CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 1, First-in-Human, Open-label Single Agent Study of SUPLEXA Therapeutic Cells in Patients with Metastatic Solid Tumours and Haematologic Malignancies
Protocol Number:	SUPLEXA-101
Study Intervention:	SUPLEXA Therapeutic cells, a single agent autologous adoptive cellular immunotherapy derived from patient peripheral blood mononuclear cells (PBMC)
Study Phase:	1
Clinical Sites	Up to 4 sites in Australia
Sponsor Name:	Alloplex Australia Pty. Ltd.
Legal Registered Address:	58 Gipps St, Collingwood, VIC 3066, Australia
Version:	4.0, Amendment 3
Approval Date:	30 Sep 2022
NCT:	NCT05237206

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SPONSOR SIGNATORY

Protocol Title:	A Phase 1, First-in-Human, Open-label Single Agent Study of SUPLEXA Therapeutic Cells in Patients with Metastatic Solid Tumours and Haematologic Malignancies
Protocol Number:	SUPLEXA-101
[redacted]	[redacted]
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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol Title: A Phase 1, First-in-Human, Open-label Single Agent Study of SUPLEXA Therapeutic Cells in Patients with Metastatic Solid Tumours and Haematologic Malignancies

Short Title: Phase 1 Study of SUPLEXA in Patients with Metastatic Solid Tumours and Haematologic Malignancies

Rationale

SUPLEXA Therapeutic cells (referred to as SUPLEXA throughout this protocol) are a heterogeneous mixture of PBMC-derived activated white blood cells, comprised predominantly of natural killer (NK) cells, natural killer T (NKT) cells, gamma/delta (γδ) positive T cells, and alpha/beta (αβ) positive T cells of both the cytotoxic CD8-positive and CD4-positive T lymphocytes (CTL) variety. All cell types have individually been shown by other researchers to contribute to the anti-tumour response. SUPLEXA cells have the ability to rapidly lyse a variety of tumour lines at exceedingly low effector to target cell ratios in an *in vitro* functional cytolysis assay. Moreover, flow sort data reveal that the cytolytic activity resides in both the CD56-positive (NK cell population) as well as the CD56-negative populations (T cell population), indicating that a minimum of two distinct SUPLEXA subpopulations possess anti-tumour activity.

SUPLEXA has been demonstrated to show anti-tumour activity on all tumour cell line tested to date irrespective of origin (e.g., melanoma, colorectal, breast, prostate, leukemia, glioma, ovarian, renal, glioma, and leukemia), while simultaneously showing no adverse impact on normal resting peripheral blood mononuclear cells (PBMC) derived from either allogeneic or autologous sources, suggesting that resting normal naïve immune cells are not targeted by SUPLEXA. Additionally, SUPLEXA demonstrates no fratricide, indicating that normal activated immune cells are not targeted either.

During manufacturing, expanding SUPLEXA are supported by cytokines interleukin (IL)-7 and IL-15. After formulation in cryogenic media, controlled freezing, storage under liquid nitrogen, and controlled thawing, SUPLEXA remain highly efficacious against tumour targets.

Additional nonclinical studies in organoids, as well as mouse patient derived xenografts (PDX) and xenograft models support the anti-tumour activity of SUPLEXA, as follows:

1) Champions Oncology conducted two human organoid studies, (1) lung cancer cells and (2) colorectal cancer cells, to show that SUPLEXA cells display a highly statistically significant result within the first 24 hours post-thaw.
2) Charles River conducted a xenograft study with a melanoma xenograft using a single low dose of SUPLEXA cells alone and found a statistically significant difference between the treated and untreated groups. SUPLEXA was safe and well tolerated.
3) Crown Bio conducted lung cancer PDX studies. The study used a repeat SUPLEXA dosing strategy and showed a statistically significant difference between the treated and untreated groups. Once again, SUPLEXA was safe and tolerated well.

This Phase 1, first-in-human (FIH), open-label study is designed to assess the safety, tolerability, and preliminary clinical efficacy of repeated intravenous (IV) infusions of SUPLEXA

monotherapy in subjects with measurable metastatic solid tumours and haematologic malignancies.

Objectives and Endpoints (Primary and Secondary)

Objectives	Endpoints
Primary	
• To assess safety and tolerability of SUPLEXA in subjects with malignant solid tumours and haematologic malignancies.	• Incidence of dose limiting toxicities (DLTs) (as described in Section 6.5.1. • Incidence of adverse events (AEs), and serious adverse events (SAEs) overall, by severity, by relationship to each study intervention, and those that led to discontinuation of study intervention.
Secondary	
• Solid tumours cohort: To assess the efficacy of SUPLEXA in subjects with malignant solid tumour as assessed by the Investigator based on response evaluation criteria in solid tumours (RECIST) v1.1 or by changes in tumour-derived blood biomarkers.	• Objective response rate (ORR) defined as the proportion of subjects with best overall response (BOCR) of either a complete response (CR) or partial response (PR). • Time to Progression (TTP).
• Haematologic malignancies cohort: To assess the efficacy of SUPLEXA in subjects with haematologic malignancies (multiple myeloma, lymphoma, and chronic lymphocytic leukemia).	• Objective response rate as defined by standard of care.

Overall Design

This is a FIH Phase 1, non-comparative, open-label, basket-design study. The study will consist of 2 cohorts:

- Solid tumours cohort: This cohort will include subjects with histologically or cytologically confirmed measurable solid tumours (e.g., various squamous cell carcinomas (skin, cervical, vaginal, oesophageal, lung), melanoma, prostate, and breast cancer)), radiographically confirmed as Stage 2 to 4 cancer. Subjects must fulfill entry criteria and not be currently receiving or under the residual influence of immunosuppressive therapies.
- Haematologic malignancies cohort: This cohort will include subjects with histologically or cytologically confirmed multiple myeloma, lymphoma, and chronic lymphocytic leukemia (collectively termed as haematologic malignancies for the purposes of this protocol). Subjects must fulfill entry criteria and have relapsed or refractory advanced malignancy for which no standard therapy exists.

A Data Safety Monitoring Committee (DSMB) will provide oversight of the study and will monitor safety on a regular basis throughout the study to recommend on any modification of the study. Refer to Section 9.3.6.

The study will be comprised of 3 periods. Screening, Treatment and Follow-up. Throughout the study, subjects will be evaluated as specified in the Schedule of Activities (SoA) in Section 1.3. Study schema is provided in Figure 2.

Screening Period – All Subjects

Prior to enroling in the study, and before performance of any procedures, potential subjects will attend a Screening session where they will be provided with full information concerning details of the study assessments and procedures. They will also be provided with a Participant Information Sheet and Informed Consent Form (PICF). Prior to being required to sign the consent form, subjects will be given time to review study information and ask questions.

After signing the PICF, potential candidates will undergo screening procedures over 2 visits during a Screening period lasting up to 5 weeks (Section 1.2, Figure 1). During Screening Visit 1, blood will be drawn for safety laboratory assessment (~5 mL), for processing and manufacturing of SUPLEXA batch 1 (~50 mL of whole blood) and for exploratory studies (~20 mL of whole blood). Subjects who meet the safety laboratory inclusion criteria and have adequate evidence of blast formation at the manufacturing facility (notification of status will require 5 days from the initiation of culture), will proceed to Screening Visit 2. Subjects in whom the SUPLEXA blast formation does not occur will be considered screen failures and be replaced. This is expected to be < 10 % of subjects.

Standard of care tests/procedures that were performed prior to signing the consent can be used as part of the screening assessments if the procedures meet the protocol-required timelines (i.e., within 5 weeks of consent) and it is documented in the source documents that these procedures performed prior to signing the consent were standard of care procedures.

Eligibility criteria for study entry will be assessed locally by the Investigator; for the solid tumour cohort, screening radiographic scans (within 5 weeks of consent) will be collected and held for possible future retrospective evaluation by Sponsor or blinded independent central review (BICR). Safety laboratory assessments of all subjects will be rechecked for eligibility on the day of the first treatment with the local hospital laboratory (and the central laboratory for documentation), prior to first dose with study intervention.

Treatment Period

All eligible subjects will initially receive approximately weekly dosing of SUPLEXA, with a target of 2.5B cells per dose (range of 1.9 to 3.1 billion cells) per dose.

Dosing will be done as follows:

- **First 3 SUPLEXA infusions (from batch 1)**

Initially, SUPLEXA will be administered at Day 1 (baseline), Week 1 and Week 2 (Section 1.2, Figure 2). Subjects will be monitored closely at the clinic after each of these 3 weekly infusions with follow-up phone calls as described below.

The first 3 subjects in each cohort will be enroled and subsequently dosed in a staggered manner, at least 1 week apart to allow for evaluation of safety. These subjects will be monitored for safety

in the clinic for 6 hours after each of the 3 weekly infusions and be contacted by phone on a daily basis (weekdays) between these weekly infusions for up to 5 days post final treatment. While the Investigator will review safety data on a continual basis, the DSMB will have an opportunity to review the first 3 subjects in each cohort who receive at least 3 doses of SUPLEXA to further evaluate safety and make a recommendation to the Sponsor concerning continuation or enrolment, pause in enrolment or study termination.

