CLINICAL STUDY PROTOCOL

A PHASE IIA DOSE OPTIMISATION STUDY OF ASLAN003 IN ACUTE MYELOID LEUKEMIA

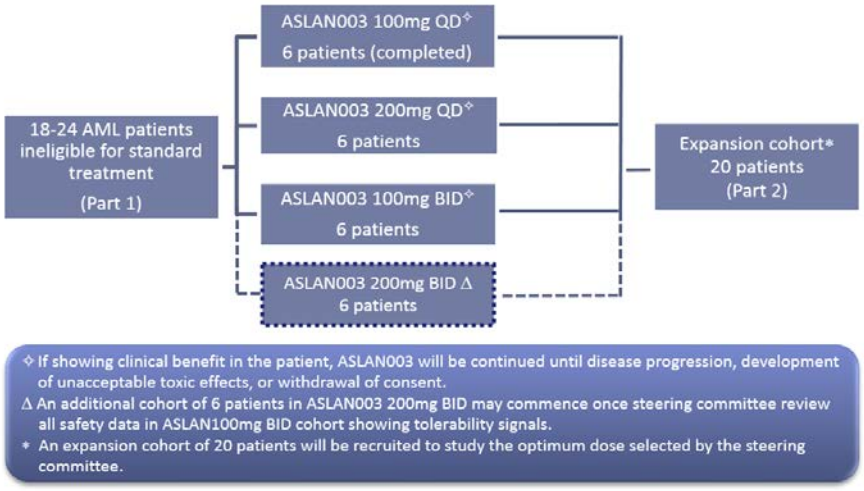
Sponsor:	ASLAN Pharmaceuticals Pte. Ltd. 83 Clemenceau Avenue #12-03 UE Square Singapore 239920
Clinical Research Organization:	IQVIA PAREXEL
Sponsor Protocol No.:	ASLAN003-003
Study Drug Name:	ASLAN003
Development Phase:	Phase IIA
Date of Protocol:	**31 May 2018**
Version of Protocol:	**Version 3.0 (Final)**
Date of Previous Protocol:	29 Jan 2018

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki[1], and with other applicable regulatory requirements.

PROTOCOL SYNOPSIS

Protocol Number:	ASLAN003-003
Protocol Title	A PHASE IIA DOSE OPTIMISATION STUDY OF ASLAN003 IN ACUTE MYELOID LEUKEMIA
Sponsor:	ASLAN Pharmaceuticals Pte. Ltd.
Investigational Product:	ASLAN003
Study Centers:	The study will be conducted at multiple centers in Australia, Singapore and other countries.
Phase:	Phase IIA
Objectives:	***Primary Objective*** **Part 1:** • To determine the optimum dose of ASLAN003 monotherapy based on the efficacy, safety and tolerability profile in Acute Myeloid Leukemia (AML) patients who are ineligible for standard therapy. **Part 2:** • To provide a preliminary estimate of the efficacy of ASLAN003 at the optimum dose selected from Part 1. ***Secondary Objective*** **Part 1:** • To evaluate the pharmacokinetics (PKs) of ASLAN003 and its metabolite LAS186558 in patients with AML. **Part 2:** • To further assess the safety and tolerability data of ASLAN003 at the optimum dose selected from Part 1. ***Exploratory Objectives:*** • To examine the myeloid differentiation effects of ASLAN003 using assays including but not limited to an *ex vivo* flow cytometry assay. • To explore possible relationships between molecular abnormalities and measures of clinical response in patients with AML.

Study Design:	This is a multicenter, single arm, non-randomised Phase IIA Study to evaluate ASLAN003 as a monotherapy in patients with AML. AML patients who are ineligible for standard treatment including, but not limited to the following conditions, will be enrolled in the study: • Newly diagnosed patients who are ineligible for standard therapy i.e., standard dose induction chemotherapy and reduced dose chemotherapy; • Patients with relapse from prior remission; • Patients with failed response to prior therapy including chemotherapy, hypomethylating agents, and bone marrow (BM) transplantation. Up to a total of 18-24 patients will be enrolled into this study - 6 patients in each dose cohort. The planned sequence of cohort enrollment is 100 mg QD - 200 mg QD - 100 mg BID. Furthermore, an additional cohort of 200 mg BID may also be enrolled, subject to agreement from the steering committee (SC) based on a review of safety data from the 100 mg BID cohort. A SC meeting will be set up and will meet to review all clinical information, including efficacy, safety and PK data obtained from this Study. Details of the SC outcome will be specified in the SC charter. An expansion cohort of 20 patients (Part 2) will be recruited to study the optimum dose selected by the SC. The optimum dose will be selected from at least one cohort showing tolerable safety profile and clinical benefit in disease presentation. Details will be specified in the SC charter. Patients with especially high blast cell count should be closely monitored for a possible differentiation syndrome. Investigators could manage suspected patients proactively according to the recommendations in the National Comprehensive Cancer Network (NCCN) guidelines acute promyelocytic leukemia (APL) differentiation syndrome section. Bone marrow aspiration samples (BMA) will be collected before the first day of treatment, will be cultured *in vitro* and incubated with ASLAN003 to examine the efficacy of ASLAN003 *ex vivo*. Molecular studies will also be done to check for any phenotypic and genotypic changes in the patients' BM sample. A BM aspiration smear will be collected and processed locally before the first day of treatment. *Ex vivo* assay and molecular assessment will be processed centrally (Please refer to the BMA lab manual for details). This will be done in selected sites to be determined by the Sponsor. All patients will continue to receive ASLAN003 until disease relapse, treatment failure, unacceptable toxicity, withdrawal of consent or death.



Abbreviations: AML = acute myeloid leukemia; QD = once daily, BID = twice daily.

Number of patients:	Up to a total of 18-24 patients are planned to be enrolled in Part 1 of this Phase IIA study to be conducted in Australia, Singapore and other countries. Approximately 20 patients are planned to be enrolled in the expansion cohort of Part 2 of this Phase IIA study to be conducted in Australia, Singapore and other countries.
Study Population:	**Inclusion Criteria** Patients who meet all of the following criteria are eligible for enrollment in the study: 1. Patients who are of or older than the legal age in the respective countries at the time when written informed consent is obtained 2. Patients who are able to understand and willing to sign the informed consent form (ICF) 3. Patients who are diagnosed with AML according to the 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia (refer to Appendix 1: WHO Classification of Acute Myeloid Leukemia) 4. Patients who have a sufficient archival or fresh BM aspiration sample for the evaluation of relevant exploratory endpoint. *Note*: *Patients who do not have sufficient archival BM aspiration sample and refuse to repeat the procedure may be enrolled in the trial only after written confirmation by ASLAN*

	5. Patients who are ineligible for standard treatment of AML including but not limited to the following conditions: • Newly diagnosed patients who are ineligible for standard therapy namely standard dose induction chemotherapy and reduced dose chemotherapy; • Patients who relapsed from prior remission; • Patients who failed to respond to prior therapy including chemotherapy, hypomethylating agents, and bone marrow transplantation. 6. Patients who have an ECOG performance status of ≤ 2 7. Patients with adequate renal and hepatic function, as defined below: • Estimated Glomerular Filtration Rate (eGFR) or creatinine clearance (CrCl) (CrCl calculated by the Cockroft and Gault method) ≥ 40 ml/min/1.73 m2 • Total bilirubin, AST, and ALT ≤ 1.5 × ULN **Exclusion Criteria:** Patients with any of the following criteria will be excluded from the study: 1. Patients who are diagnosed with *de novo* myeloid sarcoma without BM involvement 2. Patients who are diagnosed with acute promyelocytic leukemia/retinoic acid receptor alpha (*PML-RARA)* 3. Patients who received any other standard or investigational treatment for their leukemia within the last 7 days before starting the first dose of study drug, with the exception of leukapheresis and hydroxyurea 4. Patients with unresolved serious toxicity (≥ CTCAE 4.03 Grade 2) from prior administration of standard or investigational treatment for their leukemia 5. Patients who have a positive test for human immunodeficiency virus (HIV), viral hepatitis C infection (patients with sustained viral response are not excluded), active viral hepatitis B infection (positive hepatitis B surface antigen [HBsAg]) with hepatitis B virus deoxyribonucleic acid (DNA) exceeding 2000 IU/ml 6. Patients who have a known history of liver cirrhosis Child-Pugh score B or C 7. Patients who have any history of other malignancy unless in remission for more than 1 year (skin carcinoma and carcinoma-in-situ of uterine cervix treated with curative intent is not exclusionary) 8. Female patients who are pregnant or breast-feeding 9. Patients with a known history of alcohol or drug addiction on the basis that there could be a higher risk of non-compliance to study treatment per Investigator's discretion

	10. Patients with a history or presence of a clinically significant condition which in the opinion of the Investigator could jeopardize the safety of the patient or the validity of the study results 11. Patients who have been previously treated with ASLAN003
Study Endpoints:	**Primary Endpoints:** **Part 1:** • The primary objective of determining the optimum monotherapy dose of ASLAN003 in AML patients is based on the following endpoints: o Overall Complete Remission Rate (OCRR): Defined as the proportion of patients with a best response of complete remission (CR) or complete remission with incomplete hematologic recovery (CRi), defined in accordance with the International Working Group (IWG) Response Criteria in AML. o Safety and tolerability: Based on AEs, safety assessments (including vital signs, electrocardiogram [ECG] parameters, clinical laboratory tests) and treatment exposure/dose intensity. **Part 2:** • Overall Complete Remission Rate (OCRR) **Secondary Endpoints:** • Efficacy **(Parts 1 and 2)**: o Relapse Free Survival (RFS): Defined as the time the criteria for remission (CR or CRi) are first met until there is evidence of patient relapse, regardless of whether the patient is still taking study drug. Relapse is defined as: ➢ The reappearance of leukemic blasts in the peripheral blood or > 5% blasts in the BM not attributable to any other cause; ➢ The appearance of new dysplastic changes; ➢ The reappearance of or development of cytologically proven extramedullary disease; ➢ The reappearance of a cytogenetic or molecular abnormality. o Clinical Benefit Rate (CBR): defined as the proportion of patients with an AML IWG best response of CR, CRi or PR. o % change from baseline in BM blasts at Day 29. • Safety and tolerability **(Part 2 ONLY)**: o Based on AEs, safety assessments (including vital signs, electrocardiogram [ECG] parameters and clinical laboratory tests) and treatment exposure/dose intensity.

	• Pharmacokinetics **(Part 1 ONLY)**: If estimable, the following parameters will be calculated on Days 1 and 8, Cycle 1: o PK parameters for ASLAN003: maximum observed plasma concentration (C_{max}), C_{max} at steady state ($C_{max\ ss}$), trough plasma concentration (C_{trough}), time corresponding to occurrence of C_{max} (t_{max}), and $C_{max\ ss}$ ($t_{max\ ss}$), AUC over the dosing interval (AUC_{tau}), AUC_{tau} at steady state ($AUC_{tau\ ss}$), terminal elimination half-life ($t_{1/2}$), effective elimination half-life at steady state ($t_{1/2\ eff}$), apparent total clearance of the drug from plasma after oral administration (CL/F), apparent volume of distribution at steady state after oral administration (Vss/F), accumulation ratio for AUC (RacAUC) and accumulation ratio for C_{max} ($RacC_{max}$). o PK parameters for LAS186558: C_{max}, C_{trough}, t_{max}, AUC_{tau}, $t_{1/2}$, $t_{1/2\ eff}$, RacAUC, $RacC_{max}$, metabolic ratio (MR) for C_{max} (MRC_{max}) and AUC (MRAUC). **Exploratory Endpoint (Parts 1 and 2):** • Assessment of the degree of blast cell differentiation by ASLAN003 using assays including but not limited to *ex vivo* flow cytometry assay using selected myeloid cell markers (such as CD11b). • Assessment of the molecular abnormalities of AML blast cells at baseline.
Study Treatment:	**Part 1:** Patients will be administered with the study drug, ASLAN003. The starting dose of ASLAN003 is 100 mg QD given orally (PO). The maximum dose for optimum dose determination is 200 mg BID. It is recommended to administer ASLAN003 with food or within 30 minutes after food intake. **Part 2:** An optimum dose selected by the SC from Part 1 is given orally (PO). It is recommended to administer ASLAN003 with food or within 30 minutes after food intake. **Visit Schedule:** In order to address the primary objectives of the study, if treatment is interrupted for any reason, it is important that all planned safety and efficacy assessments are performed at the scheduled time, regardless of whether the patient is receiving study treatment, or not, at the time.
Study Duration:	**Screening Period:** 28 days

	Treatment Period: All patients will receive a continuous 28-day treatment cycle of ASLAN003 until disease relapse, treatment failure (defined as failure to achieve a PR or higher within 4 cycles), development of unacceptable toxicity, withdrawal of consent or death. **Follow-up Period:** All patients will be required to complete a safety follow-up visit within 28 days after the last dose of study treatment. All patients achieving CR or CRi will be followed for survival every 12 weeks post end of treatment (EOT) until disease relapse or death (in the absence of disease relapse) to find out the RFS. The planned duration of entire study (treatment and follow-up) is approximately 2 years.
Study Assessments:	The schedule of the assessment for the study is provided in Table 1. **Safety Assessments:** Patient safety will be evaluated based on the incidence of AEs and serious AEs (SAEs), physical examination, vital signs (blood pressure [systolic and diastolic], heart rate, respiratory rate, weight, and body temperature), ECG parameters, and clinical laboratory tests (hematology, clinical chemistry, coagulation and urinalysis). All AEs will be evaluated according to NCI-CTCAE 4.03 and will be captured from the time of informed consent and continued until the safety follow-up assessment (28 days after last administration of study treatment). For the purpose of this study, fluctuations of pre-existing conditions that do not represent a clinically significant exacerbation or worsening are not to be considered AEs. **Pharmacokinetic Assessments (Part 1 ONLY):** The blood samples for determination of plasma concentration of study drug will be collected on Day 1 and Day 8 at the following timepoints of Cycle 1 for QD regime: pre-dose, 1, 2, 4, 5, 6, 8, and 24 hours post dose. In BID regime i.e 100mg BID and 200mg BID the PK sampling will be done at following timepoints: pre-dose, 1,2, 4, 5, 6, 8, and 12 hours (or evening pre-dose). The plasma concentration-time data will be used to calculate the PK parameters for ASLAN003 and metabolite." **Part 2**: will be determined by SC if needed.

	Efficacy Assessments: For patients who do not have a sufficient archival of BM aspiration sample, a BM aspiration will be performed during Screening. Efficacy will be evaluated with BM aspiration and peripheral blood based on the IWG Criteria for AML (Cheson, 2003) every 4 weeks, on Day 1 of every cycle from Cycle 2 to Cycle 5 and every 12 weeks thereafter. Patients who have already achieved CR can omit the BM aspiration at subsequent assessments if there is a normal complete blood count with differential of the peripheral blood. Investigator may perform additional efficacy assessment if required based on clinical judgment. Bone marrow aspiration smears will be processed locally. Note: If treatment is interrupted for any reason, the scheduled efficacy assessments should be performed at the intended time point, regardless of whether the patient is currently receiving study treatment. Repeat assessments at the resume of treatment may be performed at the investigator's discretion. **Other Assessments:** Assays including but not limited to *ex vivo* flow cytometry assay using selected myeloid cell markers (such as CD11b) will be performed to assess the degree of blast cell differentiation upon treatment with ASLAN003. The percentage of CD11b positive cells will be determined before and after *ex vivo* treatment with ASLAN003. Molecular abnormalities of AML patients will also be assessed using polymerase chain reaction (PCR) or next-generation sequencing (NGS) The *ex vivo* assay and molecular assessment will be processed centrally (Please refer to the BMA lab manual for details).
Prohibited Medications	Any approved or investigational treatment given for the purpose to treat the leukemia, including but not limited to chemotherapy, hypomethylating agents, herbal medicine, Chinese medicine, leukapheresis, etc. will be prohibited during the study. For the management of leukocytosis, hydroxyurea use per site practice is allowed for patients with peripheral blast count more than 20,000 cells/uL in the first two weeks of study treatment. Once the peripheral blast count drops to less than 20,000 cells/uL, site is required to discontinue with hydroxyurea to ensure no impact on efficacy readout. Hydroxyurea use is allowed for suspected or confirmed differentiation syndrome.
Statistical Analysis:	**Part 1:** The proposed design has been selected to provide an assessment of the efficacy, safety and tolerability of different doses of ASLAN003 in

	patients with AML, whilst limiting the number of patients exposed to experimental treatments and procedures. Up to a total of 18-24 patients will be recruited in the study. **Part 2:** The study is not formally powered. The sample size of 20 patients has been selected to provide further efficacy and tolerability data at the selected dose level, prior to conducting larger randomized trials. ***Methods of Analysis:*** There are no formal statistical analyses planned. All primary and secondary endpoints will be listed and summarized using appropriate descriptive statistics and graphical displays. Safety will be assessed in the *safety population* and efficacy will be assessed in the *evaluable for response (EFR)* population. Furthermore, waterfall plots of the % change from baseline in BM blasts at Day 28, and the best % change from baseline in BM blasts will be presented. ***Pharmacokinetics:*** Concentrations and PK parameters will be listed and summarized using descriptive statistics in tables and graphs, as appropriate.

