to include the following:

- Protocol Synopsis – all changes as noted below are included in synopsis, as needed.
- Study Schema was revised to better reflect the current study design.
- Section 1.6 Summary of Clinical Data was updated with data as of 12 September 2022. Additional details are available in the SL-172154 IB. Incorporation of this data is also in Section 1.81, Section 3.
- Section 1.8.1 Potential Risks – additional explanation has been added to the Safety profile of SL-172154 in the context of azacitidine and venetoclax:

"*Anemia without evidence of hemolysis, and transient decreases in lymphocyte and platelet counts have been observed with SL-172154. These hematologic effects are not a consequence of myelosuppression. The expression of CD40 on platelets and B cells may explain the hematologic effects observed with CD40 agonists. Inwald et al. showed that the binding of sCD40L to CD40 induces P-selectin expression and partially activates $\alpha_{IIb}\beta_3$ without inducing platelet aggregation [Inwald 2003]. We and others have shown that ligation of CD40 receptor on B cells by CD40 agonists lead to transient egress of B cells from the circulation [Lakhani 2021; Vonderheide 2007].* ~~Thus, other than fatigue,~~ It is not expected that SL-172154 would exacerbate the *myelosuppression* ~~toxicities~~ commonly observed with azacitidine alone or in combination with venetoclax."

- Contraception requirement has been clarified and country-specific requirements have been included:

Inclusion Criteria #14) "*Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test within 72 hours of the first dose of study treatment. NOTE: females are defined as being of childbearing potential unless they are surgically sterile (i.e., have undergone a complete hysterectomy, bilateral tubal ligation/occlusion, bilateral oophorectomy or bilateral salpingectomy), have a congenital or acquired condition that prevents childbearing or are naturally post-menopausal for at least 12 consecutive months. Documentation of post-menopausal status must be provided. To avoid pregnancy, FCBP must start using a highly effective method of contraception (i.e., <1% failure rate), as described in Section 16.3, at least 14 days prior to initiation of study treatment, and continue use during treatment and for 30 days (which exceeds 5 half-lives) after the last dose of SL-172154, or for the duration required by local prescribing information after the last dose of azacitidine (i.e., for sites in UK and Spain, at least 6 months after the last dose of azacitidine in either combination regimen).*"

Inclusion criteria #14) "*Male subjects with female partners must have azoospermia from a prior vasectomy, an underlying medical condition, or agree to use a highly effective method of contraception (i.e., <1% failure rate) during treatment and for 30 days (which exceeds 5 half-lives) after the last dose of SL-172154, or for the duration required by local prescribing information after the last dose of azacitidine (i.e., for sites in UK and Spain, at least 3 months; for sites in Canada, at least 6 months).*"

- Section 4.1 (Inclusion Criteria 14 and 15), Section 6.2 footnote "i", Section 16.3

- Footnote "i" in Table in Section 6.1 and 6.2 Schedule of Assessments have been revised to include pregnancy tests every 4 weeks for females of child-bearing potential in Spain.
- Frequency of SL-172154 doses on Cycle 3 Day 1 and beyond has been changed throughout.
- Duration of SL-172154 infusion has been prolonged for doses at 1.0 mg/kg or higher.
  - Section 3.1.1 Table 1, Section 3.2.1 Table 2, Section 5.1.1, 6.1.1, 6.2.1.
- Duration of infusion prolonged for subjects who experience CRS.
  - Section 3.8.2
- Section 2 Exploratory Objectives and Outcome Measures – modifications were made to include biomarker analysis of peripheral blood in Section 2:

Exploratory Objectives	**Outcome Measures**
To assess pharmacodynamic biomarkers in *peripheral blood and* bone marrow aspirate prior to, on-treatment and following treatment with SL-172154 administered alone or with azacitidine OR azacitidine + venetoclax in subjects with higher-risk MDS or AML	Pharmacodynamic biomarkers in *peripheral blood and bone marrow* aspirate may include: • Changes in T cells subsets, B cells, macrophages and DCs • Evidence of SL-172154 localization (CD47 or CD40 receptor occupancy) on hematopoietic cells and/or leukemic cells in the bone marrow and peripheral blood

- Receptor occupancy analysis for bone marrow aspirate has been added with associated changes of scheduled bone marrow aspirate:

"Receptor occupancy of SL-172154 on CD47 and CD40 on bone marrow cells will be measured by flow cytometry for specimens from the bone marrow aspirate. Receptor occupancy will be analyzed for the bone marrow aspirate specimens collected on Cycle 2 Day 1, on Cycle 3 Day 1 (if a bone marrow aspirate is required) and on Cycle 5 Day 1 in SL-172154 monotherapy cohort, or on Cycle 2 Day 2, on Cycle 3 Day 2 (if a bone marrow aspirate is required) and on Cycle 5 Day 2 in either combination regimen. If this is not feasible, make every effort to perform bone marrow aspirate within 24 hours from the completion of SL-172154 dose (as an example for SL-172154 monotherapy, bone marrow aspirate should be performed on Cycle 2 Day 2 within 24 hours after SL-172154 dose was completed on Cycle 2 Day 1; as an example for the combination therapy, bone marrow aspirate should be performed on Cycle 2 Day 3 within 24 hours after SL-172154 dose was completed on Cycle 2 Day 2). Alternatively, bone marrow aspirate can be performed on the day of a prior dose (e.g. Cycle 1 Day 22 for monotherapy; Cycle 1 Day 23 for combination therapy) or on the day of a subsequent dose (e.g. Cycle 2 Day 8 for monotherapy; Cycle 2 Day 9 for combination therapy); in these cases, bone marrow aspirate must be performed after the completion of SL-172154 administration on the day. If this is still not feasible, make every effort to perform bone marrow aspirate within 24 hours from the completion of SL-172154 dose (as an example for SL-172154 monotherapy, bone marrow aspirate should be performed on Cycle 1 Day 23 within 24 hours after SL-172154 dose was completed on Cycle 1 Day 22; as an example for the combination therapy, bone marrow aspirate should will be performed on Cycle 1 Day 24 within 24 hours after from the completion of when SL-172154 dose was completed on Cycle 1 Day 23)."

- Section 6.1, Section 6.2, Section 6.4.7, Section 6.8.2.

- Peripheral blood collection for receptor occupancy analysis has been added:

"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."

  - Section 6.1, Section 6.1.1, Section 6.2, Section 6.2.1, Section 6.4.7, Section 6.7.2.

- Peripheral blood collection for hematology and clinical chemistry analysis has been added.
  - SL-172154 Monotherapy Dose Escalation Cohorts

    Hematology has been added on Cycle 1 Day 3.
    - Table 6.1

    Hematology and clinical chemistry have been added on Cycle 2 Day 2.
    - Table 6.1

    Blood sample collection for cytokines has been moved from Cycle 1 Day 4 (72 hour post-EOI) to Cycle 1 Day 2 (24 hour post-EOI).
    - Tables 6.1 and 6.1.1

    Blood sample collection for cytokines has been moved from Cycle 2 Day 3 (48 hour post-EOI) to Cycle 2 Day 2 (24 hour post-EOI).
    - Tables 6.1 and 6.1.1
  - SL-172154 Combination Cohorts, Dose Escalation or Dose Expansion (SL-172154 with Azacitidine or Azacitidine and Venetoclax)

    Hematology has been added on Cycle 1 Day 4, Cycle 2 Day 4, Cycle 2 Day 9 and Cycle 2 Day 23.
    - Table 6.2

    Hematology and clinical chemistry have been added on Cycle 2 Day 3.
    - Table 6.2

    Blood sample collection for cytokines has been moved from Cycle 1 Day 5 (72 hour post-EOI) to Cycle 1 Day 3 (24 hour post-EOI).
    - Tables 6.2 and 6.2.1

    Blood sample collection for cytokines has been moved from Cycle 2 Day 4 (48 hour post-EOI) to Cycle 2 Day 3 (24 hour post-EOI).
    - Tables 6.2 and 6.2.1

- Monitoring time after completion of SL-172154 infusion has been shortened at Cycle 4 Day 1 and beyond when subjects meet required criteria (Section 5.1.4).
- An alternative schedule of azacitidine, 4-2-3 schedule (i.e. azacitidine administration on Days 1-4 and 7-9), has been added.
- The condition to initiate the enrollment of the dose escalation cohort of the combination of SL-172154 and azacitidine has been clarified.

"When the SL-172154 monotherapy cohort completes the DLT evaluation period in Dose Level 2 (3.0 mg/kg), enrollment may begin in parallel to the dose escalation cohorts investigating SL-172154 (starting dose 1.0 mg/kg) administered with azacitidine to maximize the potential for clinical benefit to participating subjects*."*

- Study Schema footnote, Section 1.7, Section 3, Section 3.3.1, Section 3.2.1

- The following sentence has been removed because the dose of 6.0 mg/kg is not currently included in the study, SL03-OHD-101.

  ~~Doses explored in SL03-OHD-104 will not exceed the highest dose cleared for safety in SL03-OHD-101.~~

  - study schema footnote, section 1.8.1, 3.1.1, 3.2.1, 3.2.2, 7.8

- The following rule has been added to SL03-OHD-104:

"To escalate the dose of SL-172154 in combination with azacitidine, the corresponding monotherapy dose level for SL-172154 will have been cleared for safety."