While the DSMB reviews the data from the first 3 subjects in each cohort, additional subjects will be screened and enroled into each cohort. These additional subjects will not be dosed until the first 3 subjects in their cohort are cleared by the DSMB. The dosed subjects in Protocol Amendment #2 and #3 will be monitored closely at the clinic for at least 3 hours after each of the 3 weekly infusions with follow-up phone calls every 2 business days between treatments and for up to 5 days post the 3rd infusion. If any of these subjects experience an adverse event of Grade 3 or greater, the longer in-clinic monitoring window of 6 hours post each of the first 3 weekly infusions and daily calls will be reimplemented as done for the first 3 subjects. During the observation period post SUPLEXA administration, subjects will be monitored for any AEs and immediate post infusion reaction(s) every 90 minutes.

The first subjects in Amendment #2 and #3 were enroled and treated, and evaluated for DLTs, 1 week after the 1st dose and 2nd dose (prior to administration of 2nd dose and 3rd dose, respectively). The DLT criteria and DLT assessment period(s) are defined in Section 6.5.

- **Subsequent weekly infusions (after dose 3 with SUPLEXA batch 1 and batch 2)**

After completion of the first 3 weekly SUPLEXA batch 1 infusions, based on emerging data from prior subjects, disease evaluation (as described below), the discretion of the Investigator, and in agreement with the subject, treating physician and the Sponsor's Medical Monitor (or designee), the treatment period of SUPLEXA may be extended as follows:

Subjects will continue to receive SUPLEXA treatments of approximately 5 B cells, every 2 weeks with a wider window -1 day to +7 days until either, a) depletion of SUPLEXA batch 1 doses *, or b) disease progression is assessed by the Investigator per iRECIST v1.1, or c) unacceptable toxicity, or other reasons for discontinuation as described in Section 7.2.

The 5 B cells will be provided as two bags of SUPLEXA targeted at 2.5B cells until all product used, unless there is only a single dose unit left, upon which time the subject may receive a single bag until more SUPLEXA is manufactured for them.

An additional SUPLEXA batch #2 may be manufactured for a subject based on (a) last dose of batch 1 and the investigator and subject and sponsor agree, then prior to the administration of the last SUPLEXA dose, blood can be drawn for SUPLEXA manufacturing of batch 2; or (b) > 2 weeks and < 8 weeks after the last dose of SUPLEXA administered, blood is collected for batch 2.

Note that subjects enroled in SUPLEXA-101,Version 3.0 or 2.0, and had SUPLEXA manufacturing started on or before October 31, 2022, may logistically be unable to have the consecutive administration of the recommended dosing regimen. These patients are therefore exempt from the defined gap in dosing, and the sequential dosing regimen described above. However, upon possible restarting additional doses of SUPLEXA, the dosing must be sequential until either, a) depletion of SUPLEXA batch 1 doses *, or b) disease progression is assessed by

the Investigator per iRECIST v1.1, or c) unacceptable toxicity, or other reasons for discontinuation as described in Section 7.2.

Subjects will be monitored at the clinic for at least 90 minutes (+/- 30 min) after each infusion for AE and ISR.

To account for the well-recognized phenomenon of tumor pseudo-progression or delayed response with immunotherapies, subjects may continue to receive SUPLEXA beyond RECIST v1.1 defined progression at the discretion of the Investigator. To confirm disease progression according to iRECIST, pseudo-progression will be further assessed at the next tumor assessment imaging time point after 4 weeks later but not exceeding 8 weeks from the date of initial documentation of suspected disease progression, and provided no other drug related adverse event occur warranting immediate cessation for clinical reasons. Otherwise, patients will continue to be dosed until all doses are used or progression is confirmed, whichever comes first.

*For each subject treatment duration will be variable and will depend on SUPLEXA manufacturing yield. It is anticipated that batch 1 (manufactured during screening) may be sufficient for up to 15 individual 2.5M SUPLEXA doses. In this regimen that would mean 3 doses as once a week dose, thereafter 3 doses at 2-week intervals, and one dose at the two-week interval to exhaust all product made. When batch 1 is depleted, batch 2 will be prepared (as described above during screening). During batch 2 manufacturing period, there may be a gap of up to 60 days in dosing.

Decision for treatment extension will be based on:

- Subject's overall safety status including AE rate, clinically significant findings from safety laboratory (including parameters indicative of TLS, e.g., uric acid elevation), physical examination, vital signs; or
- Subject deriving clinical benefit from treatment with SUPLEXA based on RECIST v1.1 and iRECIST for solid tumours and laboratory parameters for haematological malignancies; Subjects who are already enroled and received at least 3 weekly doses, treatment extension will be based on their latest radiographic scan / laboratory evaluation; or
- Exploratory outcomes (pharmacodynamics and correlative biomarkers), if available for review.

Disease Evaluation

For subjects in the solid tumours cohort, the on-treatment radiographic assessments of chest, abdomen, and pelvis will be performed per standard of care intervals throughout the course of the study. The first radiographic scan after receiving SUPLEXA will be performed at Week 6-12 weeks after the 1st SUPLEXA infusion and thereafter every 6-12 weeks depending on tumour type and as clinically indicated per investigator's discretion.

These scans should be available for assessment by the Sponsor, if requested. The response evaluation will be assessed by the Investigator according to RECIST v1.1 and iRECIST until unequivocal radiographic disease progression, or until the subject starts a subsequent anticancer therapy (whichever comes first). The tumour assessment (imaging) for confirmation of response should be performed no less than 4 weeks after the criteria for response are first met. All

radiographic scans will be collected and held for possible future retrospective evaluation by BICR.

For subjects in the haematological malignancies cohort, disease evaluation will be conducted every 4 weeks, as clinically indicated throughout the study.

Follow-up – All Subjects

All subjects will be followed up every 8 weeks for 48 weeks post last dose of study intervention for PFS and OS; visits are in-clinic unless patient is being followed for survival status only. The end of study (EOS) or early termination (ET) visits must be done in person within 30days of decision for ET or EOS. Beyond 48 weeks post last dose of study intervention, subjects may be contacted for survival status, disease status and initiation of subsequent anticancer therapies every 12 weeks up to a maximum of 24 months after the last dose of study intervention or earlier if the study is terminated by the Sponsor.

Subjects who permanently discontinue study intervention early will be encouraged to remain in the study (refer to Section 7.2). Subjects who begin new anti-cancer therapy will be permanently withdrawn from the study with no further long-term follow up.

Subjects who withdraw early from the study may be followed-up via phone or in person every 12 weeks at a minimum or sooner as required by the Investigator to determine OS and PFS until they begin new anti-cancer therapy.

Number of Subjects

Up to 60 subjects may be enroled with a cap of about 8 subjects per individual tumour type with a prioritization and focus on melanoma, breast, prostate, lung, and haematological malignancies. If promising anti-tumour activity coupled with acceptable safety is observed, overall sample size and/or cap per tumour type may be expanded.

Study Duration

For each subject, the study duration is expected to be as follows:

Screening:	Up to 5 weeks.
Treatment:	Minimally 3 weeks for subjects starting at recommended dose. Optional additional doses will be at discretion of the investigator in agreement with Sponsor. Subjects may receive additional treatment with study intervention depending on emerging data and SUPLEXA manufacturing yield. If 2 batches of SUPLEXA with optimal 15 units, this could be up to 24 weeks.
Follow-up:	Every 8 weeks for up to 48 weeks from last dose of study intervention or earlier if the study is terminated by the Sponsor. Beyond Week 48, subjects may be contacted every 12 weeks up to a maximum of 24 months after the last dose of

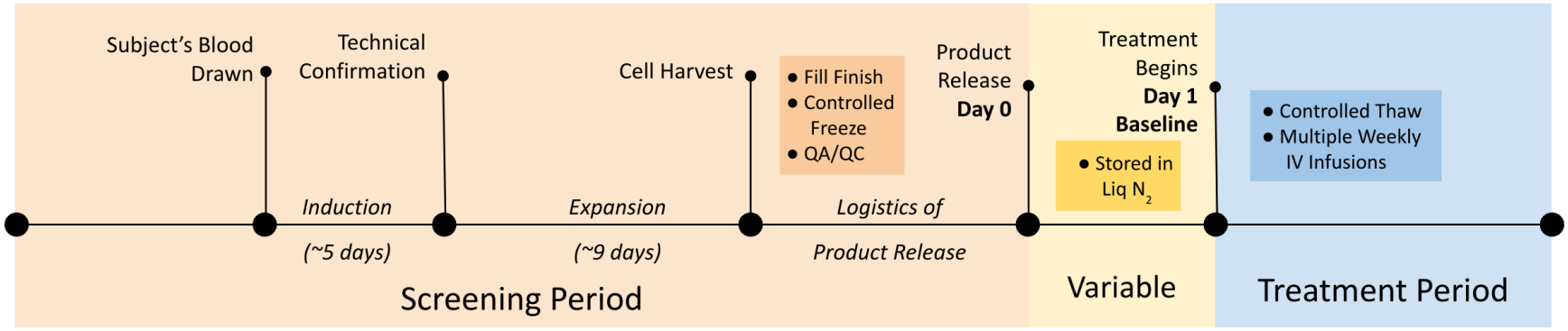
	SUPLEXA or earlier if the study is terminated by the Sponsor.