Table 1: Schedule of Study Assessments

Study Visit	**Screening**	**StudyTreatment Period**							**End of Treatment**	**Safety Follow-up**	**Survival Follow-Up**
Treatment Cycles (28 days per cycle)	**Day -28 to 0**	**Cycle 1**					**Cycle 2**	**Subsequent Cycles**	**EOT**	**28 days after last administration of study medication**	**Every 12 weeks post EOT for RFS**
Study Days		**Day 1**	**Day 8**	**Day 10**	**Day 15**	**Day 22**	**Day 1**	**Day 1**			
Study Allowed Window	**NA**	**NA**	**±1**	**+1**	**±2**	**±2**	**±2**	**±2**	**Within 7 days of last dose of study treatment**	**±7**	**±7**
General and Safety Assessments											
Informed Consent	X										
Eligibility Criteria	X	X									
Demographics	X										
Medical History	X										
Physical Examination	X	X	X		X	X	X	X	X	X	
Vital Signs (blood pressure, heart rate, respiratory rate, temperature)	X	X	X		X	X	X	X	X	X	
12-Lead Electrocardiogram	X				X		X		X	X	
Eastern Cooperative Oncology Group Performance Status (ECOG)	X	X							X		
Body weight	X	X					X	X	X		

Study Visit	**Screening**	**StudyTreatment Period**							**End of Treatment**	**Safety Follow-up**	**Survival Follow-Up**
Treatment Cycles (28 days per cycle)	**Day -28 to 0**	**Cycle 1**					**Cycle 2**	**Subsequent Cycles**	**EOT**	**28 days after last administration of study medication**	**Every 12 weeks post EOT for RFS**
Study Days		**Day 1**	**Day 8**	**Day 10**	**Day 15**	**Day 22**	**Day 1**	**Day 1**			
Study Allowed Window	**NA**	**NA**	**±1**	**+1**	**±2**	**±2**	**±2**	**±2**	**Within 7 days of last dose of study treatment**	**±7**	**±7**
Adverse Events/Serious Adverse Events[a]	X	X	X		X	X	X	X	X	X	
Prior and Concomitant Medication	X	X	X		X	X	X	X	X	X	
Laboratory Assessments											
Serum / urine β-human Chorionic Gonadotropin[b]	X								X		
Hematology	X	X	X		X	X	X	X	X		
Clinical Chemistry, Urinalysis[c]	X	X	X	X[d]	X	X	X	X	X		
Serology[e]	X										
Coagulation[f]	X				X				X		
Blood Pharmacokinetics Sampling[g]		X	X								
Bone Marrow Aspiration[h]	X						X	X			

Study Visit	**Screening**	**StudyTreatment Period**							**End of Treatment**	**Safety Follow-up**	**Survival Follow-Up**
Treatment Cycles (28 days per cycle)	**Day -28 to 0**	**Cycle 1**					**Cycle 2**	**Subsequent Cycles**	**EOT**	**28 days after last administration of study medication**	**Every 12 weeks post EOT for RFS**
Study Days		**Day 1**	**Day 8**	**Day 10**	**Day 15**	**Day 22**	**Day 1**	**Day 1**			
Study Allowed Window	**NA**	**NA**	**±1**	**+1**	**±2**	**±2**	**±2**	**±2**	**Within 7 days of last dose of study treatment**	**±7**	**±7**
Other Assessment											
Survival status contact by phone[i]											X
Study Drug Administration											
ASLAN003		X		X	X		X	X			

Abbreviations: ALT = alanine aminotransferase; AST = Aspartate aminotransferase; CR = complete remission; CRi = complete remission with incomplete hematologic recovery; DNA = deoxyribonucleic acid; eCRF = electronic case report form; EOT = end of treatment; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; NA = not applicable; PK=pharmacokinetics; RFS = relapse free survival.

Footnotes:

a. Adverse event collection starts at the time of informed consent and continues until 28 days after the last administration of study drug If a patient never receives study drug, but experience AE after informed consent form is signed, ONLY events the Investigator assessed as may have been caused by a study specific protocol procedure will be reported in eCRF.
b. Serum or urine pregnancy test to be performed at the Screening visit for all females except those surgically sterile or 2 years postmenopausal. Serum or urine pregnancy tests will be performed at EOT. Unscheduled serum or urine pregnancy tests are allowed at the Investigator's discretion.
c. Screening clinical laboratory tests (clinical chemistry, urinalysis and coagulation) must be completed from Day -28 to 0. Screening clinical laboratory tests may be used in lieu of pre-treatment, Cycle 1 Day 1 tests, if performed within 1 week prior to the first administration of study drug.
d. **ONLY AST, ALT and total bilirubin to be performed on Cycle 1 Day 10.**
e. Serology tests must be completed from Day -28 to 0. If HBsAg result indicate active infection then test HBV DNA.
f. Coagulation laboratory test will be performed at Screening, Cycle 1 Day 15 and EOT visit, however the Investigator may perform coagulation tests at other visits if required based on clinical judgment.

g. Blood samples for PK analysis of ASLAN003 and LAS186558 for QD regime include: Day 1 and Day 8: pre-dose, 1, 2, 4, 5, 6, 8, and 24 hours post dose. In BID regime i.e 100mg BID and 200mg BID the PK sampling will be done at following timepoints: pre-dose, 1, 2, 4, 5, 6, 8, and 12 hours (or evening pre-dose). For Part 2- Steering Committee will decide whether PK analysis is required or not and ASLAN pharmaceuticals will be updated accordingly.
h. Bone marrow aspiration is mandatory to be performed every 4 weeks on Day 1 of every cycle from Cycle 2 to Cycle 5 and every 12 weeks thereafter. Patients who have already achieved CR could omit the bone marrow aspiration at subsequent assessments if there is a normal complete blood count with differential of the peripheral blood. The Investigator may perform additional monthly bone marrow aspirate if required based on clinical judgment. Bone marrow aspiration smear will be processed locally. ONLY BMA collected during screening visit will be used to perform *ex vivo* assay and molecular assessment centrally (Please refer to the lab manual for details).
i. Survival follow-up by either telephone or clinic visit will be performed in patients achieving CR or CRi every 12 weeks post EOT until disease relapse or death (in the absence of disease relapse) to enable the assessments of RFS.
j. Cycle 2 Day 1 corresponds to day 29 of the study treatment.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ADL	Activities of Daily Living
ALT	alanine aminotransferase
AML	acute myeloid leukemia
aPTT	activated partial thromboplastin time
APL	Acute promyelocytic leukemia
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the plasma concentration curve
AUC_{tau}	AUC over the dosing interval
$AUC_{tau\ ss}$	AUCtau at steady state
AUC_{0-24}	area under the curve during 24 hours
AUC_{0-inf}	area under the curve from time 0 extrapolated to infinite time
BM	Bone marrow
BMA	Bone Marrow Aspiration
°C	degrees Celsius
CART	Chimeric antigen receptor-T
CBR	clinical benefit rate
Cell/uL	cells per micro liter
CI	Confidence interval
CL/F	Apparent total clearance of the drug from plasma after oral administration
C_{max}	maximum observed plasma concentration
$C_{max\ ss}$	C_{max} at steady state
CNS	central nervous system
CSR	clinical study report
CR	complete remission
CRi	complete remission with incomplete hematologic recovery
CRF	case report form
CRO	clinical research organization
CrCl	creatinine clearance
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough plasma concentration
CYP	cytochrome P450
DHODH	dihydroorotate dehydrogenase
DLT	dose-limiting toxicity
DNA	deoxyribose nucleic acid
eCRF	electronic case report form
ECG	electrocardiogram

EDC	electronic data capture
ED_{90}	concentration producing 90% effect
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration rate
EOT	end of treatment
EPO	erythropoietin
FAS	full analysis set
FDA	Food and Drug Administration
FLT3	fms-related tyrosine kinase 3 gene
FOB	Functional Observational Battery
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
GO	Gemtuzumab ozogamicin
GSH	glutathione
h	hour
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HgbA1c	hemoglobin A1c
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICH	International Conference on Harmonization
ICF	informed consent form
IDH	Isocitrate dehydrogenase
IEC	Independent Ethics Committee
IFN	interferon
INR	international normalized ratio
IRB	Institutional Review Board
ITD	tandem duplication mutation
i.p.	intraperitoneal
i.v.	intravenous
IWG	International Working Group
MAD	multiple ascending dose
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MNPCE	micronucleated polychromatic erythrocytes
MR	metabolic ratio
MRC_{max}	metabolic ratio for C_{max}
MRAUC	metabolic ratio for AUC

NADPH	nicotinamide adenine dinucleotide phosphate
NCCN	National Comprehensive Cancer Network
NGS	next-generation sequencing
NOEL	no observed effect level
OCRR	overall complete remission rate
OS	overall survival
PCR	polymerase chain reaction
PK	pharmacokinetic(s)
PML-RARA	promyelocytic leukemia/retinoic acid receptor alpha
PO	*per os* (by mouth/orally)
PR	partial remission
QD	once daily
RacAUC	accumulation ratio for AUC
$RacC_{max}$	accumulation ratio for C_{max}
RBC	red blood cell (count)
RFS	relapse free survival
SAD	single ascending dose
SAP	statistical analysis plan
SAE	serious adverse event
SC	Steering Committee
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	elimination half-life
$t_{1/2\ eff}$	effective elimination half-life at the steady state
TEAE	treatment-emergent adverse event
TK	tyrosine kinase
TKD	tyrosine kinase domain
TLF	Tables, listings and figures
t_{max}	time corresponding to occurrence of C_{max}
$t_{max\ ss}$	t_{max} at steady state
ULN	upper limit of normal
Vss/F	apparent volume of distribution at steady state after oral administration
WBC	white blood cell (count)

1 INTRODUCTION

ASLAN003 (LAS186323) is a novel inhibitor of the enzyme dihydroorotate dehydrogenase (DHODH); it was initially discovered and patented by Almirall, S.A. In May 2012, global rights to the compound LAS186323 were granted to ASLAN Pharmaceuticals and the compound was then re-named as ASLAN003. The molecule was initially evaluated for the treatment of rheumatoid arthritis; and is currently being investigated for the treatment of acute myeloid leukemia (AML). ASLAN003 is a potent, small molecule, reversible, selective inhibitor of dihydroorotate dedrogenase (DHODH), with a pharmacokinetic (PK) profile allowing once daily (QD) administration.

1.1 Disease Background

AML, a heterogeneous hematologic malignancy, is the most common acute leukemia among adults and characterized by abnormal proliferation and differentiation of a clonal population of myeloid blasts in the bone marrow (BM) and peripheral blood. AML accounts for 25% of all leukemia of adults in the Western world, with the highest incidence rates occurring in the United States, Australia and Europe.[2] In 2016 in the United States, about 19,950 people were diagnosed with AML and 10,430 patients died from this disease. The median age of diagnosis is at 67 years and the incidence increases with age, with 54% of patients diagnosed at ≥ 65 years and approximately a third diagnosed at ≥ 75 years of age.[3] In Australia, AML accounts for about 1.1% of all cancer cases annually;[4] an age-standardized incidence rate of 3.8 per 100,000 persons: 4.7 per 100,000 persons in males and 3.0 per 100,000 persons in females is reported as per 2014 overview.[5] The incidence of AML in the white population (3.8 per 100,000 person) is higher than that of the Asian population (3.2 per 100,000 person).[6] According to the Singapore Cancer Registry 2015, myeloid neoplasms were the 10th most common cancer amongst males in Singapore in 2008-2012; and AML was the most common myeloid neoplasm accounting for 35.9% of 1,434 cases.[7] In the majority of cases, AML develops as a *de novo* malignancy in previously healthy individuals. Many environmental factors, underlying hematological diseases (e.g. myelodysplasia) and prior chemotherapy for solid tumors or hematologic malignancies increase the risk of developing AML.[3,8]

Based on their cytogenetic and molecular abnormalities, AML can be categorized into favorable-, intermediate- and poor-risk groups.[3] Patients with chromosomal rearrangements t(8;21), t(15;17), t(16;16) or inv(16) are associated with favorable prognosis with longer remission and survival, whereas patients with monosomy 5 or 7, t(6;9), t(9;22), inv(3), t(3;3), 11q23 abnormalities, monosomal karyotype or complex karyotype (>3 clonal chromosomal abnormalities) are associated with poor prognosis with higher risk of treatment failure and death. In contrast, patients with normal karyotype AML (NK-AML), +8 alone or t(9;11) are regarded as intermediate-risk group with an intermediate risk of relapse. Differences in molecular abnormalities are associated with varied clinical outcomes.[3,8] In general, TP53 mutations are associated with a poor prognosis. On the contrary, bi-allelic mutation of CCAAT Enhancer Binding Protein (CEBPα) and mutation of nucleophosmin 1 in the absence of fms-related tyrosine kinase 3 gene (FLT3)-ITD are associated with favorable overall survival (OS) or a higher complete response (CR).[3,8-10]

1.2 Currently Available Treatments for Acute Myeloid Leukemia

The current standard treatment of AML includes induction therapy and consolidation therapy. For patients younger than age 60 years, the continuous infusion of the standard-dose cytarabine for 7 days with 3 days of anthracycline is commonly used for induction therapy to remove excess blasts and achieve CR.[3] Elderly patients usually present with poor performance profile and are often unable to tolerate the toxicity of chemotherapy. Studies show hypomethylating agents (e.g. decitabine and azacitidine), which are used for the treatment of myelodysplastic syndrome, improved survival in elderly patients when compared to supportive care or low dose cytarabine.[3,8] Although established chemotherapy regimens achieve 60% to 80% CR in *de novo* AML patients after induction therapy, approximately 50% to 55% of patients in the high risk group will relapse after consolidation therapy or transplantation.[8,11]

Inhibition of tyrosine kinase (TK) receptors have been used successfully in various solid and hematological malignancies. Mutations in the FLT3 are found in 30% of adults with newly diagnosed AML.[12] Approximately three quarters of these patients have a FLT3 internal tandem duplication mutation (ITD), while 8% of patients with newly diagnosed AML have a FLT3 point mutation in the tyrosine kinase domain (TKD). Furthermore, FLT3-ITD mutations have been associated with increased risk of relapse, while the prognostic relevance of FLT3-TKD mutations is controversial. Due to poor prognosis in patients with FLT3-ITD mutation, targeting this tyrosine kinase has been considered as a potential therapeutic strategy in AML. Several anti-FLT3 agents are being developed, including the first-generation inhibitors such as sorafenib and midostaurin, and second-generation agents such as quizartinib and crenolanib. However, with exception to crenolanib which is currently being studied in clinical trials, the effects of other FLT-3 inhibitors are limited due to relapse or the rapid development of resistance.[8,9]

The gain of function mutations in Isocitrate dehydrogenase 1 or 2 (IDH1 or IDH2) enzymes are found in approximately 20% of AML cases. Recent attempts have been made to target these mutant enzymes as a potential treatment for AML. Preliminary results in the clinical study of an IDH1 inhibitor, AG120, showed response in 7 out of 14 IDH-1 positive patients. An IDH2 inhibitor, AG221, demonstrated an improvement on survival in an AML xenograft model. A Phase I trial of AG221 in IDH2 mutated leukemia patients is currently ongoing.[8]

In addition to small molecular inhibitors, antibody therapies in AML are also currently under development. Gemtuzumab ozogamicin (GO) is a humanized recombinant antibody against CD33; the latter is a transmembrane protein expressed on cells of myeloid lineage. GO is conjugated to calicheamicin, a deoxyribonucleic acid (DNA)-cleaving cytotoxic agent, and able to be internalized in CD33-positive cells.[8] GO was approved by Food and Drug Administration (FDA) in 2000 to treat AML in the patients 60 years or older with AML recurrence. However, it was withdrawn in 2009 since the post approval clinical trial was stopped early with no improvement in clinical benefit but with an increased number of deaths in the patients treated with GO plus chemotherapy compared to chemotherapy alone.[13] Chimeric antigen receptor-T (CART) cells against AML is also a therapeutic strategy under development. Both CD33-directed and β member of the folate receptor

family (FRβ) -directed CART cell therapy showed efficacy in AML *in vitro* models, as well as, in an AML xenograft model. However, the investigations are still at an early stage.[8,9]

Despite several novel agents being investigated for the treatment of AML, the backbone of the induction regimen has remained the same for decades as no convincing improvements in overall survival (OS) has been demonstrated for the new agents. While AML comprises many disparate genetic subtypes, one shared hallmark is the arrest of leukemic myeloblasts at an immature and self-renewing stage of development. Thus, therapies that overcome differentiation arrest may represent a powerful treatment strategy.