  - study schema footnote, section 3.2.1

- Washout period of CYP3A inducers in Section 3.7.1 (Prohibited Medications or Treatments) has been updated to be consistent with the washout period defined in the Exclusion Criterion 6 in Section 4.2.
- Clarifications have been added to Section 3.7.1 for use of immunosuppressive medications and systemic corticosteroids:

"~~Immunosuppressive medications for primary prophylaxis against IRRs are not permitted. Subjects who require immunosuppressive medications (e.g., corticosteroids) for management of IRRs should be managed per Toxicity Management Guidelines in Section 3.8.~~

- *Immunosuppressive medications (except to treat a drug-related AE).*
- *Systemic corticosteroids > 10 mg daily prednisone equivalent except that the followings are permitted.*
  - *Topical, intranasal, inhaled, ocular, intraarticular corticosteroids.*
  - *Physiological doses of replacement steroid (e.g., for adrenal insufficiency).*
  - *A brief course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., transfusion reactions, delayed-type hypersensitivity reaction caused by contact allergen).*
  - *Treatment for a drug-related AE (See Section 3.8)."*

- Clarification of permitted and prohibited steroid use has also been updated in Section 4.2 (Exclusion Criterion 6):
  - "Physiological doses of replacement steroid (e.g., for adrenal insufficiency) ~~not to exceed 10 mg/day of prednisone or equivalent~~
  - Steroid premedication for hypersensitivity reactions (e.g., reaction to IV contrast*) or a brief course of treatment of non-autoimmune conditions (e.g., transfusion reactions, delayed-type hypersensitivity reaction caused by contact allergen)*."

- Removed blood sample collection for TCR analysis as this will no longer be done.
  - Section 6.1, 6.2, and 6.4.7
- Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (Section 16.4) has been updated.
- Table 4 TLS Classification was corrected and updated:

  - Corrected value of phosphorus for hyperphosphatemia. The original version of Howard's paper (N Engl J Med 2011) included incorrect values. The values here should correct to be consistent with the values after erratum of Howard's paper.
  - Updated value of ionized calcium for hypocalcemia was corrected to <4.5 mg/dL (1.12 mmol/L) in TLS classification Table 4 per ref (https://www.nejm.org/doi/full/10.1056/NEJMx180018?query=recirc_curatedRelated_article)
- A minimum 3-day stagger between dosing the first and second subject at each SL-172154 dose level has been added.

  "*…At each dose level, a minimum 3-day stagger between dosing the first and second subject is required."*
  - Section 3.1.1, 3.2.1
- Revised conditions for exclusion of CAR-T therapy.

  "CAR-T cell therapy *within 3 months from the first dose of the study drug*."
  - Section 4.2, Exclusion 1
- Step-up dose schedule of SL-172154 at 6.0 or 10.0 mg/kg has been included in the following sections:
  - Section 3.1, Section 3.2, Section 16.10
- Multigated Acquisition (MUGA) scans are included as an assessment method for left ventricular ejection fraction.
  - Table 6.1, Table 6.2, Section 6.4.6

Country-Specific Revisions:

- Edits have been incorporated to clarify that, for newly diagnosed secondary AML, enrollment is restricted to the subjects who are unlikely to benefit from standard intensive induction therapy or refuse intensive induction therapy at the time of enrollment
  - Section 4.1 (Inclusion criterion 8c)

"Subjects with newly diagnosed secondary AML *and who are unlikely to benefit from standard intensive induction therapy or refuse intensive induction therapy at time of enrollment* are eligible for enrollment."

- Clarification has been added to exclude subjects who are eligible for rescue chemotherapy and allogeneic-hematopoietic cell transplantation (HCT) at the time of screening.
  - Section 4.1 (Inclusion criteria 5 and 6)

"Subjects must not be eligible for rescue chemotherapy and allogeneic-HCT per local or institutional guidelines at the time of screening."

- Exception for Covid-19 regarding use of live attenuated vaccine has been removed and clarification added:

"Receipt of live attenuated vaccine within 30 days of first dose of SL-172154 treatment~~, the exception is that vaccines for COVID-19 are permitted~~."
  - Section 3.7.1, Section 4.2 (exclusion criterion 7)

"Live attenuated vaccines during the study through 30 days after the last dose of SL-172154~~, the exception is that vaccines for COVID-19 are permitted~~."

- Section 3.7.1 Prohibited Medications or Treatments

"Vaccines for COVID-19 are permitted as they are not live attenuated vaccines. 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."