Data Safety Monitoring Committee

A Data Safety Monitoring Committee (DSMB) will be composed of at least 3 external members and include experts in the field of oncology and clinical studies, or biostatistics will regularly monitor overall safety, as well as general aspects of study conduct, to ensure that the benefits and risks of study participation remain acceptable. The DSMB will make recommendations to the Sponsor regarding any modifications to the study. Refer to Section 9.3.6.

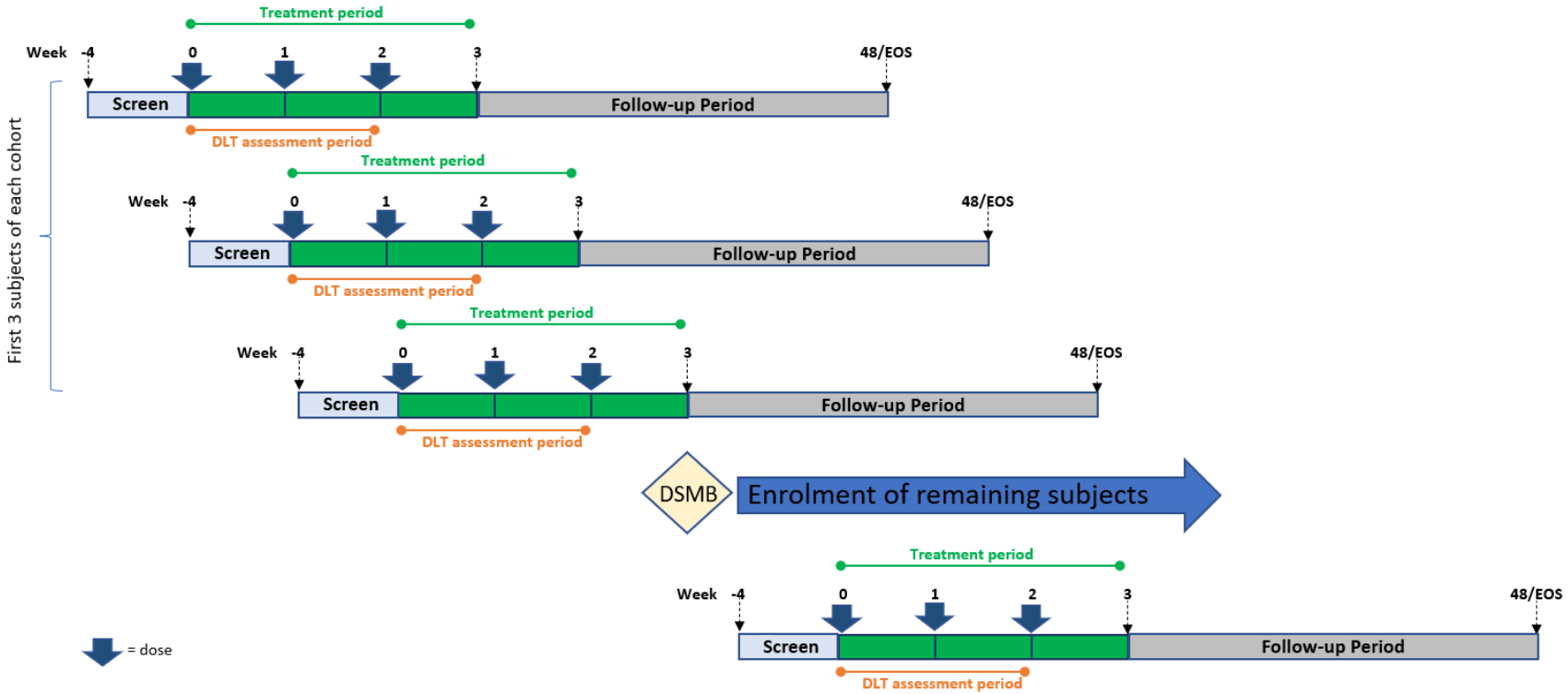
1.2 SCHEMA

Figure 1: Study Schema – Screening and Manufacturing Period (Day -35 to Day 1) in All Subjects



Treatment period is minimally 3 doses one week apart
Abbreviations: IV= intravenous; Liq N_2= liquid nitrogen; QA = quality assurance; QC = quality control

Figure 2: Study Schema – Overview (minimally 3 doses)



Abbreviations: DLT= dose limiting toxicities; EOS = end of study

1.3 SCHEDULE OF ACTIVITIES

Study period	**Screening**		**Treatment Period (Weekly dosing)**			**TREATMENT GAP**	**Treatment Extension Period**	**Follow Up after last dose**			**Notes** End of Study (EOS) will be conducted within 30d for all subjects who completed the study per protocol; Early termination (ET) visit will be conducted within 30d or subjects who withdraw from the study prematurely. **1.** Continued dosing per discretion of the investigator until depletion of manufactured SUPLEXA batch or confirmed disease progression by RECIST v1.1 or iRECIST, or withdrawal of consent by subject, whichever occurs first.
			SUPLEXA Batch 1				**Batch 2**				
Study Treatment Week	**-5**	**-5 to -1**	**First 3 infusions**		**Additional doses [1]**		**Doses [1]**				
			Week 0 Day 1/ Baseline	**1, 2**				**Every 8 weeks up to 48 weeks from last dose**		**EOS/ ET**	
Visit Window (days)		**±2**		**±2**	**-1 to +7**	**60**	**-1 to +7**	**±5**		**±28**	
Informed consent	X										
Demographic and medical history	X[a]										**a.** Medical history of the prior 3 years including any co-morbid conditions requiring active treatment and significant surgeries.
Inclusion/Exclusion	X	X									
Solid tumour/haematologic malignancy diagnosis confirmation and disease staging	X[b]										**b.** Radiology reports and photography images from imaging that occurred within 4 weeks of signing informed consent and throughout the study should also be noted as available for later access by Sponsor (if required).
History of prior anti-cancer therapy		X[c]									**c.** Information on all interventions (systemic therapy, surgery, radiation treatment) related to the subject's cancer will also be collected. Prior immunotherapy dosing concentration and cycle numbers should be captured.
Prior & concomitant medications		X	X	X	X		X	X	X	X	

Study period	**Screening**		**Treatment Period (Weekly dosing)**			**TREATMENT GAP**	**Treatment Extension Period**	**Follow Up after last dose**			**Notes** End of Study (EOS) will be conducted within 30d for all subjects who completed the study per protocol; Early termination (ET) visit will be conducted within 30d or subjects who withdraw from the study prematurely. **1.** Continued dosing per discretion of the investigator until depletion of manufactured SUPLEXA batch or confirmed disease progression by RECIST v1.1 or iRECIST, or withdrawal of consent by subject, whichever occurs first.
			SUPLEXA Batch 1				**Batch 2**				
Study Treatment Week	**-5**	**-5 to -1**	**First 3 infusions**		**Additional doses [1]**		**Doses [1]**				
			Week 0 Day 1/ Baseline	**1, 2**				**Every 8 weeks up to 48 weeks from last dose**		**EOS/ ET**	
Visit Window (days)		**±2**		**±2**	**-1 to +7**	**60**	**-1 to +7**	**±5**		**±28**	
Survival status and subsequent anticancer therapy									[d]	[d]	**d.** Beyond Week 48, subjects enrolled in the trial may be contacted every 12 weeks up to a maximum of 24 months after the last dose of SUPLEXA or earlier if the study is terminated by the Sponsor.
Physical exam and height[e]	X		X	[f]	[f]		[f]	X		X	**e.** Height at screening only **f.** Symptom-directed physical exam
Vital signs and weigh	X		X	X	X		X	X		X	
Performance status	X		X	X	X		X	X		X	Eastern Cooperative Oncology Group (ECOG) for solid tumours; Karnofsky for haematologic malignancies.
Electrocardiogram (ECG)		X	X	[g]	[g]		[g]			X	**g.** As clinically indicated
Disease evaluation by Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 and immune RECIST (iRECIST) (solid tumours only)		[h]			[i]		[i]	[i]		[i]	**h.** Scans within 4 weeks of screening will be accepted. **i.** Using standard of care scan schedule for the specified solid tumour. The first radiographic scan after receiving SUPLEXA will be performed at Week 6-12 weeks after the 1st SUPLEXA infusion and thereafter every 6-12 weeks depending on tumour type and as clinically indicated per investigator's discretion.