Recent data from the Harvard School of Medicine, pointed to a very specific effect on blast maturation and a screen of 330,000 compounds revealed that this effect was uniquely linked to DHODH inhibition.[14] Using a conditional myeloid differentiation arrest system with HoxA9, a high-throughput phenotypic screen and identification of small compounds able to remove the differentiation block was carried out. DHODH enzyme inhibitors were found to be the most active compounds enabling myeloid differentiation in human and mouse AML models. *In vivo*, DHODH inhibitors reduced leukemic cell burden, decreased levels of leukemia-initiating cells, and improved survival.[13] These data demonstrate the role of DHODH as a metabolic regulator of differentiation and point to its inhibition as a strategy for overcoming differentiation blockade in AML.

1.3 ASLAN003 (The Investigational Drug)

ASLAN003 is small molecule inhibitor that targets the enzyme DHODH. It was initially investigated in the treatment of rheumatoid arthritis with the aim of improving several features of leflunomide (ARAVA®)/teriflunomide, namely increasing its potency against the human DHODH enzyme, extending its terminal elimination half-life, and improving its side effect profile. ASLAN003 has a higher *in vitro* potency than teriflunomide for both inhibiting the human DHODH enzymatic activity and human T-cell proliferation.

The investigational product consists of an orange-colored hard gelatin capsule containing 10 mg or 50 mg of ASLAN003 for oral administration. Each capsule contains ASLAN003, lactose monohydrate, colloidal silicon dioxide and sodium stearyl fumarate.

The pre-clinical pharmacology and toxicology findings for ASLAN003 are summarized below. Clinical experience with ASLAN003 has also been included in the sections below. For more details, please refer to the Investigator's Brochure for ASLAN003.[15]

1.3.1 Pre-clinical Pharmacology of ASLAN003

The effectiveness of ASLAN003 has been extensively investigated using *in vitro* and *in vivo* experimental models. ASLAN003 is a potent human DHODH inhibitor showing a 31-fold increase in potency compared to teriflunomide, the active metabolite of leflunomide (half maximal inhibitory concentration [IC_{50}] of 35 nM vs. 1083 nM, respectively). The metabolites of ASLAN003, the O-demethylated metabolite (LAS186558) and its hydroxylated metabolite (LAS186876) were less active than the

parent compound (IC50 of 247 nM and 157 nM, respectively) against human DHODH. ASLAN003 is a selective inhibitor of DHODH with no significant inhibition (>50% at 10 μM) against a large panel of enzymes, receptors and ion channels except for ML2, a melatonin receptor involved in sleep disorders. Although the relevance of this finding is unknown, it should be noted that ASLAN003 does not cross the blood-brain barrier.

ASLAN003 has demonstrated efficient inhibition of human lymphocyte proliferation from human peripheral blood mononuclear cells (PBMC), with an IC_{50} of 1.4 μM, which was about 30-fold more potent than teriflunomide (46 μM). Similarly, ASLAN003 efficiently inhibited the proliferation of immortalized human epidermal keratinocytes with an IC_{50} of 0.58 μM, while the IC_{50} for teriflunomide is 15 μM in the same assay. In agreement with results obtained in both the enzymatic and PBMC proliferation assays, ASLAN003 was found to be more potent than teriflunomide (100-fold) in inhibiting interferon-gamma (IFNγ) secretion by stimulated lymphocytes from whole blood samples (IC_{50} of 2.5 μM vs. 259 μM, respectively). ASLAN003 was not cytotoxic to Chinese Hamster Ovary cells at concentrations up to 100 μM, while a 63% reduction in adenosine triphosphate (ATP) was observed at 200 μM. ASLAN003 was not toxic to cultured human hepatocytes *in vitro* despite its potency as human DHODH inhibitor. The *in vitro* therapeutic index, defined as the ratio IC_{50} cytotoxicity/IC_{50} PBMC proliferation, is 67 for ASLAN003 compared with 1.9 for teriflunomide. These data indicate that the inhibition of DHODH by ASLAN003 is not related to a direct toxicity in hepatocytes.

ASLAN003 has also been studied in selected AML cell lines of various morphology subtypes – HL-60, MOLM-14, THP-1, KG-1 and NB4. ASLAN003 induced differentiation of AML cell lines: KG-1, MOLM-14 and THP-1, at nanomolar concentrations with minimal cell toxicity effects, as shown by up-regulation of CD11b on the surface of the treated AML cells. In contrast, acute promyelocytic leukemia cell lines, NB-4 and HL-60, showed limited differentiation response upon treatment with ASLAN003 even at micromolar concentrations. Supplementation with 50 μM uridine abrogated the differentiation effect of ASLAN003, demonstrating that differentiation resulted from the inhibition of DHODH, since uridine is a product of the *de novo* pyrimidine synthesis pathway. The differentiation effects of ASLAN003 were also observed in *ex vivo* assays conducted with primary blast cell samples obtained from AML patients' bone marrow. Please refer to the Investigator's Brochure for more details.[15]

1.3.2 Safety Pharmacology of ASLAN003

The effects of ASLAN003 were investigated on vital functions such as cardiovascular, respiratory, central nervous system (CNS), and liver function in various pre-clinical models. The cardiovascular safety profile was studied in both *in vitro* and *in vivo* studies. ASLAN003 up to 10 μM concentrations had no effects on the hERG current (IKr) expressed in HEK-293 cells in *in vitro* studies. At 30 and 100 uM concentrations, ASLAN003 showed a weak block of hERG with a maximum reduction of 17% in current amplitude. Assessment of the action potential in piglet Purkinje fibers in the

presence of ASLAN003 showed no changes at a concentration of 3 µM but showed a progressive lengthening of the action potential duration at 40% and 90% repolarization (APD40 and APD90), at concentrations of 10 or 30 µM that probably reflected a potassium channel blocking effect. At 100 µM, ASLAN003 reduced the resting membrane potential, the maximum rate of depolarization, and the APD40 and APD90 in a manner consistent with a sodium/calcium channel blocking effect. ASLAN003 given at 10 mg/kg i.v. to anaesthetized guinea pigs were devoid of effects including any effects upon QTc. In anesthetized Beagle dogs, ASLAN003, at doses as high as 200 mg/kg intraduodenally, did not produce clinically relevant changes in electrocardiogram intervals.

Vertebral blood flow was decreased at the highest dose (200 mg/kg) by 45% although when dosed at 10 mg/kg intravenous (i.v.) to pithed rats, ASLAN003 did not produce a change in the blood pressure. In contrast, leflunomide produced a significant increases in diastolic blood pressure. When dosed to rats at 100 mg/kg, ASLAN003 had no effects upon respiratory function measured by tidal volume, respiratory rate or specific pulmonary resistance.

Following oral doses of 1, 10 and 100 mg/kg ASLAN003 in a Functional Observational Battery (FOB) test in rats, only a slight increase in spontaneous activity and mild exophthalmia was observed. Furthermore, in a specific test to assess motor activity, ASLAN003 did not modify the distance traveled by each animal at any of the doses tested.

An acute model of hepatotoxicity in rats and mice was developed to investigate the effects of ASLAN003 upon liver enzymes and bilirubin levels in plasma. The study design allowed comparison with teriflunomide. A dose of 100 mg/kg of teriflunomide significantly increased liver enzymes in both species. In contrast, ASLAN003 showed no effect at doses up to 300 mg/kg intraperitoneal (i.p.) suggesting a lower hepatotoxic potential for ASLAN003 than teriflunomide.

1.3.3 Pre-clinical Pharmacokinetics and Toxicokinetics of ASLAN003

The PK of ASLAN003 after the single i.v. administration was studied in Wistar rats, Beagle dogs and Cynomolgus monkeys. Following administration, ASLAN003 showed a low clearance in all animal species (< 0.1 l/h/kg) and a low value for distribution volume (apparent volume of distribution at steady state: 0.1-0.2 l/kg). The longest elimination half-life ($t_{1/2}$) was observed in rats (12-14 hour [h]), followed by monkeys (7 h) and dogs (4 h). Following a single oral dose of 1 and 10 mg/kg of ASLAN003 in Wistar rats and Beagle dogs, the t_{max} mean value found was between 1.5 and 3h. A longer t_{max} value (6 h) was found in the rats at the higher dose administered. The peak concentration (C_{max}) found for ASLAN003 was between 3 to 5 times lower in dogs than in rats. Changes in C_{max} and area under the curve during 24 hours ($AUC_{(0-24)}$) were dose-proportional at the oral dose range studied in rats, whereas the values increased less proportionally with the oral dose in dogs. Comparison of the oral dose AUC values with the results obtained after intravenous administration suggested moderate (59% to

65%) to low (21% to 35%) oral bioavailability in rats and dogs, respectively. In dogs, the $t_{1/2}$ was independent of the administration route, whereas in rats the $t_{1/2}$ after oral administration (23h) was somewhat longer than that obtained after i.v. dosing (14h) at the same dose, suggesting that the absorption constant could be much slower than the elimination rate constant.

Toxicokinetic studies carried out in rats and dogs confirmed the systemic exposure of the animals to ASLAN003, and to its metabolites LAS186558 and LAS186876. Plasma levels for both metabolites were always significantly lower than those of the unchanged parent compound. The main oxidative metabolites found *in vivo* were the same as those formed by human liver microsomes. In liver microsomes, ASLAN003 was extensively metabolized (NADPH-dependent) mainly via CYP1A2 and CYP2C9. Two main oxidative metabolites have been identified in all toxicological species and humans: LAS186558 (O-demethylated metabolite) and LAS186876 (hydroxylated metabolite). Phase II metabolism was also demonstrated in all species by the formation of a glucuronide derivative of ASLAN003 (LAS186323) in all the species studied. Exploratory studies performed to assess the potential of ASLAN003 to inhibit different human CYP450 enzymes suggested that ASLAN003 has some inhibitory effects on CYP2C9 (IC_{50} 5-25 µM), but it is unlikely to modify its own metabolic clearance and/or the metabolic clearance of concomitant medication. The formation of reactive metabolites (glutathione [GSH]-adducts) was studied in rats and human liver microsomes. The potential of ASLAN003 to form reactive intermediates was considered to be low.

1.3.4 Toxicology of ASLAN003

The preclinical safety of ASLAN003 was assessed following single (rats and mice) and repeated oral dose administration (rats and dogs).

ASLAN003 was acutely toxic at high doses above 500 mg/kg. Following high doses, generalized clinical signs including hypothermia, piloerection and decreased activity were observed. Necropsy observations in mice included the presence of blackish content in the stomach and duodenum and blackish punctiform areas in the glandular mucosa.

In rats in a 4-week repeated dose toxicity study, showed ASLAN003 was severely toxic when dosed at 15 mg/kg necessitating dose reduction to 10 mg/kg and subsequently discontinuation of dosing in females. The main histopathological changes were decreased cellularity in organs of the immune system, hematopoietic system and presence of cytotoxic enteropathy in the GI. Decrease in red blood cell (RBC) parameters together with an increase in platelets and reticulocytes were seen in male animals that received 7.5 mg/kg or 10 mg/kg but not in females, probably due to the severe bone marrow toxicity was seen in female animals. Following a 2-week recovery period, all of the hematological and histopathological changes had completely resolved. The no observed effect level (NOEL) in rats was established at 2.5 mg/kg/day.

In dogs, the main clinical finding was diarrhea and the main histopathological change was cytotoxic enteropathy. These adverse effects were probably related to the anti-proliferative activity of DHODH inhibition and were fully reversible. Following dosing at 20 mg/kg/day, the effects on clinical condition were sufficiently severe to justify dose reduction to 17.5 mg/kg/day and discontinuation in 2 dogs at 17.5 mg/kg/day/dose and 1 dog at 15 mg/kg/day dose. In addition to the cytotoxic enteropathy, decreased cellularity of the bone marrow and lymphoid atrophy were observed following 15 to 20 mg/kg/day. The NOEL in dogs were established at 7.5 mg/kg/day.

ASLAN003 was non irritating to the rabbit skin or eyes. ASLAN003 did not exhibit phototoxic potential in guinea pigs.

ASLAN003 showed no evidence of mutagenic activity in a bacterial reverse mutation assay (Ames Test) or in an *in vitro* chromosomal aberration test in human peripheral lymphocytes. In an *in vivo* mouse micronucleus test, produced a small but statistically significant ($p<0.05$) increase in the micronucleated polychromatic erythrocytes (MNPCE) in male mice, at a dose of 2000 mg/kg of ASLAN003. A second study in male mice confirmed this weak response at dose levels above 1000 mg/kg and established 500 mg/kg to be the no effect dose for induction of MNPCE. The increased frequencies of MNPCE produced by ASLAN003 were associated with preceding increase in plasma concentrations of erythropoietin (EPO). Since increased erythropoiesis is an accepted physiological mechanism by which MNPCE frequencies increase, the effect of ASLAN003 on MNPCE frequency is considered secondary to its effect on EPO rather than the intrinsic genotoxicity of the molecule.

In vitro analysis of liver safety biomarkers in elderly human patients who experienced elevations in liver enzymes in the Phase I study (ASLAN003-001), as well as mechanistic studies of cytotoxicity of ASLAN003 in human hepatocytes were performed. It demonstrated that DHODH inhibition by high doses of ASLAN003 caused reversible hepatocyte apoptosis via the induction of p53. The transient elevation in liver enzymes is accompanied by a delayed increase in circulating biomarker of liver regeneration.

1.4 Clinical Experience with ASLAN003

ASLAN003 has been administered to healthy subjects in 3 Phase I studies.

The safety, tolerability and PKs of ASLAN003 and its metabolites have been evaluated in healthy male subjects following oral administration of single ascending doses of 1, 2, 5, 10, 25, 50 and 100 mg (7 dose levels) of ASLAN003 in healthy male Caucasian subjects in a Phase I study (***Study M/186323/01***). Although $t_{1/2}$ was consistent across the different dose levels, C_{max} and AUC increased less proportionally with increasing dose. The main metabolite circulating in plasma was LAS186558 with mean AUC values across all administered doses between 3.4% and 9.8% of the mean AUC values of the parent drug; metabolite. LAS186876 was a minor metabolite and was formed at less than 2% of parent drug AUC. ASLAN003 was well-tolerated at all doses studied.

In another Phase I, randomized, double-blind, placebo-controlled, 2-part study (***Study ASLAN003-001***), the safety, tolerability and PKs of single ascending doses (SAD) and multiple ascending doses (MAD) of ASLAN003 were evaluated in healthy Asian subjects. ASLAN003 administered as single and multiple doses of 100 mg, 200 mg, and 400 mg under fed and fasted conditions safe and well-tolerated in healthy subjects. For ASLAN003 and its 2 oxidative plasma metabolites, there was no evidence of departures from dose proportionality following a single dose under fasted conditions in terms of area under the curve from time 0 extrapolated to infinite time ($AUC_{(0\text{-}inf)}$), whereas the analyses revealed less dose proportional increase in C_{max}.

Following a single oral dose of 200 mg ASLAN003 with a high-fat meal (fed state), the median t_{max} was delayed by 1.5 hours as compared to the 200 mg dose in the fasted state. The C_{max} and AUC of ASLAN003 were increased by 29% and 18% respectively and inter-subject variability was reduced. Mean $t_{1/2}$ was similar under both fed and fasted dosing conditions for both parent drug and the 2 metabolites.

In the MAD part of the study (100 mg, 200 mg, and 400 mg, QD for 7 days), the plasma AUC_{tau} and C_{max} for ASLAN003 and LAS186876 revealed no evidence of departures from dose proportionality with increasing doses of ASLAN003 when taken after a meal. However, the AUC_{tau} and C_{max} for LAS186558 increased in a less dose-proportional manner.

The t_{max} and $t_{1/2}$ for ASLAN003 were dose-independent following QD doses across the selected dose range; 5 and 16 hours, respectively. Steady-state concentrations of ASLAN003, LAS186558, and LAS186876 were achieved by Day 4 across the selected dose range. Following daily repeated dosing, exposure to ASLAN003 and LAS186558 (AUC) appeared to accumulate slightly (less than 30% increase). The exposure was higher in elderly subjects (AUC_{tau}) of ASLAN003 was increased by 53% and C_{max} by 41%), which may be explained by their lower body weight. Renal elimination of free (unconjugated) ASLAN003, LAS186558, and LAS186876 were negligible (<0.8% of the administered dose). Phase II metabolism appeared to be an important route of elimination. Conjugation was most prevalent for ASLAN003 and LAS186558.