- Section 3.7 Concomitant Medications, Treatments and Procedures

- Edits have been incorporated to indicate that the marketed agents azacitidine and venetoclax are included in this study in combination regimens under investigation.

  Section 1.7: "…Azacitidine and venetoclax are commonly used in clinical practice ~~standard of care (SOC) therapies~~ in these patient populations, with well-described safety and PK profiles for the individual agents and the combination. *This is the first clinical trial to investigate the combination of these agents with SL-172154.* Each component is anticipated to have activity on distinct targets, and these ~~SOC~~ agents combined with SL-172154 have the potential to further bridge innate and adaptive immunity, thus potentially improving treatment outcomes without increasing toxicity."

  Section 3.2.2: "Azacitidine (75 mg/m^2, IV or SQ on Days 1 to 7 or alternative 5-2-2 *or 4-2-3* schedule) and venetoclax (target dose of 400 mg, oral, once daily) will be administered ~~at their standard dose and schedule~~ *as described* (Section 5.2 and Section 5.3) in 28-day cycles."

  Section 3.4: The RP2D is a dose of SL-172154 that can be safely administered with ~~standard of care doses of~~ azacitidine or azacitidine with venetoclax.

- Reference has also been added to the current country's prescribing information for guidance on use and toxicity management for azacitidine-related or venetoclax-related toxicities.

  Section 3.2.1: During therapy, management of azacitidine-related toxicity should follow the guidelines provided in the *country's current prescribing information (e.g., USPI, SmPC, or Product Monograph)* ~~current USPI or local guidelines in other countries~~.

  Section 3.2.2: During therapy, management of azacitidine-related or venetoclax-related toxicity should follow the guidelines provided in the *country's current prescribing information (e.g., USPI, SmPC, or Product Monograph)*~~current USPI or local guidelines in other countries~~.

- Use of "prescribing information" has been amended to "the country's current prescribing information (e.g., USPI, SmPC, or Product Monograph)" in the following locations:
  - Section 3.7.1, Section 3.7.2, Section 3.9, Section 3.10, Section 5.2, Section 5.3

16.13 Summary of Changes for Protocol Amendment 3.1

This amendment was done to address FDA's comments on previous amendments and it applies to all Investigator sites participating in this study. Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 3.1.

Minor editorial changes (including protocol version number and approval date, table of contents) as well as minor clarification edits to text are incorporated in this amendment.

This protocol was amended to include the following:

- Alternative schedule of 4-2-3 for administration of azacitidine was removed from the protocol. Changes are reflected in the following Sections.

  Protocol synopsis; Section 3.2.1; Section 3.2.2; Section 5.2, Section 5.3, Section 6.2

- In Section 3.14: Study Treatment Discontinuation Criteria. The following text was modified for clarification.

  A subject meeting the response criteria of relapsed or progressive disease, or determination of clinical progression is considered a sufficient reason to discontinue study drug treatment. However, if the determination of progression is equivocal *for a subject with AML*, the Investigator may continue study drug treatment ~~until it is considered to be no longer beneficial to the subject.~~ *when a subject with transfusion independence at baseline remains post-treatment transfusion independent or when a subject with transfusion dependence at baseline become post-treatment transfusion independent. Transfusion independence at baseline is defined as no transfusion during the 4-week period prior to the first dose of study drug treatment. Post-treatment transfusion independence is defined as no transfusion for ≥ 56 days at any time point after the first dose of study drug treatment. When the determination of progression is equivocal for a subject with MDS, the investigator may continue study drug treatment until relapse/ disease progression is confirmed after 4 weeks from an initial finding unless there is clinical deterioration.*

16.14 Summary of Changes for Protocol Amendment 3.2

This amendment was done to address FDA's comments on previous amendments and it applies to all Investigator sites participating in this study. In addition, this amendment includes added assessments of post-infusion hematology to evaluate hemoglobin level changes immediately after infusion. Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 3.2.

Minor editorial changes (including protocol version number and approval date, table of contents) as well as minor clarification edits to text are incorporated in this amendment.

This protocol was amended to include the following:

- In Section 3.14: Study Treatment Discontinuation Criteria. The following text was modified for clarification.

  A subject meeting the response criteria of relapsed or progressive disease, or determination of clinical progression is considered a sufficient reason to discontinue study drug treatment. However, if the determination of progression is equivocal for a subject with AML, the Investigator may continue study drug treatment ~~when a subject with transfusion independence at baseline remains post-treatment transfusion independent or~~ when a subject with transfusion dependence at baseline become post-treatment transfusion independent. Transfusion ~~in~~dependence at baseline is defined ~~as no~~ *by* transfusion *requirement* during the 4-week period prior to the first dose of study drug treatment.