Study period	Screening		Treatment Period (Weekly dosing)			TREATMENT GAP	Treatment Extension Period	Follow Up after last dose			Notes
			SUPLEXA Batch 1				Batch 2				End of Study (EOS) will be conducted within 30d for all subjects who completed the study per protocol; Early termination (ET) visit will be conducted within 30d or subjects who withdraw from the study prematurely. **1.** Continued dosing per discretion of the investigator until depletion of manufactured SUPLEXA batch or confirmed disease progression by RECIST v1.1 or iRECIST, or withdrawal of consent by subject, whichever occurs first.
Study Treatment Week	**-5**	**-5 to -1**	**First 3 infusions**		**Additional doses [1]**		**Doses [1]**				
			Week 0 Day 1/ Baseline	**1, 2**				**Every 8 weeks up to 48 weeks from last dose**		**EOS/ ET**	
Visit Window (days)		**±2**		**±2**	**-1 to +7**	**60**	**-1 to +7**	**±5**		**±28**	
											Assessment by RECIST v1.1 and iRECIST will be done before the first dose of study intervention until end of study (EOS visit). Scans and photography will be assessed locally by the Investigator. Lesions will be numbered identically for each visit as Target and Non-target, New lesions.
Disease evaluation for haematologic malignancies only		X			X*		X*	X*		X	*As clinically indicated, may also be conducted every 4 weeks, starting 4 weeks after the 3rd dose
Complete blood count (CBC) with differential and blood chemistry	X		X[j]	X[j, k]	X[j]		X[j]	X		X	Refer to Table 5 for list of parameters to be evaluated **j.** Predose **k.** Repeat at baseline in local hospital lab for stat results, and central lab sample to be shipped
Collect blood for pharmacodynamic immune assessments, including cytokines			X	X	X		X	X[l]			Refer to Section 8.4 for list of parameters to be evaluated **l.** collected where possible post dose

Study period	**Screening**		**Treatment Period (Weekly dosing)**				**Treatment Extension Period**	**Follow Up after last dose**			**Notes**
			SUPLEXA Batch 1			**TREATMENT GAP**	**Batch 2**				End of Study (EOS) will be conducted within 30d for all subjects who completed the study per protocol; Early termination (ET) visit will be conducted within 30d or subjects who withdraw from the study prematurely. **1.** Continued dosing per discretion of the investigator until depletion of manufactured SUPLEXA batch or confirmed disease progression by RECIST v1.1 or iRECIST, or withdrawal of consent by subject, whichever occurs first.
Study Treatment Week	**-5**	**-5 to -1**	**First 3 infusions**		**Additional doses [1]**		**Doses [1]**				
			Week 0 Day 1/ Baseline	**1, 2**				**Every 8 weeks up to 48 weeks from last dose**		**EOS/ ET**	
Visit Window (days)		**±2**		**±2**	**-1 to +7**	**60**	**-1 to +7**	**±5**		**±28**	
Serology		X[m]									Refer to Table 5 for list of parameters to be evaluated **m.** HIV positivity is disqualifying as this might be amplified in ex vivo stimulation
Syphilis screening test		X									
Pregnancy test (WOCBP only)		X								X	Women of childbearing potential (WOCBP) Negative test must be performed within 72 hours prior to first study intervention
Urinalysis		X	X[n]				X[n]			X	Refer to Table 5 for list of parameters to be evaluated **n.** As clinically indicated; urinalysis to include dipstick and microscopic examinations when findings are abnormal
Blood sample for SUPLEXA manufacturing	X[o]					X[p]					**o.** Batch 1: Subjects who will have adequate evidence of blast formation at the manufacturing facility (notification of yield will be 5 days after the blood collection), will proceed to next Screening

Study period	Screening		Treatment Period (Weekly dosing)			TREATMENT GAP	Treatment Extension Period	Follow Up after last dose			Notes
			SUPLEXA Batch 1				Batch 2				End of Study (EOS) will be conducted within 30d for all subjects who completed the study per protocol; Early termination (ET) visit will be conducted within 30d or subjects who withdraw from the study prematurely. **1.** Continued dosing per discretion of the investigator until depletion of manufactured SUPLEXA batch or confirmed disease progression by RECIST v1.1 or iRECIST, or withdrawal of consent by subject, whichever occurs first.
Study Treatment Week	**-5**	**-5 to -1**	**First 3 infusions**		**Additional doses [1]**		**Doses [1]**				
			Week 0 Day 1/ Baseline	**1, 2**				**Every 8 weeks up to 48 weeks from last dose**		**EOS/ ET**	
Visit Window (days)		**±2**		**±2**	**-1 to +7**	**60**	**-1 to +7**	**±5**		**±28**	
											visit. Subjects with insufficient yields will be considered screen failures and will be replaced. **p.** Batch 2: After completion of Batch 1 and if subjects are eligible to continue to receive SUPLEXA, batch number 2 manufacturing and processing will take place.
Pre-treatment prophylaxis			X	X	X		X				The following pretreatment regimen is suggested, although a different regimen based on local standard of care/institutional practices is permitted: Administer acetaminophen 1000 mg (PO) for potential fever, diphenhydramine 12.5 mg PO (for potential rash) and allopurinol (100 mg) IV or PO for potential TLS in subjects who are at intermediate risk for TLS approximately 1 hour (60 min ± 20 min) before SUPLEXA infusion, Refer to Section 6.8.1 and 10.8Section 10.8 for further details.
SUPLEXA administration IV			X[q]	X[q]	X[r]		X[r]				q. Weekly 2.5 billion cells **r.** Additional treatment every 2 weeks at 5.0 B cells will be the investigator's assessment and in

Study period	**Screening**		**Treatment Period (Weekly dosing)**				**Treatment Extension Period**	**Follow Up after last dose**			**Notes**
			SUPLEXA Batch 1			**TREATMENT GAP**	**Batch 2**				End of Study (EOS) will be conducted within 30d for all subjects who completed the study per protocol; Early termination (ET) visit will be conducted within 30d or subjects who withdraw from the study prematurely. **1.** Continued dosing per discretion of the investigator until depletion of manufactured SUPLEXA batch or confirmed disease progression by RECIST v1.1 or iRECIST, or withdrawal of consent by subject, whichever occurs first.
Study Treatment Week	**-5**	**-5 to -1**	**First 3 infusions**		**Additional doses [1]**		**Doses [1]**				
			Week 0 Day 1/ Baseline	**1, 2**				**Every 8 weeks up to 48 weeks from last dose**		**EOS/ ET**	
Visit Window (days)		**±2**		**±2**	**-1 to +7**	**60**	**-1 to +7**	**±5**		**±28**	
											consultation with Sponsor' Medical Monitor. Cumulative dose depends on the individual subject SUPLEXA manufacturing yield in batch 1 and in batch 2.
Dose limiting toxicity (DLT) assessment			DLT assessment period								Refer to Section 6.5 for DLT criteria. DLT assessment periods: Period 1: 1 week after the 1st dose (before 2nd dose administration) Period 2: 1 week after 2nd dose (before 2nd 3rd dose administration)
			1	2							

Study period	Screening		Treatment Period (Weekly dosing)			TREATMENT GAP	Treatment Extension Period	Follow Up after last dose			Notes
			SUPLEXA Batch 1				Batch 2				End of Study (EOS) will be conducted within 30d for all subjects who completed the study per protocol; Early termination (ET) visit will be conducted within 30d or subjects who withdraw from the study prematurely. **1.** Continued dosing per discretion of the investigator until depletion of manufactured SUPLEXA batch or confirmed disease progression by RECIST v1.1 or iRECIST, or withdrawal of consent by subject, whichever occurs first.
Study Treatment Week	**-5**	**-5 to -1**	**First 3 infusions**		**Additional doses [1]**		**Doses [1]**				
			Week 0 Day 1/ Baseline	**1, 2**				**Every 8 weeks up to 48 weeks from last dose**		**EOS/ ET**	
Visit Window (days)		**±2**		**±2**	**-1 to +7**	**60**	**-1 to +7**	**±5**		**±28**	
AE assessment	X	X	X[s]		X[s] X[s]		X	X		X[t]	**s.** The first 3 subjects in each cohort will be monitored closely at the clinic for at least 6 hours after each of the first 3 weekly infusion and be contacted by phone on a daily basis (weekdays) between these weekly infusions for up to 5 days post the 3rd treatment. During the observation period (as specified above), all subjects will be monitored for post infusion reaction(s) and AEs every 90 minutes. Subsequent subjects will be monitored for 90 min post dose for post infusion reaction(s) and AEs. If any of these subjects experience an adverse event of Grade 3 or greater, the longer in-clinic monitoring window of 6 hours post each of the first 3 weekly

Study period	Screening		Treatment Period (Weekly dosing)			TREATMENT GAP	Treatment Extension Period	Follow Up after last dose		Notes
			SUPLEXA Batch 1				Batch 2			End of Study (EOS) will be conducted within 30d for all subjects who completed the study per protocol; Early termination (ET) visit will be conducted within 30d or subjects who withdraw from the study prematurely. **1.** Continued dosing per discretion of the investigator until depletion of manufactured SUPLEXA batch or confirmed disease progression by RECIST v1.1 or iRECIST, or withdrawal of consent by subject, whichever occurs first.
Study Treatment Week	**-5**	**-5 to -1**	**First 3 infusions**		**Additional doses [1]**		**Doses [1]**			
			Week 0 Day 1/ Baseline	**1, 2**				**Every 8 weeks up to 48 weeks from last dose**	**EOS/ ET**	
Visit Window (days)		**±2**		**±2**	**-1 to +7**	**60**	**-1 to +7**	**±5**	**±28**	
										infusions and daily calls will be reimplemented as done for the first 3 subjects. **t.** For subjects with unresolved treatment-related toxicity at last dosing visit, follow as medically appropriate until stabilization. Only SAEs that are believed related to study intervention will collected.