Most frequently reported adverse events (AEs) across this ASLAN003-001 study were abnormality in laboratory investigations and included elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyltransferase, blood cholesterol increased, blood creatine phosphokinase increased, electrocardiogram (ECG) PR, and blood glucose increased. The safety assessment results reported in patients aged ≥ 55 years were mostly comparable with those of younger subjects other than for greater changes in the laboratory assessments in the elderly subjects compared to the younger subjects, notably the liver function tests.

Another Phase IB study (***Study ASLAN003-002***) evaluated the safety, tolerability and PKs of multiple doses of 100 mg of ASLAN003 QD for 14 days in healthy elderly Asian subjects (age > 55 years old). The study was conducted at a single center in Singapore where 7 of the planned 8 elderly subjects were enrolled into Stage 1 of the study, of which

5 subjects received ASLAN 100 mg QD on Day 1; and 4 of these subjects received ASLAN 100 mg QD on Day 8. Only 1 subject completed 14 days of QD dosing. Stage 2 of the study was not conducted. Following daily repeated dosing, mean plasma exposure to ASLAN003 expressed as $AUC_{(0-24)}$ increased 1.2-fold after multiple dosing on Day 8 compared to a single dose on Day 1. Following repeat QD dosing, the relative systemic exposures to the metabolites LAS186558 and LAS186876 were around 10% and 1%, respectively.

Elevations in liver function tests in ASLAN003-002 study was similar to the observation in the previous study (ASLAN003-001). This is likely to be a class effect of DHODH inhibitors. Monitoring of liver function in patients is recommended. It is possible that elderly subjects could be more susceptible to these effects.

1.5 Known or Potential Risks Associated with ASLAN003

ASLAN003 has demonstrated an acceptable safety profile in nonclinical toxicology studies and completed Phase I studies in humans. However, as with any new investigational drug, unexpected AEs may occur with the use of ASLAN003. The following is a summary of potential risks; additional details are presented in the IB:

- ASLAN003 must not be administered to pregnant or nursing women.
- ALT, AST, and total bilirubin along with signs or symptoms of liver toxicity should be monitored during ASLAN003 treatment.

1.6 Rationale for the Study

A recent publication by Sykes et al. (2016)[14] summarized 5 years of primary science and identified DHODH as a critical enzyme in the differentiation of human AML blast cells to granulocytes. *In vitro* studies with ASLAN003 have demonstrated that the compound induces the differentiation of AML cell lines: KG-1, MOLM-14 and THP-1, through inhibition of DHODH. *Ex vivo* analyses with ASLAN003 have also demonstrated myeloid differentiation of primary AML blast cells obtained from patients.

In Phase I studies, ASLAN003 was generally well-tolerated. No clinically significant changes in liver transaminase enzymes were noted in healthy male volunteers (except for elderly subjects who had greater liver function alterations) when ASLAN003 was dosed at clinically relevant exposures. ASLAN003 may offer an important addition to induction therapies, or in combination with other therapies such as azacytidine, or as a monotherapy.

We now intend to study the effects of ASLAN003 over a dose range, with the purpose to a) study efficacy in AML patients, and b) determine the dose optimum dose based on the combined efficacy and safety data.

ASLAN003 is very potent in inducing differentiation of AML cells lines (ED_{90} < 50 nM for THP-1). From these predictions, a starting dose of 100 mg QD would be most appropriate to obtain a good coverage of ED_{90} values. Since ASLAN003 is an acidic compound, the protein binding effect in human plasma should be considered. A starting

dose of ASLAN003 100 mg should obtain full 24-hour coverage of the effect. The fact that blast cell counts vary drastically among AML patients, suggests that a higher treatment dose might be necessary to show the optimum efficacy in some patients. Considering that AML patients are generally older in age and often carry comorbidities, it may be prudent to use doses lower than the maximum dose (400 mg) employed in healthy subjects. Therefore, the study will use 3-4 dose groups: 100 mg QD, 200 mg QD, 100 mg BID and potentially an additional cohort of 200 mg BID, which may only commence, subject to agreement from the steering committee based on a review of safety data from the 100 mg BID cohort. .

According to the pharmacokinetic data from the patients who had been treated with ASLAN003 100mg once daily in this study, the trough plasma concentration is below the IC50 of enzymatic hDHODH. A simulation model shows increasing the frequency of ASLAN003 administration keeps the plasma concentration of ASLAN003 above the IC50. Therefore, the dose and dosing frequency in two cohort (ASLAN003 100 mg BID and ASLAN003 200 mg BID) are changed and one additional cohorts with dosing ASLAN003 twice daily is added to the study design. The daily total dose of ASLAN003 is still within the maximum dose, tested safe in prior trials.

2 STUDY OBJECTIVES

2.1 Primary Objective

Part 1:

- To determine the optimum dose of ASLAN003 monotherapy based on the efficacy, safety and tolerability profile in AML patients who are ineligible for standard therapy.

Part 2:

- To provide a preliminary estimate of the efficacy of ASLAN003 at the optimum dose selected from Part 1.

2.2 Secondary Objective

Part 1:

- To evaluate the PKs of ASLAN003 and its metabolite LAS186558 in patients with AML.

Part 2:

- To further assess the safety and tolerability data of ASLAN003 at the optimum dose selected from Part 1.

2.3 Exploratory Objectives

- To examine the myeloid differentiation effects of ASLAN003 using assays including but not limited to an *ex vivo* flow cytometry assay.
- To explore possible relationships between molecular abnormalities and measures of clinical response in patients with AML.

3 OVERALL DESIGN AND PLAN OF THE STUDY

3.1 Study Design Overview

This is a multicenter, single arm, non-randomized, Phase IIA Study to evaluate ASLAN003 as a monotherapy in patients with AML.

AML patients who are ineligible for standard treatment including, but not limited to the following conditions, will be enrolled in the study:

- Newly diagnosed patients who are ineligible for standard therapy i.e., standard dose induction chemotherapy and reduced dose chemotherapy;
- Patients with relapse from prior remission;
- Patients with failed response to prior therapy including chemotherapy, hypomethylating agents, and bone marrow transplantation.

Rationale for dose selection: ASLAN003 is very potent at inducing differentiation in AML cells lines (ED_{90}< 50 nM for THP-1). From these predictions, a starting dose of 100 mg QD would be the most appropriate to obtain a good coverage of ED_{90} values. Since ASLAN003 is an acidic compound, the protein binding effect in human plasma will be high leading to lower levels of free drug, a starting dose of 100 mg QD is recommended to provide full 24-hour coverage.

Blast cell counts vary widely among AML patients, which may indicate that a higher treatment dose of ASLAN003 might be necessary to obtain the optimum efficacy. However, it is also important to consider the age and fitness of the AML patients who might have multiple comorbidities, and the maximum experienced dose (400 mg QD) established in healthy subjects might not be tolerated. Considering that AML patients are generally older in age and often carry comorbidities, it may be prudent to use doses lower than the maximum dose (400 mg) determined in healthy subjects.

Up to a total of 18-24 patients will be enrolled in Part 1 of this study - 6 patients in each dose cohort. The planned sequence of cohort enrollment is ASLAN003 100 mg QD, 200 mg QD, 100 mg BID and potentially an additional cohort of 200 mg BID (this additional cohort of 6 patients may commence, subject to agreement by the steering committee (SC) based on a review of safety data in 100 mg BID cohort).
A SC meeting will be set up to review all the clinical information including efficacy, safety, and PK data. Details of the SC outcome will be specified in the SC charter.

An expansion cohort of 20 patients (Part 2) will be recruited to study the optimum dose selected by the SC. The optimum dose will be selected from at least one cohort showing tolerable safety profile and clinical benefit in disease presentation. Details will be specified in the SC charter.

Patients with especially high blast cell count should be closely monitored for a possible differentiation syndrome. Investigators could manage suspected patients proactively

according to the recommendation in the National Comprehensive Cancer Network (NCCN) guidelines APL differentiation syndrome section.

Bone marrow aspiration samples will be collected before the first day of treatment, will be cultured *in vitro* and incubated with ASLAN003 to examine the myeloid differentiation efficacy of ASLAN003 *ex vivo*. Molecular studies will also be done to check for any phenotypic and genotypic changes in the patients' bone marrow sample. A bone marrow aspiration smear will be processed locally. *Ex vivo* assay and molecular assessment will be processed centrally (Please refer to the lab manual for details).

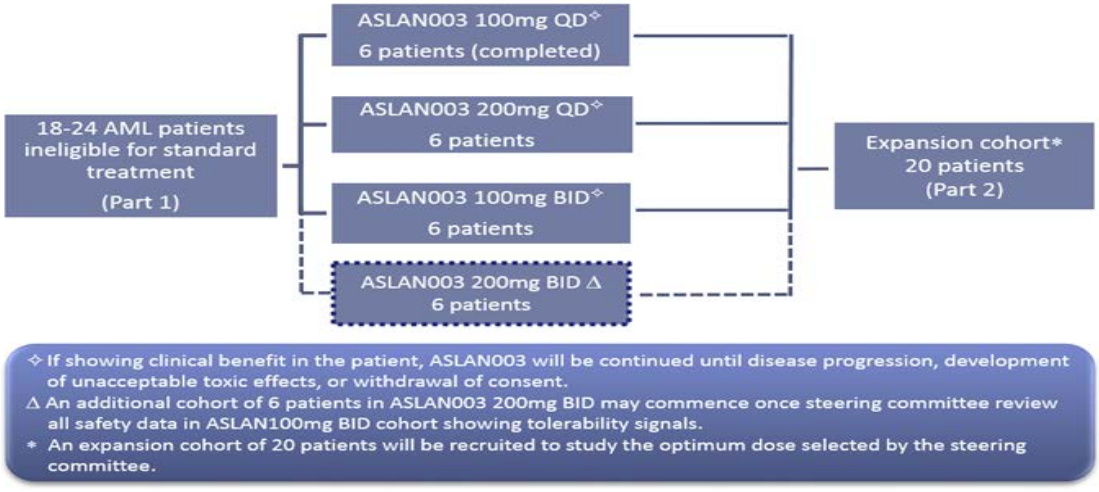
All patients will continue to receive ASLAN003 until disease relapse, treatment failure, unacceptable toxicity, withdrawal of consent or death.

For the PK evaluations, blood samples will be collected at the following timepoints on Day 1 and Day 8 of the QD, 28-day treatment cycle: pre-dose, 1, 2, 4, 5, 6, 8, and 24 hours post dose. In BID regime i.e 100mg BID and 200mg BID the PK sampling will be done at following timepoints: pre-dose, 1, 2, 4, 5, 6, 8, and 12 hours (or evening pre-dose).

For Part 2 PK evaluations- Steering Committee will decide whether PK analysis is required or not and ASLAN pharmaceuticals will be updated accordingly

The schedule of the assessments are presented in Table 1.

Figure 1: Study Design Description



Abbreviations: AML = acute myeloid leukemia; QD = once daily, BID = twice daily.

3.2 Steering Committee

A Steering Committee (SC) will be established for the purpose of assessing the efficacy, safety, tolerability, and PK data for the duration of the study.

The SC will evaluate the progress of the study on an ongoing basis and will make key decisions on the study in the best interest of the patients. Examples include continuation or discontinuation of the study, investigation of a lower dose level not stated in the protocol if efficacy is observed at a higher dose level. Details of the steering committee outcome will be specified in the SC charter.

An expansion cohort of 20 patients (Part 2) will be recruited to study the optimum dose selected by the SC. The optimum dose will be selected from at least one cohort showing tolerable safety profile and clinical benefit in disease presentation. Details will be specified in the SC charter.

3.3 Criteria for Evaluation of the Study

3.3.1 Primary Endpoints

Part 1:

The primary objective of determining the optimum monotherapy dose of ASLAN003 in AML patients is based on the following endpoints:

- **Overall Complete Remission Rate (OCRR):** Defined as the proportion of patients with a best response of complete remission (CR) or complete remission with incomplete hematologic recovery (CRi), defined in accordance with the International Working Group (IWG) Response Criteria in AML.
- **Safety and tolerability:** Based on AEs, safety assessments (including vital signs, ECG parameters, clinical laboratory tests) and treatment exposure/dose intensity.

Part 2:

- **OCRR:** defined as described above for ***Part 1***.

3.3.2 Secondary Endpoints:

- Efficacy ***(Parts 1 and 2)***:
    - **Relapse Free Survival (RFS)**: Defined as the time the criteria for remission (CR or CRi) are first met until there is evidence of patient relapse, regardless of whether the patient is still taking study drug. Relapse is defined as:
        - The reappearance of leukemic blasts in the peripheral blood or > 5% blasts in the bone marrow not attributable to any other cause;
        - The appearance of new dysplastic changes;
        - The reappearance of or development of cytologically proven extrameduallary disease;
        - The reappearance of a cytogenetic or molecular abnormality.

- **Clinical Benefit Rate (CBR)**: defined as the proportion of patients with an AML IWG best response of CR, CRi or partial remission (PR).
- % change from baseline in BM blasts at Day 29.

- Safety and tolerability ***(Part 2 ONLY)***:
  - Based on AEs, safety assessments (including vital signs, electrocardiogram [ECG] parameters, clinical laboratory tests) and treatment exposure/dose intensity.
- Pharmacokinetics (Part 1 ONLY):

  If estimable, the following parameters will be calculated on Days 1 and 8, Cycle 1:

  - PK parameters for ASLAN003: maximum observed plasma concentration (C_{max}), C_{max} at steady state ($C_{max\ ss}$), trough plasma concentration (C_{trough}), time corresponding to occurrence of C_{max} (t_{max}), and $C_{max\ ss}$ ($t_{max\ ss}$), AUC over the dosing interval (AUC_{tau}), AUC_{tau} at steady state ($AUC_{tau\ ss}$), terminal elimination half-life at steady state ($t_{1/2}$), effective elimination half-life at steady state ($t_{1/2\ eff}$), apparent total clearance of the drug from plasma after oral administration (CL/F), apparent volume of distribution at steady state after oral administration (Vss/F), accumulation ratio for AUC (RacAUC), and accumulation ratio for C_{max} ($RacC_{max}$).
  - PK parameters for LAS186558: C_{max}, C_{trough}, t_{max}, AUC_{tau}, $t_{1/2\ eff}$, RacAUC, $RacC_{max}$, metabolic ratio (MR) for C_{max} (MRC_{max}) and AUC (MRAUC).

3.3.3 Exploratory Endpoint (Parts 1 and 2):

- Assessment of the degree of blast cell differentiation by ASLAN003 using assays including but not limited to *ex vivo* flow cytometry assay using selected myeloid cell markers (such as CD11b).
- Assessment of the molecular abnormalities of AML blast cells at baseline.

3.4 Duration of the study participation

The study duration consists of the following periods:

Screening Period: 28 days

Treatment Period: All patients will receive a continuous 28-day treatment cycle of ASLAN003 until disease relapse, treatment failure (defined as failure to achieve a PR or higher within 4 cycles) unacceptable toxicity, withdrawal of consent or death.

Follow-up Period: All patients will be required to complete a safety follow-up visit within 28 days after the last dose of study treatment. All patients achieving CR or CRi will be followed for survival every 12 weeks post end of treatment (EOT) until disease relapse or death (in the absence of disease relapse) to find out the RFS.

Visit Schedule: In order to address the primary objectives of the study, if treatment is interrupted for any reason, it is important that all planned safety and efficacy assessments are performed at the scheduled time, regardless of whether the patient is receiving study treatment, or not, at the time.

The planned duration of entire study (treatment and follow-up) is approximately 2 years.

4 STUDY POPULATION

The study population consists of AML patients who are ineligible for standard treatment including but not limited to the following conditions:

- Newly diagnosed patients who are ineligible for standard therapy namely standard dose induction chemotherapy and reduced dose chemotherapy;
- Patients who relapsed from prior remission;
- Patients who failed to respond to prior therapy including chemotherapy, hypomethylating agents, and bone marrow transplantation.

Patients must be able to provide written consent; meet all the inclusion criteria and none of the exclusion criteria, stated below.