- Step-up dose was removed from the Protocol. Sections 3.1.1, 3.2.1 and 3.2.2 were updated to reflect this change. Appendix 6.10 (Step-up dose schedule of SL-172154) was removed.
- Schedule of assessments 6.1: A post-infusion hematology sample 2 hours from the end of infusion was added on C1D1, C1D8, C1D15 and C2D1 for monotherapy cohorts.
- Schedule of assessments 6.2: A post-infusion hematology sample 2 hours from the end of infusion was added on C1D2, C1D9, C1D16 and C2D2 for combination cohorts. A hematology sample prior to SL-172154 infusion was also added on C2D2 for evaluation of baseline counts.
- Schedule of assessment 6.1.1: C1D1 and C2D1 blood sample for receptor occupancy assessment was changed from 1.5hr post-EOI to 2.0hr post-EOI time point. In addition, C1D15 blood sample time point was changed from 1.5hr post-EOI to 2.0hr post-EOI.
- Schedule of assessment 6.2.1: C1D2 and C2D2 blood sample for receptor occupancy assessment was changed from 1.5hr post-EOI to 2.0hr post-EOI time point. In addition, C1D16 blood sample time point was changed from 1.5hr post-EOI to 2.0hr post-EOI.

16.15 Summary of Changes for Protocol Amendment 4.0

This amendment applies to all Investigator sites participating in this study. The purpose of this amendment is to update prophylactic premedication for infusion related reactions, update IRR management guidelines, update enrollment numbers and clarify schedule of assessments. Minor editorial changes as well as minor clarification edits to the text are incorporated in this amendment.

- **Section: Study Schema**

  Description of change: Updated the subject numbers for Part A and Part C.

  Rationale: To be consistent with the changes made in the protocol

- **Section: Synopsis**

  Description of change: Updated the synopsis with the changes made in the protocol.

  Rationale: To be consistent with the body of the protocol

- **Section: Throughout the Protocol**
- **Description of change:** 'patient' was updated to 'subject'**.**
- **Rationale:** For consistency
- **Section: Throughout the Protocol**

  Description of change: Reference to Spain was removed throughout the protocol.

  Rationale: The study will not be conducted in Spain due to regulatory approval challenges

- **Section: Throughout the Protocol**

  Description of change: Updated number of subjects to be enrolled in Part A from approximately 20 subjects to approximately 30 subjects and the number of subjects to be enrolled in Part C from approximately 10 subjects to up to 20 subjects.

  Rationale:

  Increasing 30 treatment naïve subjects with higher-risk MDS in Part A will allow enrollment and analysis of response data for subjects with wild-type TP53 and TP53 gene mutation/deletion. Clinical outcomes are shown to be distinct between these patient populations.

  In Dose Expansion Cohort Part C, subjects with previously untreated de novo AML or secondary AML with TP53 gene mutation or deletion are eligible. The recent AML classification defines AML with mutated TP53 as disease with somatic TP53 mutation (variant allele frequency: Variant Allele Frequency, VAF, > 10%). Nonetheless, it is not currently feasible to obtain the results of VAF and further details of TP53 alterations during screening, which make it challenging to know how many subjects will have VAF > 10% or multi-hit TP53 alterations. Thus, increasing the size to up to 20 subjects could provide scientifically meaningful interpretation by conducting VAF and further details of TP53 alterations later. The enrolment of up to 20 subjects will also provide a narrow confidence interval.

- **Section 1.6 Summary of Clinical Data**

  Description of change: Updated the section with data available as of 25May2023. Updated the summary of data for SL03-OHD-101, a Phase 1 first-in-human study.

  Rationale: To provide updated clinical information to the investigators**.**

- **Section 1.8.1 Potential risks**

  Description of change: Added updated data from SL03-OHD-101, a Phase 1 first-in-human study.

  Rationale: To provide updated clinical information to the investigators.

- **Section 3.1 Description of Study Design (Table 1, Table 2); Section 6 Study assessments and procedures (Table 11, Table 12)**

  Description of change: Duration of infusion for 3 mg/kg SL-172154 was updated from 120 minutes (± 15 minutes) to 180 minutes (± 15 minutes)

  Rationale: Based on the available data from SL-172154 studies, decreasing the rate of infusion has been shown to help in reducing the incidence of infusion related reactions.

- **Section 3.7.1 Prohibited Medications or Treatments**

  Description of change: Corticosteroids use as prophylactic premedication was added under permitted exceptions.

  Rationale: Dexamethasone will be given as a premedication prior to each SL-172154 administration

- **Section 3.7.3 Prophylactic Premedication for Infusion-Related Reactions (IRR) (All Subjects) and throughout the protocol**

  Description of change: Added Dexamethasone (8 mg IV, administered at least 30 minutes prior to each SL-172154 administration) as a prophylactic premedication.