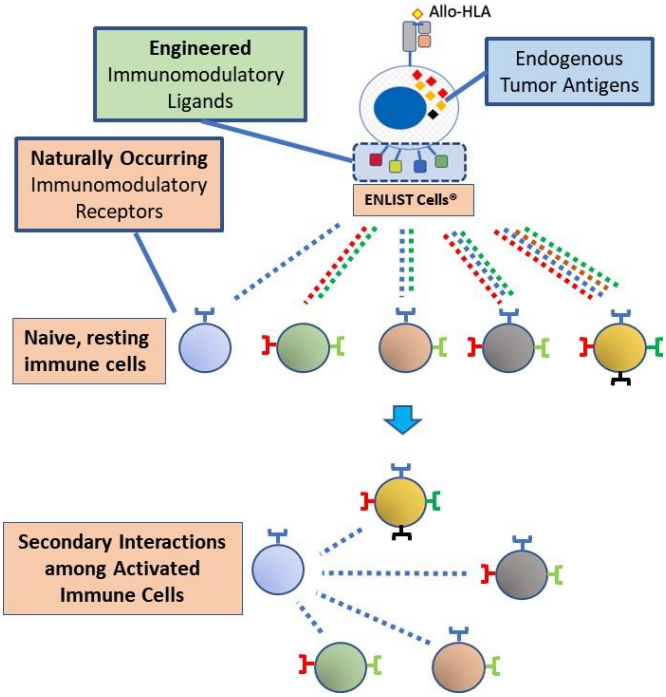
2 INTRODUCTION

2.1 STUDY RATIONALE

This Phase 1, first-in human (FIH), open-label study is designed to assess the safety, tolerability, and preliminary clinical efficacy of repeated intravenous (IV) infusion of SUPLEXA therapeutic cells (referred to as SUPLEXA throughout this protocol) monotherapy in subjects with measurable metastatic solid tumours and haematologic malignancies.

SUPLEXA is manufactured using an *ex vivo* procedure that employs proprietary **EN**gineered **L**eukocyte **ST**imulator (ENLIST™) cells (Figure 3). ENLIST cells are derived from a standard melanoma cell line (SK-MEL-2) sourced from the National Institute of Health (NIH) and have been genetically engineered to express an array of immunomodulatory ligands.

Figure 3: SUPLEXA Manufacturing Overview



Abbreviations: Allo-HLA, allogeneic human leukocyte antigen; ENLIST, **EN**gineered **L**eukocyte **ST**imulator.

The ENLIST Induction Reagent (IR) are designed to specifically engage and activate multiple subsets of naïve resting peripheral blood mononuclear cells (PBMC) through their naturally expressed cell surface receptors. Once activated, these immune cell subsets are capable of secondary interactions which further augment their activation state.

The ENLIST cells are subjected to multiple cycles of freeze-thaw prior to coincubation with PBMC, to render them incapable of replication and thus eliminating the possibility that living tumour cells enter the manufacturing reaction. The overall manufacturing process requires minimal manipulation during the PBMC-ENLIST co-incubation period, resulting in a heterogenous, autologous, non-genetically engineered cell mixture that comprises SUPLEXA.

SUPLEXA therapeutic cells differ from their naïve, untreated, resting PBMC precursors profiles with respect to their composition, phenotype, and function, observed after incubation with

ENLIST. This is evident by their enhanced proliferation state and enhanced cytokine production profile. They are predominantly comprised of natural killer (NK) and T cell receptor (TCR)-gamma/delta (γδ)-positive T cells of cytotoxic CD8-positive and CD4-positive T lymphocytes (CTL). Note, all cells described are known to individually possess some anti-tumour activity. Remarkably, this mixed cell population has the ability to rapidly lyse a variety of tumour lines at exceedingly low effector-to-target cell ratios in an *in vitro* functional cytolysis assay. Moreover, flow sort data reveal that the cytolytic activity resides in both the CD56-positive (NK cell population) and CD56-negative populations, indicating that multiple sub-populations of SUPLEXA are independently capable of lysing tumour. SUPLEXA represents an autologous, multifaceted, tumour killing strategy requiring no further sub-fractionation to display activity.

Furthermore, SUPLEXA has been demonstrated to show anti-tumour activity on all tumour cell lines tested to date irrespective of origin (e.g., melanoma, colorectal, breast, prostate, leukemia, glioma, ovarian, renal, glioma, and leukemia), while simultaneously showing no impact on allogeneic or autologous naïve normal PBMC.

Nonclinical studies have shown that a single, sub optimal IV dose of 3 million cells of SUPLEXA in a mouse xenograft model yielded statistically significant anti-tumour activity with no apparent safety signals. A trend toward tumour growth inhibition was observed between treated and untreated animals as early as about 10 days following administration and achieved statistical significance within 3 weeks. No safety signals were observed in the animal followed for 40 days and a highly statistically significant difference in average tumour size was observed at about 3 weeks ($p<0.05$) which improved through 5 weeks ($p<0.005$).

In the LU5200 subcutaneous non-small cell lung cancer patient derived xenografts (PDX) model, multiple SUPLEXA doses of 20 million cells administered weekly for 3 weeks. Treatment resulted in statistically significant tumour growth inhibition that was apparent at approximately 1-2 weeks following first dose. Repeated dosing did not show any adverse health effects in the mice. SUPLEXA was thus deemed safe and well tolerated.

2.2 BACKGROUND

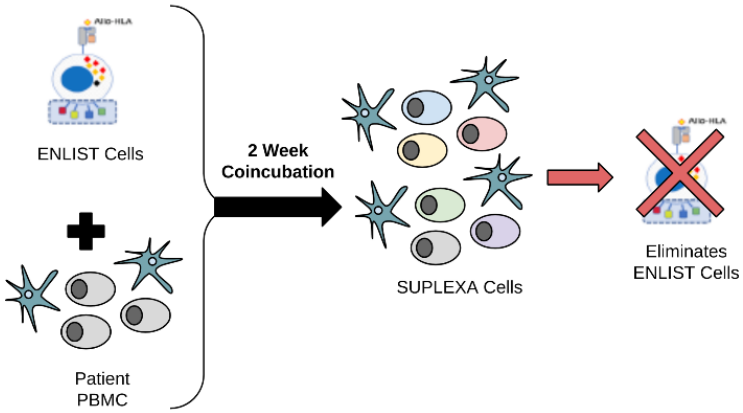
The therapeutic landscape for many metastatic cancers has recently been transformed by the approval of molecular targeted agents and immunotherapy including immune checkpoint inhibitors (e.g. monoclonal antibodies (mAbs) against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and programmed death-1 (PD-1)), bispecific biologics and chimeric antigen receptor (CAR)-cellular therapies (Kruger, 2019; Liu, 2019). The field of immunotherapy is currently expanding in hopes of offering durable anti-tumour immune responses for patients with advanced solid tumours and haematologic malignancies. Arguably one of the most comparable, yet distinct approaches to SUPLEXA cells is tumour infiltrating lymphocytes (TIL) therapy being advanced by Iovance. Like Alloplex, Iovance starts with primary autologous immune cells from a patient, requiring a resected tumour, followed by *ex vivo* activation/expansion and finally administration back to the patient. The approaches, however, are quite distinct in that the cells adoptively transferred to the patient by Iovance are predominantly tumour reactive CD8-positive cells while those comprising SUPLEXA have a more heterogeneous phenotype. Manufacturing, which is integral to any cellular therapy-is also vastly different. Iovance has to contend with variable efficiency of TIL isolation; employing feeder cells to expand the TILs *ex vivo*, and then providing evidence to regulators that neither feeder cells nor residual tumour cells are in the final

product. In contrast, SUPLEXA manufacturing begins with a standard blood draw and undergoes a simple and robust *ex vivo* expansion that yields low interpatient variability and provides for multiple dosing.

2.2.1 Study Intervention Overview

Alloplex is developing SUPLEXA as a multicellular adoptive immunotherapy for solid tumours and haematologic malignancies. SUPLEXA is not engineered but minimally manipulated *ex vivo* to enhance their anti-tumour activity. SUPLEXA is derived by stimulation of naturally occurring receptors on the PBMC with physiologic membrane expressed immunomodulatory ligands expressed in the ENLIST cells. SUPLEXA being a non-engineered product presumably retains all the homeostatic mechanism typical of normal immune cells. As SUPLEXA acquire the ability to kill tumour types in the *ex vivo* manufacturing process, they recognize the stimulatory ENLIST cells as tumour derived and eliminate any living in the co-culture manufacturing procedure (Figure 4). As ENLIST cells in the final protocol have already been rendered non-viable by repeated cycles of freeze-thaw, this latter observation is not relevant to the clinical study.

Figure 4: SUPLEXA Mechanism of Action Overview



When the SUPLEXA cells are harvested they contain no detectable ENLIST cells, avoiding subject exposure to tumour-derived cells. SUPLEXA is thus a differentiated cellular mixture of the patient's own PBMC's which are predominantly comprised of natural killer (NK), T cell receptor (TCR)-gamma/delta (γδ) positive T cells, CD8-positive and CD4-positive cells.