4.1 Inclusion Criteria

Patients will be enrolled into the study only if they meet all of the following criteria:

1. Patients who are of or older than the legal age in the respective countries at the time when written informed consent is obtained
2. Patients who are able to understand and willing to sign the informed consent form (ICF)
3. Patients who are diagnosed with AML according to the 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia (refer to Appendix 1: WHO Classification of Acute Myeloid Leukemia)
4. Patients who have a sufficient archival or fresh BM aspiration sample for the evaluation of relevant exploratory endpoint.
   Note: *Patients who do not have sufficient archival BM aspiration sample and refuse to repeat the procedure may be enrolled in the trial only after written confirmation by ASLAN*
5. Patients who are ineligible for standard treatment of AML including but not limited to the following conditions:
   - Newly diagnosed patients who are ineligible for standard therapy namely standard dose induction chemotherapy and reduced dose chemotherapy;
   - Patients who relapsed from prior remission;
   - Patients who failed to respond to prior therapy including chemotherapy, hypomethylating agents, and bone marrow transplantation.
6. Patients who have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2
7. Patients with adequate renal and hepatic function, as defined below:
   - Estimated Glomerular Filtration Rate (eGFR) or creatinine clearance (CrCl) (CrCL calculated by the Cockroft and Gault method) ≥ 40 ml/min/1.73 m^2
   - Total bilirubin, AST, and ALT ≤ 1.5 x ULN

4.2 Exclusion Criteria

Patients will be not be enrolled in the study if they meet any of the following criteria:

1. Patients who are diagnosed with *de novo* myeloid sarcoma without bone marrow involvement

2. Patients who are diagnosed with acute promyelocytic leukemia/retinoic acid receptor alpha (*PML-RARA*)
3. Patients who received any other standard or investigational treatment for their leukemia within the last 7 days before starting the first dose of study drug, with the exception of leukapheresis and hydroxyurea
4. Patients with unresolved serious toxicity (≥ CTCAE 4.03 Grade 2) from prior administration of standard or investigational treatment for their leukemia
5. Patients who have a positive test for human immunodeficiency virus (HIV), viral hepatitis C infection (patients with sustained viral response are not excluded), active viral hepatitis B infection (positive hepatitis B surface antigen [HBsAg]) with hepatitis B virus DNA exceeding 2000 IU/ml
6. Patients who have a known history of liver cirrhosis Child-Pugh score B or C
7. Patients who have any history of other malignancy unless in remission for more than 1 year (skin carcinoma and carcinoma-in-situ of uterine cervix treated with curative intent is not exclusionary)
8. Female patients who are pregnant or breast-feeding
9. Patients with a known history of alcohol or drug addiction on the basis that there could be a higher risk of non-compliance to study treatment per Investigator's discretion
10. Patients with a history or presence of a clinically significant condition which in the opinion of the Investigator could jeopardize the safety of the patient or the validity of the study results
11. Patients who have been previously treated with ASLAN003

4.3 Patient Withdrawal and Replacement

Patients may withdraw from any part of the study at any time without penalty and for any reason without prejudice to his or her future medical care. The Investigator will advise the Sponsor of the withdrawal of any patient.

Patients must be withdrawn from study drug under the following circumstances:

- Patient voluntarily withdraws from study participation;
- Disease recurrence;
- Ineffective treatment;
- Unacceptable toxicity;
- Patient's withdrawal of consent;
- Death;
- Pregnancy (refer to section 6.3.1.11)
- Significant protocol deviation;
- Lost to follow-up;
- If deemed by the Investigator that it is not in the patient's interest to continue withthe study.

Withdraws from study participation (follow-up permitted):

Patients withdrawing from the study drug will be encouraged where possible to return to the site for a study follow-up visit, in particular for safety evaluations, study assessments and survival follow-up.

Disease recurrence:

Sites should continue to perform efficacy assessments for patients achieving CR or CRi until disease recurrence (or death in the absence of recurrence) in accordance with IWG criteria for AML. Patients will be withdrawn from the treatment if there is evidence of disease recurrence as defined by IWG Criteria[16] (Cheson, 2003).

Ineffective treatment:

The study drug may be discontinued in the event of:

- Treatment failure (in patients who do not achieve a PR or above after 4 cycles of treatment)
- Relapse, as defined by the IWG Response criteria (for patients with a CR or CRi)
- No longer meeting the criteria for a PR (in patients who were previously determined to have a PR)

Once ineffective treatment has been established, as described above, no further efficacy assessments are required.

Unacceptable toxicity:

If the symptoms are not controlled with standard treatments and are considered to be clinically significant, study drug will be stopped and the patient will be withdrawn from the study drug. Patients removed from study drug for unacceptable toxicity will be followed until resolution or stabilization of the AE.

Patients with a response (CR or CRi) withdrawn from the treatment prior to disease relapse should continue to be followed until the relapse in accordance with the study plan.

Consent Withdrawal:

Patients may withdraw from the study at any time at their own request. The withdrawal of consent should be explained in detail in the medical records by the Investigator and entered in the appropriate electronic case report form (eCRF) page. Details of withdrawal should indicate whether the withdrawal is from further treatment with the study drug only or also from the study procedures and/or post treatment study follow-up. CR or CRi patients who request to withdraw from further treatment and study procedures may be followed up for survival status (if consented by the patients). Similarly, CR or CRi patients who withdraw from treatment only should continue to be followed until disease relapse.

Lost to follow-up:

If a patient does not return for a scheduled visit, every effort should be made to contact the patient to reschedule the visit, by phone, e-mail, text message, and if necessary, by letter and/or certified mail, in instances where the patient is not responsive to contact attempts. On a case-by-case basis, a patient visit should be arranged. All efforts should be documented in the patient's medical source record. A patient is considered lost to follow-up if the patient cannot be reached after 3 months from the scheduled visit or before the date of data cut-off date, whichever is earlier. However, if the patient re-initiates

contact beyond 3 months, or the site is informed of the patient's survival status or date of death, the available data may still be collected on the eCRF, assuming that patient consent has not been withdrawn.

All patients who are withdrawn or discontinued from the study are required to complete a safety follow-up visit within 28 days after the last administration of study drug, where possible. If the Investigator is unable to complete the safety follow-up visit assessments, the reason(s) must be recorded in the eCRF. All AEs/SAEs will be collected until 28 days after the last administration of study drug.

If a patient discontinues study drug and is withdrawn from the study for any reason, the study center must immediately notify the medical monitor. The Investigator should also ensure the return of unused study drug.

Patient Replacement:
As a general principle, patients will not be replaced if they withdraw following the completion of Cycle 1.

4.4 Planned Sample Size and Number of Study Centers

Part 1:

It is planned to recruit up to a total of 18-24 patients across multiple centers in Australia, Singapore and other countries.

Part 2:

It is planned to recruit a total of 20 patients across multiple centers in Australia, Singapore and other countries.

4.5 Patient Identification and Allocation of Treatment

At Screening, each patient will receive a unique Screening number from electronic data capture system (EDC). The number will start with "S" and be followed by 4 digits starting with S0001 for Part 1 and S2001 for Part 2.

Part 1:

Following confirmation of eligibility, all patients will be sequentially assigned to the dose cohorts after being screened for eligibility and providing consent. At administration of the first dose of study drug, patients will be assigned with a 4-digit patient number in the order in which they are enrolled in the study starting from 0001.

Enrolled patients who drop out of the study before receiving the study drug will retain their Screening number.

Part 2:

Following confirmation of eligibility and providing consent, all patients will be sequentially assigned to the dose level selected from Part 1. At administration of the first dose of study drug, patients will be assigned with a 4-digit patient number in the order in which they are enrolled in the study starting from 2001.

Enrolled patients who drop out of the study before receiving the study drug will retain their Screening number.

5 INVESTIGATIONAL PRODUCT

5.1 Identity of Investigational Product

The investigational product for this study is ASLAN003.

ASLAN003 is supplied as a formulated orange-colored hard gelatin capsule (Size No. 2). Each capsule contains ASLAN003 drug substance 50 mg, lactose monohydrate, colloidal silicon dioxide and sodium stearyl fumarate.

5.2 Study Drug Administration

ASLAN003 will be supplied by ASLAN Pharmaceuticals Pte. Ltd. The study drug is to be administered orally, QD or BID. It is recommended to administer the study drug with food or within 30 minutes after food intake.

5.3 Permitted Dose Interruptions of Study Drug

If patients experience a CTCAE Grade ≥ 3 toxicity attributed to ASLAN003 by the investigator, the study drug should be interrupted. Patients with Grade ≥ 3 AEs which are associated with underlying disease such as anemia, bone marrow hypocellular, febrile neutropenia, and decreased lymphocyte count, neutrophil count, and platelet count may keep receiving ASLAN003 treatment at investigator's discretion. The study drug should be resumed once the AE recovers to Grade 1 or less. If study drug is interrupted for continuous 28 days due to AE, the patient must be withdrawn from the study drug and recorded as unacceptable toxicity. If upon re-introduction of ASLAN003, a Grade 2 AE of the same event re-occurs, a dose reduction on a case-by-case basis can be implemented upon agreement with the CRO/Sponsor. For Grade ≥ 3 AST, ALT, or GGT elevations, interruption of study drug is based on the assessment of Child–Pugh score (Class A, B or C, refer to Appendix 3) and is demonstrated in Table 2.

Table 2

If Grade 3 AST/ALT/GGT	
Class A: Reduce dose by 50 mg for 1 week then reassess	□G4: Refer to "If Grade □4 AST/ALT/GGT"
	*Class A, still G3: Reduce dose by 50 mg
	*Class A, G2: Maintain current dose
	*Class A, ≤ G1: Resume last higher dose
	Class □B with Grade 1 to 3: Refer to the action of "If Grade 3 AST/ALT/GGT, Class ≤ B"
Class ≥ B: Interrupt until ≤G1, then resume original or reduced dose per investigator's discretion	
If Grade 4 AST/ALT/GGT	
Dose interruption, and follow up weekly until ≤G1	Class A: Reduce dose by 50 mg or maintain original dose per investigator's discretion[#]

	Class ≥ B Reduce dose by 50 mg[#]

*Monitor dose every week until back to original dose
[#] Withdrawal if a secondary G4 event is observed

5.4 Intra-patient dose escalation

Intra-patient dose escalation is allowed when the patient has no ongoing study drug-related AE ,and all patients in the cohort of targeted dose have completed at least one cycle of treatment without unexpected safety issue identified. Prior agreement with ASLAN Pharmaceuticals would need to be obtained for the dose escalation.

5.5 Packaging, Labeling and Storage

Study drug will be packaged and labelled by the Sponsor according to all local regulatory requirements. Study drugs are packaged in aluminum foil blisters in 2 × 3 format. Blisters are further packaged using either fibreboard cartons or wallets to facilitate clinical use.

Study centers and pharmacies are to store ASLAN003 under controlled conditions 15°C -25°C. Upon dispensing to patients, study drug may be stored up to 30°C or in a fridge 2-8°C. The storage area of the study center, must be a secure, temperature controlled, locked environment with restricted access. Study centers will be required to keep a temperature log to establish a record of compliance with these storage conditions.

Accurate records must be kept regarding dispensing and return of the study drug for each individual patient in the study. Reasons for deviating from the expected dispensing or return of the study drug must be recorded.

No special procedures for the safe handling of ASLAN003 are required. The Sponsor will be permitted upon request to audit the supplies, storage, dispensing procedures and records.

5.6 Blinding

Part 1 is a single-arm, dose optimizing, non-randomized study. Hence, blinding is not applicable.

Part 2 is an open label, single arm design. All patients in Part 2 will receive the same treatment and dose, thus blinding is not applicable for Part 2.

5.7 Study Drug Accountability

The Investigator is responsible for maintaining accurate study drug accountability records throughout the study.

Each dispensing of the study drug will be documented in the eCRF.

The Investigator is responsible for returning all unused or partially used study drug to the Sponsor and must verify that all the unused or partially used drug supplies have been returned by the patient and that no remaining supplies are in the Investigator's possession.

5.8 Study Drug Compliance

The administration of all study drugs should be recorded in the appropriate sections of the eCRF. Patients will report any self-administered medication for the periods when they are not at the study center.

Patients will be issued a patient Diary Card to record drug compliance, which is to be returned to the study center at the next visit.

Treatment compliance will be assessed by regular capsule counts and comparing the entries in the patient Diary Card and the information will be recorded in the appropriate section of the eCRF.

Patients must bring all the wallets of study drug and any remaining tablets as well as the patient Diary Card with them at each scheduled visit. Patients will be instructed to notify the study center personnel of missed doses. Dates of missed or held doses will be recorded in the eCRF.

5.9 Previous and Concomitant Medications/Non-drug therapies

Any medication taken by a patient, other than the study drug, will be considered a concomitant medication. This includes herbal and other non-traditional remedies. Concomitant medication may also include those drugs which were medically indicated for any condition. All patients will be asked to provide a complete list of concomitant medications that have been taken within 4 weeks before the first treatment visit, including prescription, over-the-counter, complementary, and alternative medications. They must also inform the Investigator about any new medication that was started while on the trial.

All concomitant medications must be recorded in the eCRF. Details (including indication, doses, frequency, and start/stop dates) of concomitant medication taken, as well as concomitant therapy (including indication, start and stop dates) administered within 4 weeks before the first treatment visit, during the trial, until the completion of the safety follow-up visit, must be documented in the medical record and the appropriate eCRF.

5.9.1 Permitted Concomitant Therapy

Therapies required to treat AEs, relieve disease symptoms, concurrent diseases and supportive care agents, such as antipyretics, antibiotics, blood transfusion, colony-stimulating factor, etc. will be permitted during the study.

5.9.2 Prohibited Concomitant Therapy

Any approved or investigational treatment given for the purpose to treat the leukemia, including but not limited to chemotherapy, hypomethylating agents, herbal medicine, Chinese medicine, leukapheresis, etc. will be prohibited during the study.

For the management of leukocytosis, hydroxyurea use per site practice is allowed for patients with peripheral blast count more than 20,000 cells/uL in the first two weeks of study treatment. Once the peripheral blast count drops to less than 20,000 cells/uL, site is require to discontinue with hydroxyurea to ensure not impacting efficacy readout. Hydroxyurea use is allowed for suspected or confirmed differentiation syndrome.

6 STUDY VARIABLES AND METHODS OF ASSESSMENT

6.1 Determination of Optimum Dose

Part 1 of the study is designed with co-primary endpoints of efficacy and tolerability, in order to facilitate dose selection for further investigation. Data from Part 1 of this Phase IIA study will be reviewed in its totality to provide and understanding of the dose-response relationship, both in terms of efficacy and tolerability, in order to determine an optimum dose for further development in Part 2.

6.2 Efficacy Variables

Efficacy will be evaluated with BM aspiration and peripheral blood results based on the IWG Criteria[16] for AML (Cheson, 2003). For patients without sufficient archival BM sample, BM aspiration will be performed during Screening. All patients will receive bone marrow aspiration for efficacy assessment on Day 1 of Cycle 2, 3, 4, 5 and will be repeated every 12 weeks after Cycle 5. Patients who've already achieved CR could omit the bone marrow aspiration at subsequent visits if there is a normal complete blood count with differential of the peripheral blood. Investigator may perform more frequent exam if required based on clinical judgment. In order to address the primary objectives of the study, if treatment is interrupted for any reason, it is important that all planned safety and efficacy assessments are performed at the scheduled time, regardless of whether the patient is receiving study treatment, or not, at the time

BM aspiration smears will be processed locally.

Following treatment discontinuation, patients who have achieved a CR or CRi, will continue to be followed up for every 12 weeks to assess the relapse free survival. For patients who have not achieved a CR or CRi during treatment, no further follow-up is required following treatment discontinuation.

These criteria categorize the visit response into the following response classifications:

- CR with incomplete recovery of neutrophils and platelets (CRi):

Achievement of CRi requires patients to satisfy all of the following:

- A disappearance of blasts in the peripheral blood.
- A decrease in BM blasts to <5% total BM nucleated cells demonstrated in BM aspirate.
- Absence of Auer rods
- No persistent extramedullary leukaemia

- Complete Remission:

Patient satisfies all of the criteria above and in addition has:

- Recovery of Neutrophils to ≥1.0 x 10^9/L and Platelets to ≥ 100 x 10^9/L
- Transfusion-independence

- Partial Remission:

A PR is defined as recovery of neutrophils to to ≥1.0 x 10^9/L and Platelets to ≥ 100 x 10^9/L and either:

- If the pre-treatment bone marrow blast percentage was 50% to 100%, the percentage of blast must decrease to a value between 5% and 25%
- If the pre-treatment BM blast percentage was 20% to less than 49%, they must decrease by at least half to a value of more than 5%
- A reduction in BM blast cells to <5% but with persistence of Auer rods.

- Treatment failure:

Failure to meet the criteria for CR, CRi or PR after 4 cycles of treatment will result in a best response of treatment failure.

For the evaluation of OCRR, a binary variable will be created to indicate complete response status of each patient (complete responder or non-responder) defined as follows:

A patient will be classified as a complete responder if either of the following are achieved during the study:

- Achievement of CR
- Achievement of CRi

Patients who do not satisfy the CR criteria outlined above (including patients with PR, treatment failure and any patients without evaluable post-treatment assessments) will be classified as non-responders for the assessment of OCRR.

Best response status will also be assessed. A patient's best response is defined as the best AML visit response observed, ranked in the following order:

CR > CRi > PR > Treatment failure.