  Rationale: The safety monitoring committee reviewed emerging data from the current study and recommended dexamethasone as premedication as it may reduce the IRR incidence and symptoms.

  Description of change: changed ranitidine 50 mg PO or IV (or equivalent) to famotidine 20 mg PO or IV (or equivalent) as an example of a histamine-2 blocker.

  Rationale: Ranitidine is no longer available.

- **Section 3.8.1 Management of Infusion Related Reactions**

  Description of change: Added text to clarify that ad-hoc labs should be collected in the event of an IRR; clarified text for vital signs collection; updated guidance for SL-172154 administration for subsequent cycles in the event of Grade 2 IRR.

- **Rationale:** The safety monitoring committee reviewed emerging data from the current study and agreed with the Sponsors recommendation that SL-172154 may be administered at one

dose level lower, OR if the original dose is administered, the infusion must be administered at 50% of the rate in mg/min at which the reaction occurred.

- **Section 3.8.2 Management of Cytokine Release Syndrome**

  Description of change: Added text to clarify that ad-hoc labs should be collected in the event of a CRS; clarified text for vital signs collection; deleted examples for subsequent infusions.

  Rationale: Clarification purpose

- **Section 6: Study Assessments and Procedures; Appendix 16.5, Appendix 16.6**

  Description of change: Clarified text that if SL-172154 dose is held, then the next scheduled dose of azacitidine (and venetoclax) can be administered per the schedule, without any delay; also clarified that if the start of a subsequent cycle (e.g., Day 1) is delayed due to azacitidine-related or venetoclax-related toxicities, SL-172154 dose should also be delayed and consequently, the current cycle length is extended.

  Rationale: Clarification purpose

- **Section 6: Study Assessments and Procedures 6.2**

  Description of change: PK sample was removed from C3 onwards.

  Rationale: Based on the available data from SL-172154 studies, it was determined that these samples are not needed.

  Description of change: footnote was added for submission of previously collected bone marrow sample (if available) and collection of peripheral blood for biomarker research when bone marrow sample could not be collected.

  Rationale: To provide an option to assess biomarkers in case bone marrow sample could not be collected

  Description of change: The following footnotes were clarified.

  Footnote a: Added text to clarify that laboratory tests can be performed up to 3 days prior to the scheduled dose.

  Footnote h3: vital signs collection recommendation in the event of an IRR

  Footnote j: clarified that additional blood sample should be collected for ADA within 45-90 days of the last dose of study treatment.

  Rationale: Clarification purpose

- **Section 6.5.7: Local and Central laboratory assessments**

  Description of change: Updated the local clinical labs by adding the liver panel lab assessments under clinical chemistry labs.

  Rationale: To match the case report forms in EDC and avoid confusion

  Description of Change: Deleted ‘automated’ from WBC differential.

Rationale: Automated methodology may not always be used for WBC differential

- **Section 6.8: Bone Marrow Assessments; 6.8.2.4 Bone Marrow Aspirate for Translational or Biomarker Research and Table 14**

  Description of change: Added text that a previously collected bone marrow sample (if available) should be provided or peripheral blood can be submitted if a baseline bone marrow sample could not be collected during screening or is inadequate for analysis.

  Changes were also made to Table 14 for providing bone marrow samples for biomarker research (if collected).

  Rationale: When a baseline bone marrow sample is not available, archival bone marrow sample and or peripheral blood samples may be useful for translational or biomarker research.

- **Section 7.8: Safety Oversight**

  Description of change: Clarified the frequency of safety monitoring committee meetings during dose expansion.

  Rationale: Clarification purpose

- **Section 9.1.2 Dose Expansion; Section 9.2.1 Analysis Populations**

  Description of change: Response Rate and 90% CI out of 30 subjects was added to Table 18. ADA analysis population was defined in Section 9.2.1.

  Rationale: To show the 90% CI for 30 subjects in Part A. ADA analysis population was added for clarification.

- **Section 9.2.5 Efficacy Analysis**

  Description of change: Text was added that supplementary analysis may be conducted by applying the IWG 2023 MDS response criteria to understand preliminary efficacy further.

  Rationale: For optional analysis of efficacy data with updated MDS response criteria

- **Section 9.2.5 Research Use of Stored Human Samples, Specimens, or Specimen Data**

  Description of change: Text added to clarify that subjects 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.

  Rationale: Clarification purpose

- **Section 13.5 Future use of Stored Specimens**

  Description of change: Section was deleted.