NK cells are considered as the most effective immune cell subpopulation to monitor and to clear diseased cells in vivo. They can recognize and kill abnormal cells that lack major histocompatibility complex (MHC) restriction or prior sensitization (Vivier, 2008). Different from other lymphocytes, NK cell recognition is not controlled by antigen specificity but integration of signals from activating and inhibitory receptors recruited by ligands expressed on putative target cells. Adoptive transfer of NK cells with high yields and high quality is a direct and fundamental approach to replacing, restoring and improving the function of the immune system (Hu, 2019; Oh, 2019).

γδ T cells have unique capabilities to recognize transformed cells and kill, or to regulate the immune response against them (Simoes, 2018). These cells have remarkable flexibility employing their TCR and/or NK cell receptors for target cell recognition and their activation is

typically independent of antigen presentation by MHC molecules. Furthermore, NK cell receptors on the surface of γδ T cells allow for very fast responses against transformed cells, thus contributing to a first line of defence that precedes antigen-specific αβ T-cell responses (Carding, 2002; De Rosa, 2004; Ribeiro, 2015). Therefore, γδ T cells have the potential to overcome problems in cancer therapy especially for tumours lacking tumour-specific antigens for targeting by antibodies or CAR T cells, or unresponsive to immune checkpoint inhibitors (Pauza, 2018).

CD8-positive T cells and CD4-positive helper T cells are generated in the thymus and express the T-cell receptor. CD8-positive cytotoxic T cells express a dimeric co-receptor, usually composed of one CD8α and one CD8β chain, and recognize peptides presented by MHC Class I molecules, found on all nucleated cells. CD8-positive T cells are important for immune defence against intracellular pathogens, including viruses and bacteria, and for tumour surveillance. CD8-positive T cells have well understood anti-tumour mechanisms of action including secretion of cytokines, primarily tumour necrosis factor (TNF)-α and interferon (IFN)-γ, and the expression of cytolytic granules upon target recognition (Ostroumov, 2018).

CD4-positive T cells are the major regulatory cells of the immune system, known to support B lymphocytes and help induce CD8-positive T-cell responses by increasing antigen-presenting and co-stimulatory capacities of dendritic cells. CD4-positive T cells can directly recognize antigen on tumour cells, if these express MHC class II (Lai, 2011; Ahrends, 2018). There are however no regulatory T cells detected in SUPLEXA.

SUPLEXA is intended for IV administration and is manufactured and packaged according to current Good Manufacturing Practice (cGMP) standards. SUPLEXA has been tested in non-clinical *in vitro* functional cytolysis assay and in a single dose xenograft model in mouse, as well as a repeat dose study in PDX mouse model. A detailed description of the manufacturing process, quality control, release criteria, pharmacology, efficacy, and safety are provided in the Investigator's Brochure (IB).

2.3 BENEFIT AND RISK ANALYSIS

More detailed information about the known and expected risk-benefit ratio and reasonably expected adverse events attributable to SUPLEXA can be found in the IB.

2.3.1 Risk Assessment

There are no identified or potential risks of particular severity anticipated based on toxicological data with SUPLEXA in animals, nor based on the mechanism of action and composition (an autologous population of NK and γδ T cells, CD8-positive and CD4-positive cells). Additionally, these cellular components have individually been evaluated in clinical studies and found to be well tolerated based on the lack of SAE (Section 2.2).

SUPLEXA is a first-in-class non-engineered autologous cell therapy. This study is ongoing and as of Sept 19 2022, more than 15 subjects were enroled in the study and received from 3 to 6 doses of SUPLEXA. No treatment-related SAE or adverse events had been reported.

Although nothing has been observed to date in blood chemistry, urinalysis, hematological or any labs, nor in any reported AE/SAE, potential risks based on the ongoing study and theoretical concerns that may be associated are presented below (Table 1) based on studies involving the autologous administration of CTL (Ohtani, 2014), CAR-T (Shivani, 2018) and dendritic cells

(Anguille, 2014) as well as the allogeneic administration of NK cells (Kyle B. Lupo, 2019), and γδ T cells (Pauza, 2018).

Table 1: Potential Risks and Mitigation Strategy

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Possible Concern (not observed in nonclinical studies)		
Cytokine release syndrome (CRS) – low risk for SUPLEXA since cells have only received physiologic signals through native receptors and presumably retain all homeostatic mechanisms.	Observed in CAR-T therapy owing to the supra-physiologic T-cell activation signal conferred by an engineered CAR protein.	Cytokine storm as observed in CAR-T therapy is now well managed with a neutralizing anti-IL-6 mAb. Please refer Appendix 6, Section 10.7 for CRS toxicity treatment guidelines.
Tumour Lysis Syndrome (TLS).	Based on CAR-T therapy for hematologic malignancies, although TLS is less likely for solid tumor. When TLS is observed, it may be considered a positive signal for synchronous tumour killing by the study intervention employed.	Subjects will be followed closely throughout the study for signs and symptoms of hypersensitivity and treated per institution guidelines as needed per the TLS toxicity management guidelines as noted in Appendix 7, Section 10.8, Preconditioning with Allopurinol can ameliorate the impact of high uric acid levels derived from TLS.
Infection - low risk since endogenous immune system is not altered.	Infection risk does not appear increased with various published adoptive immune cell therapies.	Ensure sterile product through cGMP procedures.
Neurologic events – low risk.	CAR-T studies report some neuro risk possibly owing to presence of CAR defined antigen in the brain.	Avoid subjects with brain disease to avoid confounding symptoms.
Flu-like symptoms and fever – medium risk owing to immune activity of adoptively transferred cells.	Note in multiple clinical studies but not rate limiting.	As a sign of activity, flu-like symptoms should be monitored and preconditioning with Tylenol can mitigate the severity.
Study Procedure		
Injection site reactions (redness, swelling, itching and tenderness).	As with any infusion procedure, injection site reaction is possible.	IV infusion will be done by trained personnel.

2.3.2 Benefit Assessment

As this is the FIH evaluation of SUPLEXA as a monotherapy, any estimate of efficacy in humans is based entirely on hypotheses developed from non-clinical data and other cellular therapies comprising the SUPLEXA components previously tested in the clinic.

Nonclinical data with SUPLEXA provides a strong rationale for evaluating the potential clinical benefits in subjects with solid tumours and haematologic malignancies for whom available standard of care is not providing an adequate durable response as defined by complete (CR) or partial response (PR). It is anticipated that treatment with SUPLEXA may have a positive impact in subjects with advanced solid tumours and haematologic malignancies.

2.3.3 Overall Benefit: Risk Conclusion

Overall, the SUPLEXA risk-benefit profile is considered favourable in the specific subject population being recruited into this FIH study.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess safety and tolerability of SUPLEXA in subjects with malignant solid tumour and haematologic malignancies.	• Incidence of dose limiting toxicities (DLTs) (as described in Section 6.5.1. • Incidence of adverse events (AEs), and serious adverse events (SAEs) overall, by severity, by relationship to each study intervention, and those that led to discontinuation of study intervention.
Secondary	
• Solid tumours cohort: To assess the efficacy of SUPLEXA in subjects with malignant solid tumour as assessed by the Investigator based on response evaluation criteria in solid tumours (RECIST) v1.1 or by changes in tumour-derived blood biomarkers.	• Objective response rate (ORR) defined as the proportion of subjects with best overall response (BOCR) of either a complete response (CR) or partial response (PR). • Time to Progression (TTP).
• Haematologic malignancies cohort: To assess the efficacy of SUPLEXA in subjects with haematologic malignancies (multiple myeloma, lymphoma, and chronic lymphocytic leukemia).	• Objective response rate as defined by standard of care.
Exploratory	
• Exploratory efficacy outcomes	• Duration of Response (DOR) • Time to Response (TTR) • Clinical Benefit Rate (CBR) defined as CR + PR + stable disease (SD). • Progression-free Survival (PFS). • Overall Survival (OS). • Solid tumours cohort: Change in plasma biomarkers. • Haematologic malignancies cohort: Response-relationship with correlative biomarkers in blood and bone marrow including immunophenotyping of circulating PBMC and/or bone marrow, gene expression, mutational analysis.

Objectives	Endpoints
• To evaluate anti-tumor activity of SUPLEXA by based on modified RECIST v1.1 for immune based therapeutics (iRECIST)	• iORR • iPFS • iDOR • iDCR
• To evaluate changes in disease biomarkers following treatment with SUPLEXA from blood.	• Change from baseline in the following pharmacodynamic assays, including but not limited to: – Whole blood immune cell phenotyping (e.g., PBMC count and composition and select flow cytometric analysis).

4 STUDY DESIGN

4.1 OVERALL STUDY DESIGN

This is a FIH Phase 1, non-comparative, open-label, basket-design study. The study will consist of 2 cohorts:

- Solid tumours cohort: This cohort will include subjects with histologically or cytologically confirmed measurable solid tumours (e.g., various squamous cell carcinomas (skin, cervical, vaginal, esophogeal, lung), melanoma, prostate, and breast cancer), radiographically confirmed as Stage 2 to 4 cancer. Subjects must fulfill entry criteria and not be currently receiving or under the residual influence of immunosuppressive therapies.
- Haematologic malignancies cohort: This cohort will include subjects with histologically or cytologically confirmed multiple myeloma, lymphoma, and chronic lymphocytic leukemia (collectively termed as haematologic malignancies for the purposes of this protocol). Subjects must fulfill entry criteria and have relapsed or refractory advanced malignancy for which no standard therapy exists.