Based on the above definitions, the following efficacy endpoints will be evaluated:

Overall Complete Remission Rate: Defined as the proportion of patients with a best response of CR or CRi, defined in accordance with the IWG Response Criteria in AML , and described above.

Relapse Free Survival: Defined as the time the criteria for remission (CR or CRi) are first met until there is evidence of patient relapse or death from any cause (whichever happens first), regardless of whether the patient is still taking study drug.

Relapse is defined as:

- The reappearance of leukemic blasts in the peripheral blood or > 5% blasts in the BM not attributable to any other cause
- The appearance of new dysplastic changes
- The reappearance of or development of cytologically proven extrameduallary disease
- The reappearance of a cytogenetic or molecular abnormality

Clinical Benefit Rate: Defined as the proportion of patients with an AML IWG best response of CR, CRi or PR.

The percentage change from baseline in BM blasts and peripheral blood blasts at Day 29 will also be evaluated.

6.3 Safety Variables

During the study, patients will visit the study site at Screening and at scheduled visits in accordance with the schedule of assessment (Table 1). Safety assessments, physical examination, vital signs (blood pressure [systolic and diastolic], resting pulse, respiratory rate, weight and body temperature), ECG parameters, clinical laboratory tests (hematology, clinical chemistry, coagulation and urinalysis) and AEs will be completed at study visits as defined in the schedule of assessments.

6.3.1 Adverse Events

6.3.1.1 Collection of Adverse Events

It is responsibility of the Investigator to collect all AEs (both serious and non-serious) derived by spontaneous, unsolicited reports of patients, by observation and by routine open questionings e.g. "How have you felt since I last saw you?". Coding of AEs will be done as described in Section 9.4.

6.3.1.2 Definitions

An AE is any untoward medical occurrence that occurs in a patient or clinical investigation patient administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the product.

Fluctuations in the pre-existing conditions that do not represent a clinically significant exacerbation or worsening will not be considered AEs. Surgical procedures, planned before enrolment of the patient in the study, will not be considered AEs if the condition(s) was (were) known before study inclusion. In the latter case, the medical condition should be reported in the patient's medical history.

Progression of the malignancy or target disease under the study is generally not considered as an AE.

All AEs, including inter-current illnesses, occurring during the study will be documented in the eCRF. Concomitant illnesses, which existed before entry into the study, will not be considered AEs unless they worsen during the treatment period. All AEs, regardless of the source of identification (e.g., physical examination, laboratory assessment, ECG, reported by patient), must be documented.

Pre-existing conditions will be recorded in the eCRF system on the Medical History or appropriate page.

A treatment-emergent AE (TEAE) will be defined as an AE that begins or that worsens in severity after at least 1 dose of study drug has been administered.

When recording an AE, the Investigator should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The eCRF and source documents should be consistent. Any discrepancies between the patient's own words on his/her own records (e.g., diary card) and the corresponding medical terminology should be clarified in the source documentation.

Details for completion of the AE case report form (CRF) (including judgment of relationship to study drug) are described in the CRF completion guidelines.

6.3.1.3 Assessment of Adverse Events

Each AE will be assessed by the Investigator with regard to the following categories.

6.3.1.4 Seriousness

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening (This means that the patient is at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe);
- Requires in-patient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect;
- Is an important medical event(s) that may not be immediately life-threatening or result in death or hospitalization but that may jeopardize the patient or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependenc or drug abuse.

Medical and scientific judgment should be exercised in deciding whether a case is serious and whether expedited reporting is appropriate.

Events related to disease progression will not be reported as SAEs unless the events lead to death and the death will be reported as an SAE.

Hospitalization due to the following reasons should not be reported as an SAE:

- Reasons described in the protocol i.e. drug administration, protocol required procedures;

- Surgery or procedure planned prior to entry into the study;
- Surgery or procedure planned for pre-existing conditions that do not worsen after entry into the study;
- Social/administrative reasons i.e. due to distance between home and hospital, hospice placement for terminal care due to progressive disease etc.

6.3.1.5 Intensity

Investigators should assess the severity of AEs according to CTCAE v4.03. In general, CTCAE v4.03 Severity Grades are:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL) (Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.);

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.);

Grade 4: Life-threatening consequences; urgent intervention indicated;

Grade 5: Death related to AE.

All changes in severity must be recorded in the eCRF.

6.3.1.6 Causality

Causal relationship assessments to study drugs are required for purposes of reporting AEs. To promote consistency, the following guidelines should be taken into consideration along with good clinical and scientific judgment when determining the relationship of drug treatments to an AE:

The descriptions provided below will help guide the Investigator in making the assessment of causality:

Definitely Related: A clinical event, including clinical laboratory test abnormality, occurring in a plausible time relationship to the medication administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug should be clinically plausible.

Probably related: A clinical event, including clinical laboratory test abnormality, occurring in a plausible time relationship to the medication administration, which are unlikely to be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug should be clinically reasonable. Re-challenge not required.

Possibly Related: A clinical event, including clinical laboratory test abnormality, with a reasonable time sequence to the medication administration, which could also be explained by concurrent disease or other drugs or chemicals. Information on the drug withdrawal may be lacking or unclear.

Unlikely Related: A clinical event, including clinical laboratory test abnormality, with little or no temporal relationship to medication administration, and to which other drugs, chemicals or underlying disease provide plausible explanations.

Not Related: A clinical event, including clinical laboratory test abnormality that has no temporal relationship to the medication or has more likely alternative etiology.
The study conduct relatedness for SAEs will also be assessed and documented.

Note[1]: For the purpose of clinical study report (CSR) reporting, AEs listed as "possibly, probably, or definitely" related to the investigational product are considered to have a "reasonable causal relationship" to the investigational product. Adverse events listed as "unlikely" or "not unrelated" are considered to have a suspected "unrelated" causal relationship to the investigational agent.

Note[2]: The above convention for determining whether AEs have a *reasonable causal relationship* to study treatment applies to AE reporting in the tables, listings and figures (TLFs) for the CSR only. As described in Sections 3.1 and 3.2, a SC will oversee patient safety during the study, and will have the ability to halt recruitment if 2 or more *clinically significant adverse drug reactions* are observed during the first cycle for any dose cohorts. In order to be classified as a *clinically significant adverse drug reaction*, the Investigator must believe that the event is *likely* to have been related to the investigational agent, rather than *possibly* related. For this purpose, an AE must be classified as either "probably" or "definitely" related to the investigational agent.

6.3.1.7 Recording Adverse Events

All AEs will be evaluated according to CTCAE version 4.03 and will be captured from the time of informed consent and continue until the safety follow-up assessment (28 days post-last dose of study drug). For the purpose of this study, fluctuations in the pre-existing conditions that do not represent a clinically significant exacerbation or worsening are not to be considered as AEs.

Prior to receiving study drug, only AEs that were assessed as related to study procedures will be recorded and reported. If a patient begins a new anti-leukemia therapy within 28 days after the last administration of study drug, the AE reporting period for non-serious AEs ends at the time the new therapy is started.

All AEs, as per the definition stated in the protocol regardless of the relationship to study drug, will be recorded in the eCRF.

All AE reports should contain a brief description of the event, date and time of onset, date and time of resolution, intensity, treatment required, relationship to study drug, action taken with the study drug (e.g. dose not changed, dose reduced, drug interrupt,, not applicable, and whether or not the AE led to the drug withdrawal), outcome (e.g. not recovered/resolved, recovering/resolving, recovered/resolved, recovered/resolved with sequelae, fatal, or unknown), and whether the event is classified as serious.

6.3.1.8 Reporting Serious Adverse Events

All SAEs will be recorded from signing of informed consent until 28 days after the last dose of the study drug. Prior to receiving investigational product, only SAEs that were assessed as related to study procedures will be reported.
If a patient begins a new anti-leukemia therapy within 28 days after the last administration of study drug, the SAE reporting period for SAEs ends at the time the new therapy is started.
The Investigator must report any SAEs, as per the definition stated in the protocol on the SAE page of the eCRF within 24 hours of becoming aware of the event. During eCRF inaccessibility, a paper SAE Form should be sent to the Sponsor's assigned safety representative (PAREXEL) by email within 24 hours of becoming aware of the event.

Email: ASLANSafety@parexel.com

The Investigator and the Sponsor/PAREXEL will review each SAE report and the Sponsor/PAREXEL will evaluate the seriousness and the causal relationship of the event to the study drug. In addition, the Sponsor/PAREXEL will evaluate the expectedness according to the reference document Investigators Brochure (IB). Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action.
Details for the reporting of SUSARs can be found in Section 6.3.1.10.

The minimum information required for an initial report is:

- Name of the person sending the report (i.e. name, address of Investigator);
- Patient identification (Screening/randomization number, initials, NOT patient name);
- Protocol number;
- Description of SAE;
- Causality assessment, if possible.

After receipt of the initial report, PAREXEL will review the information and, if necessary, contact the Investigator, to obtain further information for assessment of the event. PAREXEL will be responsible for all information processing and will expedite the reporting to all concerned Investigators, to the IECs/IRBs, where required, and to the Regulatory Authorities of all adverse reactions that meet expedited reporting criteria according to local requirements.

6.3.1.9 Follow-up of Adverse Events

All AEs experienced by a patient, irrespective of the suspected causality, will be monitored until the AE has resolved, any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Investigator and Medical Monitor, until there is a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

6.3.1.10 Suspected Unexpected Serious Adverse Reactions

Any adverse event that is serious, associated with the use of the study drug, and unexpected suspected unexpected serious adverse reaction (SUSAR) has additional reporting requirements, as described below.

- If the SUSAR is fatal or life-threatening, associated with the use of the study drug, and unexpected, Regulatory Authorities and Independent Ethics Committees/Institutional Review Boards IECs/IRB will be notified within 7 calendar days after the Sponsor learns of the event. Additional follow-up (cause of death, autopsy report, and hospital report) information should be reported within an additional 8 days (15 days total);
- If the SUSAR is not fatal or life-threatening but is otherwise serious, associated with the use of the study drug, and unexpected, Regulatory Authorities and IECs will be notified within 15 calendar days after the Sponsor learns of the event.

The Sponsor will notify the Investigators in a timely fashion of relevant information about SUSARs that could adversely affect the safety of patients. Follow-up information will be submitted if necessary.

The Sponsor will also provide annual safety updates to the Regulatory Authorities and IECs/IRBs responsible for the study. These updates will include information on SUSARs and other relevant safety findings.

6.3.1.11 Pregnancy

There is no information regarding the effects ASLAN003 could have on the development of a human fetus. Therefore, it is important that females and the partners of male patients do not become pregnant during the study and for at least 3 months after the patient has taken their last dose of ASLAN003.

Female patients of childbearing potential and men enrolled in this study, in addition to partners of male patients must agree to use adequate contraception prior to study entry, for the duration of study participation, and for 3 months following completion of therapy.
A female of childbearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy; or
- Has not been naturally postmenopausal for at least 2 years (i.e., has had menses at any time in the preceding 2 years).

Acceptable forms of contraception

A highly effective method of birth control is defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly.

Individually hormonal, barrier or intrauterine device methods alone are not acceptable. Examples of acceptable forms of highly effective contraception for women include:

- Established use of oral, injected or implanted hormonal methods of contraception in combination with a barrier method (included; diaphragm, cervical cap, condom);
- Placement of an intrauterine device or intrauterine system in combination with a barrier method;
- Sterilized male partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate) in combination with a barrier method;
- Total abstinence: When this is in line with the patients preferred and usual lifestyle.

Examples of non-acceptable methods of contraception include:

- Barrier method alone;
- Periodic abstinence (e.g. calendar, ovulation, sympthothermal, post ovulation);
- Withdrawal;
- Spermicide.

For men it is recommended that a condom be worn for all sexual intercourse (in addition to another effective means of contraception) as it is not known if study drug may affect sperm risking the potential for congenital abnormalities.

Time Period for the Collection of Pregnancy Information:

All pregnancies in female patients and in female partners of male patients receiving study drug will be recorded from enrollment until 3 months after the last study visit.

Follow-up in the Event of a Pregnancy:

Should a woman become pregnant or suspect she is pregnant while participating in this study, or should a male patient's partner become pregnant or suspect she is pregnant while the male is participating in this study, the treating Investigator should be informed immediately. Female patients will be withdrawn from study drug, and all pregnancies will be reported along the same timelines as a SAE.

If a female patient or the female partner of a male patient who has received study drug becomes pregnant the pregnancy will be recorded. The IEC/IRB and the Sponsor will be informed. In all cases of pregnancy, the patient will be asked to provide information on the outcome of the pregnancy, including premature termination should the case arise.

Spontaneous miscarriage and congenital abnormalities will be reported as a SAE.

The follow-up period will be deemed to have ended when the health status of the child has been determined at its birth and followed up for 8 weeks following the birthof any potential abnormalities.

The Sponsor has a responsibility to monitor the outcome of pregnancies where there has been maternal exposure to the study drug.

Pregnancy alone is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication.

Elective abortions without complications should not be handled as AEs, unless they were therapeutic abortions (see below). Hospitalization for normal delivery of a healthy newborn should not be considered a SAE.

All pregnancies must be reported by the Investigator to PAREXEL/Sponsor on the initial pregnancy report form within 24 hours after becoming aware of the pregnancy. The Investigator must follow-up and document the course and the outcome of all pregnancies even if the patient was discontinued from the study or if the study has finished.
All outcomes of pregnancy must be reported by the Investigator to PAREXEL/Sponsor on the pregnancy outcome report form within 24 hours after he or she has gained knowledge of the normal delivery or elective abortion.

Any SAE that occurs during pregnancy (including SAEs occurring after last administration of study drug) must be recorded on the SAE report form (e.g. maternal serious complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.

If a female partner of a male study patient who has been exposed to the study drug becomes pregnant, the pregnancy and ou*tcome of pregnancy should be monitored.*

6.3.1.12 Laboratory Variables

Laboratory assessments will be performed locally at each center's laboratory by means of their established methods. Before starting the study, the Investigator will supply IQVIA/Sponsor with a list of the normal ranges and units of measurement.

The laboratory variables that will be assessed in accordance with the schedule of procedures described in Table 1 are summarized in Table 3.

The Investigator must review Screening laboratory results for patient eligibility prior to enrolling.

Laboratory tests can be repeated earlier than the next scheduled consecutive study visit at the Investigator's discretion and any associated safety issue should be followed up as per the Investigator's clinical judgment until resolution/stabilization.

In the event that the laboratory parameters show a significant shift from baseline values, patients will then be scheduled for an interim visit within 2 weeks to repeat the laboratory measurements.

Table 3: Laboratory Assessment

Hematology:	RBC count MCV MCH Leucocyte differential count Blasts Promyelocytes Myelocytes Metamyelocytes Band Neutrophils Segmented Neutrophils Eosinophils Basophils Lymphocytes Monocytes Platelets WBC count Hemoglobin Hematocrit	**Urinalysis**:	pH Protein Glucose Ketone Bilirubin Blood Leukocyte esterace Nitrite
Coagulation	INR aPTT		
Clinical Chemistry:	Albumin Creatinine Calcium Glucose Triglycerides Urea Uric acid Cholesterol HgbA1c Potassium Sodium Alkaline phosphatase GGT AST ALT Total bilirubin	**Bone Marrow Aspiration**	Aspiration site Cellularity Blasts Promyelocytes Myelocytes + Metamyelocytes Band + Segment Erythroid series Mono-histiocytes Eosinophils Plasma cells Lymphoid cells Miscellaneous Auer rods Dysplastic change Cytochemical
Serology*:	HIV HBsAg HBV DNA if positive HBsAg HCV antibody		
Pregnancy Test:	Serum or urine pregnancy test will be performed at the Screening and end of treatment visits for all females except those surgically sterile or 2 years postmenopausal. Subsequent serum or urine pregnancy tests are allowed at the Investigator's discretion.		

Abbreviations: ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; aPTT= activated partial; thromboplastin; DNA = deoxyribonucleic acid; GGT = Gamma glutamyl transferase; HCV = Hepatitis C virus; Hemoglobin A1c = HgbA1c; HBsAg = Hepatitis B surface antigen; HBV= hepatitis B virus; HIV = Human immunodeficiency virus; INR = international normalized ration; MCH = Mean corpuscular hemoglobin; MCV = Mean corpuscular volume, time; WBC = white blood cells; RBC = red blood cells.
* If HBsAg result indicate active infection then test HBV DNA.

6.3.2 Physical Examinations

Physical examinations will be performed in accordance with the Schedule of Assessments (Table 1).