  Rationale: Samples will not be stored for future use.

16.16 Summary of Changes for Protocol Amendment 5.0

This amendment was done to address FDA's comments on amendment 4.0 and it applies to all Investigator sites participating in this study. Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 5.0.

Minor editorial changes (including protocol version number and approval date, table of contents) as well as minor clarification edits to text are incorporated in this amendment.

This protocol was amended to include the following:

- **Section: Study Schema**
  Description of change: Updated the subject numbers for Part A, added Schema for Part D

  Rationale: To be consistent with the changes made in the protocol

- **Section: Synopsis**
  Description of change: Updated the synopsis with the changes made in the protocol.

  Rationale: To be consistent with the body of the protocol

- **Section: Throughout the Protocol**

  Description of change: Updated number of subjects to be enrolled in Part A from approximately 30 subjects to approximately 20 subjects.

  Rationale:

  In amendment 4.0, the number of treatment naïve subjects with higher-risk MDS in Part A was increased from approximately 20 subjects to approximately 30 subjects. Upon review of amendment 4.0, FDA informed the Sponsor that a control arm should be included when more than 20 subjects are enrolled in dose expansion in the study. Thus, the number of subjects in Part A was changed back to approximately 20 subjects. Instead, Part D was added into amendment 5.0 to include a control arm in which patients with HR-MDS will be treated with azacitidine monotherapy (the current standard of care).

  Section 1.7 Study Rationale

  Description of change: Part D design was summarized, and rationale was provided.

  Approximately 60 treatment naïve subjects with higher-risk MDS will be randomized to three arms (approximately 20 subjects per arm). The three arms consist of two experimental arms at two dose levels of SL-172154 (1.0 mg/kg and 3.0 mg/kg) in combination with azacitidine, and one control arm for azacitidine monotherapy. The three arms will be stratified based on TP53 mutation status (TP53m vs TP53wt) and bone marrow blasts at baseline (<5% vs ≥5%).

  Rationale: Safety and efficacy will be further explored in Part D (with randomized control arm of azacitidine monotherapy). This will help evaluate the safety, and efficacy of different doses of SL-172154, and help determine the contribution of SL-172154 to the anti-leukemic activity in the azacitidine plus SL-172154 treatment.

  Section 2.0 Study Objectives and Outcome Measures

Description of change: Primary objectives were added to evaluate safety and efficacy in Part D, a randomized cohort with untreated higher risk MDS subjects with two doses of SL-172154 in combination with azacitidine compared to control group treated with azacitidine monotherapy. Part D specific secondary objective was added to assess preliminary antitumor activity in subjects treated with SL-172154 and azacitidine compared to azacitidine monotherapy. Part D specific exploratory objectives were added to assess platelet transfusion independence and MRD (minimal residual disease) in SL-172154 and azacitidine treated higher risk MDS subjects compared to azacitidine monotherapy treated subjects. Overall survival was moved from exploratory objectives to secondary objectives.

Rationale: Part D was added in this amendment to evaluate additional safety and efficacy of SL-172154 and azacitidine combination compared to azacitidine monotherapy in previously untreated higher risk MDS subjects. The objectives and outcomes were updated to reflect Part D specific aims.

Section 3.3.4 Part D (Randomized Cohorts): SL-172154 with Azacitidine vs Azacitidine monotherapy in HR-MDS Subjects

Description of change: Study design was summarized. Approximately 60 treatment naïve subjects with higher-risk MDS will be randomized equally into three arms: 1.0 mg/kg or 3.0 mg/kg SL-172154 in combination with azacitidine, and a control arm with azacitidine monotherapy. Subjects will be stratified based on TP53 mutation status (TP53m vs TP53wt) and baseline bone marrow blast count (<5% vs ≥5%).

Rationale: Data from Part D will help evaluate the safety, and efficacy of two different doses of SL-172154 and help determine the contribution of SL-172154 to the anti-leukemic activity in the azacitidine plus SL-172154 treatment.

Section 4.1 Inclusion Criteria, Section 4.2 Exclusion Criteria

Description of change:

Part D specific inclusion criteria were added. Prior luspatercept was added as an allowed supportive care for clarification.

Rationale: To confirm that it is safe for subjects to receive SL-172154 and azacitidine combination treatment.

Section 6.2 (Schedule of Assessments: SL-172154 Combination Cohorts, Dose Escalation or Dose Expansion (SL-172154 with Azacitidine or Azacitidine and Venetoclax)

Description of change: Per FDA's request, more frequent vital sign monitoring during infusion and post-infusion was added in amendment 5 for every SL-172154 infusion.

Rationale:

After reviewing amendment 4.0, FDA recommended more frequent monitoring of vital signs during each SL-172154 infusion.