A Data Safety Monitoring Committee (DSMB) will provide oversight of the study and will monitor safety on a regular basis throughout the study to recommend to the Sponsor on any modification of the study. Refer to Section 9.3.6.

The study will be comprised of 3 periods. Screening, Treatment and Follow-up. Throughout the study, subjects will be evaluated as specified in the Schedule of Activities (SoA) in Section 1.3. Study schema is provided in Figure 2.

4.1.1 Screening Period – All Subjects

Prior to enroling in the study, and before performance of any procedures, potential subjects will attend a Screening session where they will be provided with full information concerning details of the study assessments and procedures. They will also be provided with a Participant Information Sheet and Informed Consent Form (PICF). Prior to being required to sign the consent form, subjects will be given time to review study information and ask questions.

After signing the PICF, potential candidates will undergo screening procedures over 2 visits during a Screening period lasting up to 5 weeks (Section 1.2, Figure 1). During Screening Visit 1, blood will be drawn for safety laboratory assessment (~5 mL) and for processing and manufacturing of SUPLEXA batch 1 (~50 mL of whole blood) and for exploratory studies (~20 mL of whole blood). Subjects who meet the safety laboratory inclusion criteria and have adequate evidence of blast formation at the manufacturing facility (notification of status will require 5 days from the initiation of culture), will proceed to Screening Visit 2. Subjects in whom the SUPLEXA blast formation does not occur will be considered screen failures and be replaced. This is expected to be < 10% of subjects.

Standard of care tests/procedures that were performed prior to signing the consent can be used as part of the screening assessments if the procedures meet the protocol-required timelines (i.e., within 5 weeks of consent) and it is documented in the source documents that these procedures performed prior to signing the consent were standard of care procedures.

Eligibility criteria for study entry will be assessed locally by the Investigator; for the solid tumour cohort, screening radiographic scans (within 5 weeks of consent) will be collected and held for possible future retrospective evaluation by Sponsor or blinded independent central review (BICR). Safety laboratory assessments of all subjects will be rechecked for eligibility on the day of the first treatment with the local hospital laboratory (and the central laboratory for documentation), prior to dose with study intervention.

4.1.2 Treatment Period

All eligible subjects will receive minimally 3 weekly dosing of SUPLEXA (target of 2.5 billion cells, a range of cells per 1.9 to 3.1 billion cells per dose, unless delayed due to DLTs; refer to Section 6.5.1). Thereafter additional doses may be available.

Dosing will be done as follows:

4.1.2.1 First 3 SUPLEXA infusions (from batch 1)

Initially, SUPLEXA will be administered at Day 1 (baseline), Week 1 and Week 2 (Section 1.2, Figure 2). The first 3 subjects in each cohort will be monitored closely at the clinic after each of these 3 weekly infusions with follow-up phone calls as described below.

The first 3 subjects in each cohort will be enroled and subsequently dosed in a staggered manner, at least 1 week apart to allow for evaluation of safety. These subjects will be monitored for safety in the clinic for 6 hours after each of the 3 weekly infusions and be contacted by phone on a daily basis (weekdays) between these weekly infusions and for up to 5 days post final treatment. While the Investigator will review safety data on a continual basis, the DSMB will have an opportunity to review the first 3 patients in each cohort who receive at least 3 doses of SUPLEXA to further evaluate safety and make a recommendation to the Sponsor concerning continuation or enrolment, pause in enrolment or study termination. While the DSMB reviews the data from the first 3 subjects in each cohort, additional subjects will be screened and enroled into each cohort. These additional subjects will not be dosed until the first 3 subjects in their cohort are cleared by the DSMB. These subjects will be monitored closely at the clinic for at least 3 hours after each of these 3 weekly infusions with follow-up phone calls every 2 business days between treatments and for up to 5 days post the 3rd infusion. If any of these subjects experience an adverse event of Grade 3 or greater, the longer in-clinic monitoring window of 6 hours post each of the first 3 weekly infusions and daily calls will be reimplemented as done for the first 3 subjects. During the observation period post SUPLEXA administration, subjects will be monitored for any AEs and immediate post infusion reaction(s) every 90 minutes.

The first 15 subjects in the trial will be evaluated for DLTs twice, 1 week after the 1st and 2nd dose (prior to administration of 2nd and 3rd dose, respectively). The DLT criteria and DLT assessment period(s) are defined in Section 6.5.

4.1.2.2 Subsequent Weekly Infusions (SUPLEXA Batch 1 and Batch 2)

After completion of the first 3 weekly SUPLEXA batch 1 infusions, based on emerging data from prior subjects, disease evaluation (as described below), the discretion of the Investigator, and in agreement with the subject, treating physician and the Sponsor's Medical Monitor (or designee), the treatment period of SUPLEXA may be extended as follows:

Subjects will continue to receive SUPLEXA treatments of approximately 5 B cells, every 2 weeks with a wider window -1 day to +7 days until either, a) depletion of SUPLEXA batch 1 doses *, or b) disease progression is assessed by the Investigator per iRECIST v1.1, or c) unacceptable toxicity, or other reasons for discontinuation as described in Section 7.2.

The 5 B cells will be provided as two bags of SUPLEXA targeted at 2.5B cells until all product used, unless there is only a single dose unit left, upon which time the subject may receive a single bag until more SUPLEXA is manufactured for them.

An additional SUPLEXA batch #2 may be manufactured for a subject based on (a) last dose of batch 1 and the investigator and subject and sponsor agree, then prior to the administration of the last SUPLEXA dose, blood can be drawn for SUPLEXA manufacturing of batch 2; or (b) > 2 weeks and < 8 weeks after the last dose of SUPLEXA administered, blood is collected for batch 2.

Note that subjects enroled in SUPLEXA-101,Version 3.0 or 2.0, and had SUPLEXA manufacturing started on or before October 31, 2022, may logistically be unable to have the consecutive administration of the recommended dosing regimen. These patients are therefore exempt from the defined gap in dosing, and the sequential dosing regimen described above. However, upon possible restarting additional doses of SUPLEXA, the dosing must be sequential until either, a) depletion of SUPLEXA batch 1 doses *, or b) disease progression is assessed by the Investigator per iRECIST v1.1, or c) unacceptable toxicity, or other reasons for discontinuation as described in Section 7.2.

Subjects will be monitored at the clinic for at least 90 minutes (+/- 30 min) after each infusion for AE and ISR.

To account for the well-recognized phenomenon of tumor pseudo-progression or delayed response with immunotherapies, subjects may continue to receive SUPLEXA beyond RECIST v1.1 defined progression at the discretion of the Investigator. To confirm disease progression according to iRECIST, pseudo-progression will be further assessed at the next tumor assessment imaging time point after 4 weeks later but not exceeding 8 weeks from the date of initial documentation of suspected disease progression, and provided no other drug related adverse event occur warranting immediate cessation for clinical reasons. Otherwise, patients will continue to be dosed until all doses are used or progression is confirmed, whichever comes first.

*For each subject treatment duration will be variable and will depend on SUPLEXA manufacturing yield. It is anticipated that batch 1 (manufactured during screening) may be sufficient for up to 15 individual 2.5M SUPLEXA doses. In this regimen that would mean 3 doses as once a week dose, thereafter 3 doses at 2-week intervals, and one dose at the two-week interval to exhaust all product made. When batch 1 is depleted, batch 2 will be prepared (as described above during screening). During batch 2 manufacturing period, there may be a gap of up to 60 days in dosing.

Decision for treatment extension will be based on:

- Subject's overall safety status including AE rate, clinically significant findings from safety laboratory (including parameters indicative of TLS, e.g., uric acid elevation), physical examination, vital signs; or

- Subject deriving clinical benefit from treatment with SUPLEXA based on RECIST v1.1 and iRECIST for solid tumours and laboratory parameters for haematological malignancies; Subjects who are already enroled and received at least 3 weekly doses, treatment extension will be based on their latest radiographic scan / laboratory evaluation; or
- Exploratory outcomes (pharmacodynamics and correlative biomarkers), if available for review.

4.1.2.3 Disease Evaluation

For subjects in the solid tumours cohort, the on-treatment radiographic assessments of chest, abdomen, and pelvis will be performed per standard of care intervals throughout the course of the study.

The first radiographic scan after receiving SUPLEXA will be performed at Week 6-12 weeks after the 1st SUPLEXA infusion and thereafter every 6-12 weeks depending on tumour type and as clinically indicated per investigator's discretion.

These scans should be available for assessment by the Sponsor, if requested. The response evaluation will be assessed by the Investigator according to RECIST v1.1 and iRECIST until unequivocal radiographic disease progression, or until the subject starts a subsequent anticancer therapy (whichever comes first). The tumour assessment (imaging) for confirmation of response should be performed no less than 4 weeks after the criteria for response are first met. All radiographic scans will be collected and held for possible future retrospective evaluation by BICR.