The Investigator will conduct a complete physical examination in all patients at the Screening Visit and partial physical examination in all patients during subsequent visits. The physical examinations will cover the following general appearance, head, ears, eyes, nose, throat, hair, skin, respiratory, cardiovascular, gastro intestinal, musculoskeletal, hepatic, neurological, and mental status. Clinically relevant physically examination findings during the study will be recorded as AEs. Findings will be recorded in the eCRF.

6.3.3 Vital Signs

The following vital signs will be assessed in accordance with the Schedule of Procedures (Table 1)

- Blood pressure (systolic and diastolic; mmHg);
- Heart rate (beats per minute);
- Body temperature (degree Celsius[°C]);
- Respiration rate (breaths per minute).

Any abnormal findings that are clinically significant, in the opinion of the Investigator, will be recorded as an AE. Vital sign measurements will be recorded in the eCRF.

6.3.4 Electrocardiograms

Standard 12-lead ECGs will be performed in accordance with the Schedule of Procedures (Table 1)

A 12-lead ECG will be performed at screening, the end of investigational therapy, and when clinically indicated by the Investigator. The Investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation.

6.3.5 ECOG Performance Status

ECOG will be evaluated for all patients at Screening, and during all study visits until follow-up. The detailed description of ECOG Status is provided in Appendix 2: ECOG Performance Status.

6.3.6 Additional Safety Assessments

There are no additional safety assessments planned for this study.

6.4 Pharmacokinetics Assessment (Part 1 ONLY)

The blood samples for determination of ASLAN003 and metabolite concentrations will be collected on Day 1 and Day 8 Cycle 1 in Table 4 at the following timepoints:

Table 4: ASLAN003 Pharmacokinetic Assessment Schedule

Scheduled Visit	Time Points (h)	PK Parameters
Day 1	Pre-dose	C_{max}, $C_{max\ ss}$, C_{trough}, t_{max}, AUC_{tau}, $t_{1/2}$, $t_{1/2\ eff}$, Cl/F* & Vss/F*
	Post dose: at 1, 2, 4, 5, 6, 8, 12#, and 24 hours	
Day 8	Pre-dose	$C_{max\ ss}$, C_{trough}, $t_{max\ ss}$, $AUC_{tau\ ss}$, CL/F*, $t_{1/2}$, $t_{1/2\ eff}$, MRAUC** MRC_{max}**, RacAUC, and $RacC_{max}$
	Post dose: at 1, 2, 4, 5, 6, 8, 12#, and 24 hours	

Note: Only ASLAN003 and its metabolite's (LAS186558) concentrations and PK parameters will be determined in this study.
* Parameter calculated only for ASLAN003
** Parameter calculated only for LAS186558
# Sample collected for BID regime only.
Abbreviations: AUC = area under the plasma concentration curve; AUC_{tau} = AUC over the dosing interval; $AUC_{tau\ ss}$ = AUC_{tau} at steady state; CL/F = apparent total clearance of the drug from plasma after oral administration at steady state; C_{max} = maximum observed plasma concentration; $C_{max\ ss}$ = C_{max} at steady state; C_{trough} = Trough plasma concentration; RacAUC = accumulation ratio for AUC; $RacC_{max}$ = accumulation ratio for C_{max}; t_{max} = time corresponding to occurrence of C_{max}; $t_{max\ ss}$ = time corresponding to occurrence of $C_{max\ ss}$; MR = metabolic ratio; MRAUC = metabolic ratio for AUC; MRC_{max} = metabolic ratio for C_{max}; $t_{1/2}$ = effective elimination half-life; $t_{1/2\ eff}$ = effective elimination half-life at the steady state; V_{ss}/F = apparent volume of distribution at steady state after oral administration

In BID regime i.e 100mg BID and 200mg BID the PK sampling will be done at following timepoints: pre-dose, 1, 2, 4 ,5 ,6 ,8, and 12 hours (or evening pre-dose).For Part 2- Steering Committee will decide whether PK analysis is required or not and ASLAN pharmaceuticals will be updated accordingly

6.4.1 Collection of Blood Samples

Blood samples for determination of plasma concentrations of ASLAN003 and LAS186558 will be collected from patients according to the PK sampling schedule described in Table 1: Schedule of Study Assessments. Detailed sample collection, label, storage, and shipment processes will be described in the Laboratory Manual. The exact date/time of the blood sample collection will be recorded in the patient's eCRF.

6.4.2 Determination of Drug Concentrations in Blood Samples

Determination of ASLAN003 and LAS186558 plasma concentrations by using a validated liquid chromatography/mass spectrometry methodology will be performed by a sponsor designated bioanalytical laboratory.

The analytical methods used to measure plasma concentrations of study drug will be described in a separate bioanalytical report.

The following information will be captured for blood sample collections in each patient's eCRF:

1. Patient's number and initial.
2. Date/time of the drug administration.
3. Time and date of each blood sample collected for PK analysis

6.5 Other Exploratory Assessment

Assays including but not limited to *ex vivo* flow cytometry assay using selected myeloid cell markers (such as CD11b) will be performed to assess the degree of blast cell differentiation upon treatment with ASLAN003. The percentage of CD11b positive cells will be determined before and after *ex vivo* treatment with ASLAN003. Molecular abnormalities of AML patients will be assessed using polymerase chain reaction (PCR) or next-generation sequencing (NGS). The *ex vivo* assay and molecular assessment will be processed centrally (Please refer to the lab manual for details).

6.6 Demographics and Baseline Characteristics

Demographics and baseline characteristics consist of those variables that are assessed only at Screening.

6.6.1 Patient Demography

Patient demography consists of:

- Date of birth;
- Height;
- Weight;
- Vital signs;
- Race and ethnicity;
- Gender.

Demographic information will be recorded in the eCRF

6.6.2 Disease History

For disease history the following information related to AML will be documented:

- Date of first diagnosis
- Diagnosis as per World Health Organization 2016 revised classification;
- Prior treatment, response and date;

- Date of relapse / failed response to previous therapy;

6.6.3 Medical History

For the documentation of the medical history, any relevant previous and concurrent diseases will be documented.

The medical history will be obtained by interviewing the patient or by inspecting his/her medical records. Findings will be recorded in the eCRF.

For coding of medical history, see Section 9.4

6.6.4 Previous and Concomitant Medications

Previous and concomitant medication will be documented as described in Section 5.8.

6.7 Other Variables

Not applicable.

7 STUDY CONDUCT

7.1 Schedule of Procedures

The timing and details of study procedures to be conducted, by visit, is described in Table 1.

7.2 Procedures by Visit

7.2.1 Screening (Days -28 to 0)

Prior to any study activities, patients will be asked to read and sign an ICF that has been approved by an IEC/IRB and the Sponsor and which complies with regulatory requirements.

Patients will undergo Screening during a visit that can occur up to 4 weeks prior to the Cycle 1 Day 1 Visit. This Screening period will be used to assess eligibility of patients and to allow for the washout of prohibited medications.

The following Screening and baseline assessments will be performed:

- Obtain written informed consent;
- Verify conformance with entry criteria;
- Assignment of a Screening number;
- Demographic data;
- Other medical history/prior medications;
- Complete physical examination;
- Height;
- Body weight;
- Vital signs (blood pressure, heart rate, respiratory rate, and body temperature);
- 12-lead ECGs;
- Patients' ECOG performance status;
- Prior and Concomitant Medications;
- Routine laboratory evaluations (chemistry, hematology, liver function test and urinalysis);
- Serum / urine β-human Chorionic Gonadotropin
- Serology;
- Coagulation laboratory test;
- Bone Marrow Aspiration (BMA) *[BMA smears will be processed locally. Remaining Bone Marrow Aspiration Sample will be processed as per BMA lab manual for ex vivo assay and molecular assessment]*.

7.2.2 Treatment Visits

Patients will receive study drug ASLAN003 from Day 1 in 28-day treatment cycles until disease relapse, treatment failure, unacceptable toxicity, and withdrawal of consent or death.

Treatment visits are scheduled as below:

Visit 1: Cycle 1, Day 1

Visit 2: Cycle 1, Day 8

Visit 3: Cycle 1 Day 10

Visit 4: Cycle 1, Day 15

Visit 5: Cycle 1, Day 22

Visit 6 & onwards: Cycle 2, Day 1 and onwards at Day 1 of every subsequent cycle.

7.2.2.1 Cycle 1, Day 1

The following procedures will be conducted at this visit:

- Complete physical examination;
- Body weight;
- Vital signs (blood pressure, heart rate, respiratory rate, body temperature);
- Patients' ECOG performance status;
- All AEs since the last visit will be recorded;
- Concomitant medications will be recorded;
- Routine laboratory evaluations (chemistry, hematology, liver function test and urinalysis);
- Study drug (ASLAN003) will be dispensed and administered.
- Blood sample will be collected for PK analysis at Day 1, QD regime: pre-dose, 1, 2, 4, 5, 6, 8, and 24 hours post dose In BID regime i.e 100mg BID and 200mg BID the PK sampling will be done at following timepoints: pre-dose, 1, 2, 4, 5, 6, 8, and 12 hours (or evening pre-dose). For Part 2- Steering Committee will decide whether PK analysis is required or not and ASLAN pharmaceuticals will be updated accordingly.

7.2.2.2 Cycle 1, Day 8 (±1 day)

The following procedures will be conducted at this visit:

- Complete physical examination;
- Vital signs (blood pressure, heart rate, respiratory rate, body temperature);
- All AEs since the last visit will be recorded;
- Concomitant medications will be recorded;
- Routine laboratory evaluations (chemistry, hematology, liver function test and urinalysis);
- Study drug (ASLAN003) will be dispensed and administered.

- Blood sample will be collected for PK analysis at Day 8, QD regime: pre-dose, 1, 2, 4, 5, 6, 8, and 24 hours post dose. In BID regime i.e 100mg BID and 200mg BID the PK sampling will be done at following timepoints: pre-dose, 1, 2, 4, 5, 6, 8, and 12 hours (or evening pre-dose). For Part 2- Steering Committee will decide whether PK analysis is required or not and ASLAN pharmaceuticals will be updated accordingly.

7.2.2.3 Cycle 1, Day 10 (+1 day)

The following procedures will be conducted at this visit:

- AST, ALT and total bilirubin to be performed;
- Study drug (ASLAN003) will be dispensed and administered.

7.2.2.4 Cycle 1, Day 15 (±2 days)

The following procedures will be conducted at this visit:

- Complete physical examination;
- Vital signs (blood pressure, heart rate, respiratory rate, body temperature);
- 12-lead ECG
- All AEs since the last visit will be recorded;
- Concomitant medications will be recorded;
- Routine laboratory evaluations (chemistry, hematology, liver function test and urinalysis);
- Coagulation laboratory test;
- Study drug (ASLAN003) will be dispensed and administered.

7.2.2.5 Cycle 1, Day 22 (±2 days)

The following procedures will be conducted at this visit:

- Complete physical examination;
- Vital signs (blood pressure, heart rate, respiratory rate, body temperature);
- All AEs since the last visit will be recorded;
- Concomitant medications will be recorded;
- Routine laboratory evaluations (chemistry, hematology, liver function test and urinalysis);
- Study drug (ASLAN003) will be dispensed and administered.

7.2.2.6 Cycle 2 and Subsequent Cycles - Day 1 (±2 days)

On Day 1 of Cycle 2 and all subsequent cycles, the following procedures will be conducted:

- Complete physical examination;
- Body weight;
- Vital signs (blood pressure, heart rate, respiratory rate, body temperature);
- 12-lead ECG (only on Cycle 2 Day 1);
- All AEs since the last visit will be recorded;

- Concomitant medications will be recorded;
- Routine laboratory evaluations (chemistry, hematology, liver function test and urinalysis);
- Study drug (ASLAN003) will be dispensed and administered.
- BM aspiration is mandatory to be performed on Day 1 of every cycle from Cycle 2 to Cycle 5 and every 3 months thereafter. Patients achieving CR could omit the bone marrow aspiration at a subsequent assessment if there is a normal complete blood count with differential of peripheral blood. Investigator may perform additional BM aspirate if required based on clinical judgment. BM aspiration smear will be processed locally.

7.2.3 End of Treatment (EOT) Visit

Patients who discontinue from the study drug should have an EOT visit. This visit should take place as soon as possible within 7 days of last dose of study treatment after the patient stops taking study drug. At this visit, the following procedures will be conducted:

- Complete physical examination;
- Body weight;
- Vital signs (blood pressure, heart rate, respiratory rate, body temperature);
- 12-lead ECG
- Patients' ECOG performance status;
- All AEs since the last visit will be recorded;
- Concomitant medications will be recorded;
- Routine laboratory evaluations (chemistry, hematology, liver function test and urinalysis);
- Serum / urine β-human Chorionic Gonadotropin;
- Coagulation laboratory test.

7.2.4 Safety Follow-up (±7 days)

Patient will complete a safety follow-up visit 28 days after the last dose of ASLAN003. The following procedures will be performed:

- Complete physical examination;
- 12-lead ECG
- Vital signs (blood pressure, heart rate, respiratory rate, body temperature);
- All AEs since the last visit will be recorded;
- Concomitant medications will be recorded.

7.2.5 Survival Follow-up (±7 days)

Survival follow-up by either telephone or clinic visit will be performed in patients achieving CR or CRi every 12 weeks post EOT until disease relapse or death (in the absence of disease relapse) to enable the assessment of RFS.

8 STATISTICAL METHODS

All statistical analyses will be performed by or under the direct auspices of ASLAN Pharmaceuticals, using SAS® version 9.3 or higher. Further details will be provided in the Statistical Analysis Plan (SAP).

8.1 General Statistical Considerations

There are no formal statistical analyses planned. All primary and secondary endpoints will be listed and summarized using appropriate descriptive statistics.

8.2 Sample size determination

This Phase IIA study is not formally powered. For Part 1, the proposed design of up to 6 patients per dose cohort has been selected to provide an assessment of the safety, tolerability and efficacy of up to 4 dose cohorts of ASLAN003, in order to select the most appropriate dose for further exploration in Part 2.

Part 2 is not formally powered. The sample size of 20 patients has been selected to provide further efficacy and tolerability data at the selected dose level from Part 1, prior to conducting larger randomized trials in AML.

8.3 Analysis population

8.3.1 Safety Population

The safety population will include all patients who received at least 1 dose drug in the study. Patients will be included in the safety population according to the dose initially received, regardless of any subsequent dose modifications.

The safety set will be the primary analysis set used for the assessment of safety and tolerability in the study

8.3.2 Full Analysis Set

The full analysis set (FAS) is defined as the set of patients who received at least 1 dose of study drug, regardless of any protocol deviations or dosing errors. Patients will be included in the FAS according to the intended initial dose cohort, regardless of any subsequent dose reductions, increases or interruptions.

The FAS will be used to assess the sensitivity of the primary efficacy analyses (based on the evaluable for response [EFR]) to exclusions from the EFR.

8.3.3 Evaluable for Response Set

The evaluable for response (EFR) set is defined as a subset of the FAS, excluding any patients with major protocol deviations. Deviations that would lead to exclusion from the FAS are:

- Patients who do not have AML as defined by the 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia (failure of inclusion criteria 3 in Section 4.1.

- Patients eligible for induction therapy (failure of inclusion criteria 5 in Section 4.1)
- Patients who are diagnosed with *de novo* myeloid sarcoma without bone marrow involvement (exclusion criteria 1 in Section 4.2)
- Patients who are diagnosed with acute promyelocytic leukemia with the *PML-RARA* (exclusion criteria 2 in Section 4.2)
- Patients who received any other standard or investigational treatment for their leukemia within 7 days before starting the first dose of study drug, with the exception of leukapheresis and hydroxyurea (exclusion criteria 3 in Section 4.2)

The EFR will be the primary analysis set used for the evaluation of all efficacy objectives.

8.3.4 Pharmacokinetic analysis set

The PK population contains all patients who receive one complete dose of ASLAN003 and have at least 1 measured concentration at a scheduled postdose time point without any major protocol deviations or events that affect the PK concentrations. Patients in this population will be used for all PK analyses.

This population will comprise of all patients who received study treatment as per protocol (e.g. 100 mg QD, 200 mg QD, 100 mg BID or 200 mg BID) and did not violate or deviate from the protocol and planned dosing regimen in ways that would significantly affect the PK analyses (for example skipping doses, or taking reduced doses or taking concomitant medications with the potential to cause a drug-drug interaction) during the PK sampling period. Patients who deviated from the planned dosing regimen may still provide some data for inclusion in the PK set if they have at least one usable PK profile. The population, and decisions regarding which profiles are usable, will be defined by the Study Team Physician, Pharmacokineticist, and Statistician prior to any analyses being performed.

8.4 Methods of Statistical Analysis

There are no formal statistical analyses planned. All primary and secondary endpoints will be listed and summarized using appropriate descriptive statistics.

Unless otherwise stated, data for Part 1 and Part 2 will be processed separately.