Section 6.2 Schedule of Assessments: SL-172154 Combination Cohorts, Dose Escalation or Dose Expansion (SL-172154 with Azacitidine or Azacitidine and Venetoclax); Section 6.6.1 Physical Examination

Description of change:

- Added physical examination for PTV visit.
- Added a footnote to clarify that full physical exam is required only at screening and PTV. On-treatment physical exams should be performed per standard of care. Wording in Section 6.6.1 was also clarified.

Rationale:

- Full physical examination during PTV was added for complete safety assessment. Full physical examination during PTV was also included in Part D.
- The wording in Section 6.6.1 was unclear. Added text for clarification.

Schedule of Assessments: Section 6.3 [Dose Expansion Cohort Part D (SL-172154 in Combination with Azacitidine in Previously Untreated HR-MDS Subjects)]; Section 6.3.1 [PK, ADA, Receptor Occupancy, Complement Analysis and Cytokines Sampling Schedule for Dose Expansion Cohort Part D (SL-172154 in Combination with Azacitidine in Previously Untreated HR-MDS Subjects)]; Section 6.4 [Dose Expansion Cohort Part D (Azacitidine monotherapy in Previously Untreated HR-MDS Subjects)]; Section 6.4.1 [Immunophenotyping, Complement Analysis and Cytokines Sampling Schedule for Dose Expansion Cohort Part D (Azacitidine Monotherapy in Previously Untreated HR-MDS Subjects)

Description of change:

- Schedules for assessments including safety monitoring, efficacy and administration of study drugs are provided for Part D arms.
- Sample collection schedules for assessing PK, ADA, cytokines, complement analysis and receptor occupancy/immunophenotyping are provided.

Rationale:

Data from Part D will help evaluate the safety, and efficacy of two different doses of SL-172154 and help determine the contribution of SL-172154 to the anti-leukemic activity in the azacitidine plus SL-172154 treatment.

Identification of a potential biomarker that may support the mechanism of action or the pharmacology of the SL-172154 blood samples will be collected in Part D which includes SL-172154+ azacitidine combination arms and a randomized controlled group with the azacitidine alone. Samples in the azacitidine alone group will be collected at the minimum timepoints required for comparison with the combination arms.

Section 6.5.7 Randomization

Description of change: Randomization process was summarized.

Rationale: Using the Randomization and Trial Supply Management system, subjects will be randomized equally into three arms: 1.0 mg/kg or 3.0 mg/kg SL-172154 in combination with azacitidine, and a control arm with azacitidine monotherapy.

Section 6.6.7 Local and Central Laboratory Assessments, Section 6.6.7.1 Ad Hoc Labs for IRR or CRS AEs

Description of change: Ferritin and C-Reactive Protein samples were added for screening visit and ad hoc labs.

Rationale: Screening sample will serve as baseline sample in case of an infusion related reaction (IRR) or cytokine release syndrome (CRS). Ad hoc labs are collected to assess safety in case of an IRR or CRS.

Section 6.9 Pharmacodynamic assessments in blood

Description of change: Section was updated with the description of pharmacodynamic markers included in Part D.

Rationale: Identification of a potential biomarker that may support the mechanism of action or the pharmacology of the SL-172154 blood samples will be collected in Part D which includes SL-172154+ azacitidine combination arms and a randomized controlled group with the azacitidine alone.

Section 6.10 Table 17 Bone Marrow Assessment Schedule for SL-172154 in Combination with Azacitidine or Azacitidine Monotherapy Treatment (Dose Expansion cohort Part D)

Description of change: Bone marrow sample collection schedule for disease assessment and biomarker analysis has been added.

Rationale: Specified sample collection schedule

Section 7.1.1 Events not qualifying as AE or SAE

Description of change: Deaths that are clearly determined to be due to disease progression should not be reported as AEs/SAEs.

Rationale: Clarification purpose

Section 9 Data Analysis and Statistical Considerations: Section 9.1.2 Dose Expansion, Section 9.1.3 Sample Size Determination

Description of change:

- Revised the text and Tables to reflect changing of number of subjects in Part A to approximately 20 (from approximately 30 in amendment 4.0)
- Added Statistical assumptions and considerations for sample sizes in Part D arms

Rationale: Description of statistical analysis plan for Part D

Section 9.2.1 Analysis Populations; 9.2.4 Safety Analyses; Section 9.2.5 Efficacy Analyses

Description of change:

- Intent to treat population for Part D was defined.

- Safety and efficacy analyses Sections were updated with analyses plans for Part D.

Rationale: Described populations to be analyzed in Part D and added safety and efficacy analyses plans for Part D.