8.4.1 Assessment of Efficacy

The primary outcome variable is defined in Section 6.2. A binary variable will be created to indicate complete response status for each patient (complete responder or non-responder).

For Part 1, AML response data will be listed, and summarized showing frequency and proportion of the best response (CR, CRi, PR or treatment failure), OCRR (complete responder or non-responder) and Clinical Benefit Rate (CBR) by dose cohort and overall.

For Part 2, AML response data will be listed, and summarized showing frequency and proportion of the best response, OCRR and Clinical Benefit Rate (CBR), along with

corresponding two-sided 80% CIs based on the Clopper-Pearson exact method.

Waterfall plots of the % change from baseline in BM blasts at Day 29, and the best % change from baseline in BM blasts will be presented. For Part 1, all dose cohorts will be included on the same plot, but different bar types will be used to distinguish the different dose cohorts.

Relapse-free survival will be listed. For Part 2 only, if there are sufficient events, RFS will be summarized by using the Kaplan-Meier estimates to present 25th, 50th (median), and 75th percentiles , as well as the number and percentage of events and censored observations.

8.4.2 Optimum Dose determination

The study is designed with co-primary endpoints of efficacy and tolerability, in order to facilitate dose selection for further investigation. Data from this Phase IIA study will be reviewed in its totality to provide and understanding of the dose-response relationship, both in terms of efficacy and tolerability, in order to determine an optimum dose for further development.

8.4.3 Safety Analyses

Safety data will be listed and summarized as described below. Further details will be provided in the SAP.

8.4.3.1 Adverse Events

All AE data will be listed along with information regarding patient's original dosecohort, the dose at onset of the AE, onset time (study day), duration, severity, and relationship to study treatment.

Treatment emergent AEs (TEAEs) are defined as AEs with an onset date on or after the start of study treatment. The following summaries will be produced for all TEAEs.

- An overview table of the incidence of TEAEs, Grade 3+ TEAEs, SAEs, TEAEs leading to treatment discontinuation and TEAEs leading to death, by dose cohort (Part 1 ONLY) and overall. For each summary category, the results will be shown overall (regardless of causality), and for the incidence of causally-related TEAEs. For example, the overall incidence of TEAEs will be presented, as well as the incidence of TEAEs classified as at least "possibly related" to ASLAN003 by the Investigator;
- Summary of TEAEs by system organ class (SOC) and preferred term: Both the number and percentage of patients in each category (patient-level summary) and the number of episodes (episode-level summary). This summary table will be repeated for TEAEs attributed as causally related to study treatment;

- Summary of TEAEs occurring in patients, sorted in descending order of frequency (i.e., most frequent event shown first) presented by dose cohort (Part 1 ONLY) and overall. The order of frequency will be determined by the most frequent preferred term overall. For each event, the results will be presented for all CTCAE grades, and also split by Grade 1-2, and Grade 3+;

- Summary of TEAEs attributed as causally related to study treatment, and occurring in patients, sorted in descending order of frequency (i.e., most frequent event shown first) overall. Results will be presented by dose cohort (Part 1 ONLY) and overall. For each event, the results will be presented for all CTCAE grades, and also split by Grade 1 to Grade 2, and Grade 3+;

- Summary of CTCAE Grade 3 and above TEAEs sorted in descending order of frequency (i.e., most frequent event shown first). The order of frequency will be determined by the most frequent preferred term overall. Results will be presented by dose cohort (Part 1 ONLY) and overall;

- A summary of CTCAE Grade 3 and above TEAEs attributed as causally related[1] to study treatment sorted in descending order of frequency (i.e., most frequent event shown first). The order of frequency will be determined by the most frequent preferred term overall. Results will be presented by dose cohort (Part 1 ONLY) and overall;

- Summary of SAEs by preferred term

- Summary of SAEs attributed as causally related to study treatment, sorted by descending frequency.

Additionally, the following will be listed:

- AEs with outcome of death along with the date of onset, study day, initial study dose, dose at onset, treatment status at onset (pre-treatment, ongoing or post-treatment) and Investigator's assessment of severity and relationship to study drug;

- All SAEs along with the date of onset, study day, initial study dose, dose at onset, treatment status at onset (pre-treatment, ongoing or post-treatment), date of resolution (if AE is resolved), Investigator's assessment of severity and relationship to study drug;

- AEs leading to discontinuation of study drug, listed along with the date of onset, study day, initial study dose, dose at onset, treatment status at onset (pre-treatment, ongoing or post-treatment), and investigator's assessment of severity and relationship to study drug. Dependent on the number of AEs leading to treatment discontinuation, this data may also be summarized.

For the above summaries and listings, an AE will be considered to have a possible causal relationship if a causality assessment of "possibly related", "probably related" or "definitely related" is assigned by the Investigator.

If an AE is reported more than once during the study period, the greatest severity and the worst-case attribution will be presented in summary tables. Any AEs commencing > 28 days after discontinuation of study treatment will not be included in the tabulations of AE data.

To further assess the tolerability of ASLAN003, exposure and dose intensity will be listed and summarized by dose cohort (Part 1 ONLY) and overall. Further details will be provided in the study SAP.

8.4.3.2 Clinical Laboratory Evaluations

All clinical laboratory data (clinical chemistry, hematology and urinalysis data) will be listed and summarized by visit. In addition, all data measured on a continuous scale will be displayed graphically as described below:

- Patient profile plots to show both absolute values, and the % change from baseline over time. For Pat 1, separate plots will be produced for each dose cohort.
- Box plots of the change from baseline over time, by dose cohort (Part 1 ONLY), including a horizontal reference line at zero.

8.4.3.3 Vital Signs and ECG measurements

Vitals signs and ECG data will be listed. In addition, all data measured on a continuous scale (except respiration rate and pulse) will be displayed graphically as described below:

- Patient profile plots to show both absolute values, and the % change from baseline over time. For Part 1, separate plots will be produced for each dose cohort.
- Box plots of the change from baseline over time, by dose cohort (Part 1 ONLY), including a horizontal reference line at zero.

8.4.4 Pharmacokinetic Analysis

Concentration data and all derived PK parameters will be listed and summarized using appropriate descriptive statistics.

8.4.5 Exploratory Analysis

The exploratory objectives will not form part of the CSR and will be reported separately.

9 ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

9.1 Data Quality Assurance

The Sponsor or Sponsor's designee will conduct a site visit to verify the qualifications of each Investigator, inspect the site facilities, and inform the Investigator of responsibilities and the procedures for ensuring adequate and correct documentation.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information recorded in the eCRF system for this study must be consistent with the patients' source documentation (i.e., medical records). The Investigator must permit study-related monitoring, audits, IRB/IEC review, and national or foreign regulatory inspections and provide direct access to source data documents.

Study monitors will perform ongoing source data verification to confirm that data entered in the CRF by authorized study center personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

9.1.1 Database Management and Quality Control

All data generated by the site personnel will be captured electronically at each study center using eCRFs. Data from external sources (such as laboratory data) will be imported into the database. Once the eCRF clinical data have been submitted to the central server at the independent data center, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.

If additional corrections are needed, the responsible monitor or data manger will raise a query in the EDC application. The appropriate staff at the study site will answer queries sent to the Investigator. The name of the staff member responding to the query, and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the monitor will freeze the eCRF page.

The specific procedures to be used for data entry and query resolution using the eCRF will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system/eCRF.

9.1.2 Monitoring

The Sponsor has engaged the services of IQVIA, to perform all monitoring functions within this clinical study. IQVIA monitors will work in accordance with IQVIA Standard operating procedures (SOPs) and have the same rights and responsibilities as monitors from the Sponsor organization. Monitors will establish and maintain regular contact between the Investigator and the Sponsor.
Monitors will evaluate the competence of each study site, informing the Sponsor about any problems relating to facilities, technical equipment or medical staff. During the study,

monitors will check that written informed consent has been obtained from all subjects correctly and that data are recorded correctly and completely. Monitors are also entitled to compare entries in eCRFs with corresponding source data and to inform the Investigator of any errors or omissions. Monitors will also control adherence to the protocol at the study site. They will arrange for the supply of study drugs and ensure appropriate storage conditions are maintained.

Monitoring visits will be conducted according to all applicable regulatory requirements and standards. Regular monitoring visits will be made to each site while subjects are enrolled in the study. The monitor will make written reports to the Sponsor on each occasion contact with the Investigator is made, regardless of whether it is by phone or in person.

During monitoring visits, all the checks will be 100% including the following items:

- Subject identification number;
- Subject consent obtained;
- Subject eligibility criteria (inclusion and exclusion criteria);
- Efficacy variables;
- Medical record of AE.

9.1.3 Audit and Inspections:

Study sites, the study database, and study documentation may be subject to Quality Assurance audit during the course of the study by the Sponsor or IQVIA on behalf of the Sponsor. In addition, inspections may be conducted by regulatory bodies at their discretion.

The Sponsor or Sponsor's designee will conduct a site visit to verify the qualifications of each Investigator, inspect the site facilities, and inform the Investigator of responsibilities and the procedures for ensuring adequate and correct documentation.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information recorded in the eCRFs system for this study must be consistent with the subjects' source documentation (i.e., medical records).

9.2 Case Report Forms and Source Documentation

All data obtained during this study should be entered in the eCRFs promptly. All source documents from which eCRF entries are derived should be placed in the patient's medical records. Measurements for which source documents are usually available to include laboratory assessments, ECG recordings, BM aspiration records.

The original eCRF entries for each patient may be checked against source documents at the study site by the IQVIA site monitor.

After review by the site monitor, completed eCRF entries will be uploaded and forwarded to IQVIA. Instances of missing or uninterpretable data will be discussed with the Investigator for resolution. The specific procedures to be used for data entry and query

resolution using the eCRF will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system/eCRF.

9.2.1 Data collection

The Investigators (and appropriately authorized staff) will be given access to an online web−based EDC) system which is 21 Code of Federal Regulations Part 11 compliant. This system is specifically designed for the collection of the clinical data in electronic format. Access and right to the EDC system will be carefully controlled and configured according to each individual's role throughout the study. In general, only the Investigator and authorized staff will be able to enter data and make corrections in the eCRFs.

The eCRF should be completed for each patient included in the study and should reflect the latest observations of the patients participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or immediately after the patient's visit or assessment. The Investigator must verify that all data entries in the eCRF are accurate and correct. If some assessments cannot be done, or if certain information is unavailable, not applicable or unknown, the Investigator should indicate this in the eCRF.

Computerized data-check programs and manual checks will identify any clinical data discrepancies for resolution. Corresponding queries will be loaded into the system and the site will be informed about new issues to be resolved on-line. All discrepancies will be solved on−line directly by the Investigator or by authorized staff. Off-line edit checks will be done to examine relationships over time and across panels to facilitate quality data.

After completion, the Investigator will be required to electronically sign off the clinical data. Data about all study drug dispensed to the patient and any dosage changes will be tracked on the eCRF.

9.3 Access to Source Data

During the study, a monitor will make site visits to review protocol compliance, compare eCRF entries and individual patient's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

Checking of the eCRF entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, Regulatory Authorities of certain countries, IRBs, IECs, and/or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality.

9.4 Data Processing

All data will be entered by IQVIA using an independent double data entry system (as detailed in Section 9.2.1).

The data-review and data-handling document, to be developed during the initiation phase of the study, will include specifications for consistency and plausibility checks on data and will also include data-handling rules for obvious data errors. Query/correction sheets for unresolved queries will be sent to the study monitors for resolution with the Investigator. The database will be updated on the basis of signed corrections.

Previous and concomitant medications will be coded using the World Health Organization Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Previous and concomitant diseases as well as AEs will be coded using MedDRA.

The versions of the coding dictionaries will be provided in the CSR.

9.5 Archiving Study Records

According to International Council for Harmonisation (ICH) guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable legal requirements or as advised by the Sponsor.

9.6 Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the Sponsor and Investigator abide by the principles of the Good Clinical Practice guidelines of the ICH, and of the Declaration of Helsinki[1] (2013). The study also will be carried out in keeping with local legal and/or regulatory requirements.

9.7 Informed Consent

Before each patient is enrolled to the study, informed consent will be obtained from the patient (or his/her legally authorized representative) according to the regulatory and legal requirements of the participating country. This consent form must be dated and retained by the Investigator as part of the study records. The Investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the consent and when it was obtained must also be documented in the eCRF system.

If a protocol amendment is required, the informed consent form may need to be revised to reflect the changes according to the amendment. If the consent form is revised, it must be reviewed and approved by the appropriate IEC/IRB, and signed by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

A specific written informed consent for the Screening of protein expression levels and gene mutational status of the proteins and genes will also be prepared, submitted and approved by the IRBs/IECs, and has to be signed by the patients before the blood samples are drawn.

9.8 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The Investigator must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate). Following approval, the protocol amendment(s) will be submitted to the Investigational New Drug application under which the study is being conducted.

Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

9.9 Name of Committee

Not applicable.

9.10 Duration of the Study

Patients will be treated with study drug in the study until disease progression, unacceptable toxicity, death, or discontinuation from the study drug due to any other reason i.e. lost to follow-up or withdrawal of consent.

9.11 Premature Termination of the Study

If the Investigator, the Sponsor, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to patients if the study continues, the study may be terminated after appropriate consultation between the relevant parties. The study may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study;
- Failure to enroll patients at an acceptable rate;

- A decision on the part of the Sponsor to suspend or discontinue development of the drug.

9.12 Confidentiality

All study findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participating patients must be maintained. Patients will be identified on eCRF system and other documents submitted to IQVIA by their patient number, initials and/or birth date, not by name. Documents not to be submitted to IQVIA that identify the patient (e.g. the signed informed consent) must be maintained in confidence by the Investigator.

9.13 Other Ethical and Regulatory Issues

If a significant safety issue is identified, either from an individual case report or review of aggregate data, then the Sponsor will issue prompt notification to all parties – Regulatory Authorities, Investigators, and IECs/IRB.

A significant safety issue is one that has a significant impact on the course of the clinical study or program (including the potential for suspension of the development program or amendments to protocols) or warrants immediate update of informed consent.

9.14 Liability and Insurance

The Sponsor will take out reasonable third-party liability insurance coverage in accordance with all local legal requirements. The civil liability of the Investigator, the persons instructed by him or her and the hospital, practice, or institute in which they are employed and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable law.

The Sponsor will arrange for patients participating in this study to be insured against financial loss due to personal injury caused by the study drug being tested or by medical steps taken in the course of the study.

9.15 Publication Policy

By signing the study protocol, the Investigator agrees with to the use of results of the study for the purpose of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, Regulatory Authorities will be notified of the Investigator's name, address, qualifications and extent of involvement.
An Investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with the Sponsor in advance. Details are provided in a separate document.

10 REFERENCES

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11 APPENDICES

11.1 Appendix 1: WHO Classification of Acute Myeloid Leukemia

Acute myeloid leukemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);RUNX1-RUNX1T1
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);CBFB-MYH11
AML with t(9;11)(p21.3;q23.3);MLLT3-KMT2A
AML with t(6;9)(p23;q34.1);DEK-NUP214
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);RBM15-MKL1
Provisional entity: AML with BCR-ABL1
AML with mutated NPM1
AML with biallelic mutations of CEBPA
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down syndrome

11.2 Appendix 2: ECOG Performance Status

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

11.3 Appendix 3: Child-Pugh Score

Measure	1 point	2 points	3 points
Total bilirubin, mg/dL	<2	2–3	>3
Serum albumin, g/dL	>3.5	2.8–3.5	<2.8
Prothrombin time, INR	<1.7	1.7–2.3	>2.3
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy	None	Grade I–II	Grade III–IV
Child-Turcotte-Pugh (CTP) Class obtained by adding score for each parameter (total points) Class A: 5-6 points Class B: 7-9 points Class C: 10-15 points			

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12 SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title: A PHASE IIA DOSE OPTIMISATION STUDY OF ASLAN003 IN ACUTE MYELOID LEUKEMIA

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, [2013][1] and the guidelines on GCP.

[redacted]

[redacted]

Date

Chief Medical Officer
ASLAN Pharmaceuticals Pte. Ltd.
83 Clemenceau Avenue
#12-03 UE Square
Singapore 239920

Declaration of the Investigator

Title: A PHASE IIA DOSE OPTIMISATION STUDY OF ASLAN003 IN ACUTE MYELOID LEUKEMIA

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, IB, eCRF, and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted IRB/IEC. No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except where necessary to eliminate an immediate hazard to the patients.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Responsible Investigator of the local study center

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number

13 LIST OF STUDY PERSONNEL

Sponsor	ASLAN Pharmaceuticals Pte. Ltd. 83 Clemenceau Avenue #12-03 UE Square Singapore 239920
Contract Research Organization	IQVIA
Adverse Event Reporting	PAREXEL