For subjects in the haematological malignancies cohort, disease evaluation will be conducted every 4 weeks, as clinically indicated throughout the study.

4.1.3 Follow-up – All Subjects

All subjects will be followed up every 8 weeks for 48 weeks post last dose of study intervention; visits can be done remotely or in-clinic.

The end of study (EOS) or early termination (ET) visits must be done in person.

Beyond 48 weeks post last dose of study intervention, subjects will be contacted for survival status, disease status and initiation of subsequent anticancer therapies every 12 weeks up to a maximum of 24 months after the last dose of study intervention or earlier if the study is terminated by the Sponsor.

Subjects who permanently discontinue study intervention early will be encouraged to remain in the study (refer to Section 7.2). Subjects who begin new anti-cancer therapy after discontinuation of study intervention will be permanently withdrawn from the study.

Subjects who withdraw early from the study will be followed-up via phone or in person every 12 weeks at a minimum or sooner as required by the Investigator to determine OS and PFS.

4.2 Scientific Rationale for Study Design

This FIH study will assess the safety and preliminary efficacy of repeated IV doses of SUPLEXA in the intended study population (subject with measurable solid tumours and

haematologic malignancies) in a single-arm, open-label, monotherapy study design. The study includes assessments of safety and tolerability, disease evaluation by RECIST v1.1 (solid tumours) and disease response (haematologic malignancies) as well as pharmacodynamics / biomarker assessment, and immunogenicity characterizations, to determine the recommended Phase 2 dose (RP2D) of SUPLEXA for further clinical studies.

As this is FIH study, to avoid exposing subjects to any unexpected toxicity, the study will include a staggered enrolment design whereby 3 subjects will be enroled, SUPLEXA manufactured and stored, then doses will be given in a staggered manner, at least one week apart to allow evaluation for safety before ling the remaining of the subjects. The first 15 subjects led and treated will be evaluated for DLTs after the first and second infusion.

4.3 DOSE JUSTIFICATION FOR SUPLEXA THERAPEUTIC CELL DOSE

The initial cumulative dose selected for this study was based entirely on preclinical mouse xenograft studies in which we dosed mice at ~28x the intended human regimen 3 clinical doses with an option to extend to 6 doses, with each dose approximately 2.5 B cells (range 1.9-3.9 B cells). Given the complete absence of treatment related adverse events for SUPLEXA in the ongoing human study, we propose that after the first 3 doses, administration of up to 14 additional treatments of 5B cells every 2 weeks will be well tolerated, and the actual number of doses depends on the SUPLEXA manufacturing yields for each of 2 patient-specific SUPLEXA batches.

The DSMB will provide an additional review of all safety data and predetermined points in the progress of the clinical study.

4.4 STUDY DURATION

Study Duration

For each subject, the study duration is expected to be as follows:

Screening:	Up to 5 weeks
Treatment:	Minimally 3 weeks for subjects starting at recommended dose. Optional additional doses will be at discretion of the investigator in agreement with Sponsor. Subjects may receive additional treatment with study intervention depending on emerging data and SUPLEXA manufacturing yield.
Follow-up:	Every 8 weeks for up to 48 weeks from last dose of study intervention or earlier if the study is terminated by the Sponsor. Beyond Week 48, subjects may be contacted every 12 weeks up to a maximum of 24 months after the last dose of SUPLEXA or earlier if the study is terminated by the Sponsor.

5 ELIGIBILITY CRITERIA

5.1 INCLUSION CRITERIA

Subjects are eligible to be included in the study only if all the relevant criteria for their cohort apply:

Age

1. Adult subjects at least 18 years of age at the time of signing the PICF.

Type of Subject and Disease Characteristics

Solid Tumours

2. Histologically or cytologically confirmed diagnosis of locally advanced or metastatic solid tumour.
3. Have 1 or more tumours measurable based on RECIST v1.1 as assessed by the local site Investigator. Radiographic scans should be obtained within 5 weeks of Screening. Lesions situated in a previously irradiated area are considered measurable if objective progression has been demonstrated following radiation to such lesions.
4. Subjects who did not attain a durable response after receiving at least one standard/approved therapies which may include chemotherapy, targeted agents, radio-, immuno- conjugates, check point inhibitors or where there is no approved therapy. This includes subjects who attained a long-term stable disease (SD), or partial response (PR) are eligible. Long term SD subjects on a checkpoint inhibitor may continue checkpoint inhibitor (CPI) therapy.
   * Any therapies defined as immunosuppressive require a washout period of at least 4 weeks, defined as 4 weeks (28 days) prior to blood collection for SUPLEXA manufacturing and any SUPLEXA dose administration.

Haematologic malignancies

5. Histologically or cytologically confirmed multiple myeloma, lymphoma, and chronic lymphocytic leukemia (collectively termed as haematologic malignancies for the purposes of this protocol) which has relapsed or is refractory advanced malignancy for which no curative standard therapy exists.

Pregnancy and Contraception

Contraception use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Please also refer to Appendix 4 (Section 10.4) for more information.

6. Women of childbearing potential must have a negative serum or urine pregnancy test within 72 hours prior to receiving the first study intervention administration. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

7. For women of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner, must be willing to use an adequate method of contraception from 4 weeks prior to the first study intervention administration and 60 days following last day study intervention administration and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period as it is unknown how activated SUPLEXA may impact a pregnancy. Acceptable methods include hormonal contraception (oral contraceptives – if on stable dose, patch, implant, and injection), intrauterine devices, or double barrier methods (e.g., vaginal diaphragm/ vaginal sponge plus condom, or condom plus spermicidal jelly), sexual abstinence or a vasectomized partner. Women may be surgically sterile or at least 1-year post-last menstrual period. *Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subjects.*
8. Male subjects must be surgically sterile or must agree to use adequate method of contraception during the study and at least 90 days following the last day of study intervention administration. Male subjects should also refrain from sperm donation during this time.

   Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subjects.

Informed Consent

9. Capable of giving signed PICF. The subject (or legally acceptable representative if applicable) provides written informed consent for the study which includes compliance with the requirements and restrictions listed in the PICF and in this protocol.

5.2 EXCLUSION CRITERIA

The subjects must be excluded from participating in the study if they meet any of the following:

Medical Conditions

1. Known central nervous system (CNS) metastases and/or carcinomatous meningitis.
2. Prior allogeneic transplant.
3. Diagnosis of immunodeficiency or is receiving chronic and non-physiological, systemic steroid therapy or any other form of immunosuppressive therapy.
4. Active uncontrolled bacterial, viral, or fungal infection requiring systemic therapy at screening or Day 1.
5. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating Investigator.
6. Any unresolved Grade 2 or greater reversible toxicity from a previous anticancer therapy except for alopecia or Grade 2 neuropathy.
7. Clinically significant cardiovascular disease, including any of the following:

a. Stroke or myocardial infarction within 6 months prior to first dose in the study.
b. Presence of unstable angina within 6 months prior to first dose in the study.
c. Congestive heart failure of New York Heart Association Grade 2 or higher.
d. History or presence of clinically significant ventricular arrhythmias, or conduction abnormality; presence of clinically significant atrial fibrillation and resting bradycardia.
e. Corrected QT interval (QTcF) of >450 msec (males) or >470 msec (females) using Fridericia's correction formula.
f. History of congenital long QT syndrome.

8. Known history of testing positive for human immunodeficiency virus (HIV), and/or positive test for Hepatitis B virus surface antigen (HBsAg) and/or positive Hep C antibody result with detectable hepatitis C virus (HCV) ribonucleic acid (RNA) indicating acute or chronic infection.
   Note: Subjects who have been vaccinated against Hepatitis B and hence are positive only for the Hepatitis B surface antibody are permitted to participate in the study.
9. A serious non-malignant disease (e.g., psychiatric, substance abuse, uncontrolled intercurrent illness, etc.) that could compromise protocol objectives in the opinion of the Investigator and/or the Sponsor.
10. At high risk of developing TLS per (Cairo, 2010)). Specifically:
    a) Burkitt's lymphoma
    b) ALL with LDH ≥ 2xULN or WBC ≥100 x 10^9 per µL.
    c) AML with WBC ≥100 x 10^9 per µL.
11. Any other condition that, in the opinion of the Investigator, would prohibit the subject from effectively participating in the study.

Diagnostic Assessments

12. A performance status ≥2 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale (solid tumours cohort) or Karnofsky performance scale of ≥60 (haematologic malignancies cohort)
13. Does not demonstrate adequate organ function as defined as an excursion beyond the acceptable limits below. All screening laboratories should be performed at screening and on the day of first administration of study therapy.

System	Laboratory Value
Haematological	
Absolute neutrophil count (ANC)	≤ 50% lower limit of normal (LLN)
Lymphocyte (WBC)	≤50% LLN
Platelets	<100 × 10^9/L
Haemoglobin	≤9 g/dL or, ≤5.6 mmol/L*
Renal	

Creatinine **OR**	>1.5 times upper limit of normal (ULN) **OR**
Measured or calculated**creatinine clearance (CrCl) *Glomerular filtration rate (GFR) can also be used instead of creatinine or CrCl*	< 45 mL/min for subject with creatinine levels
Hepatic	
Total bilirubin	> 1.5 × ULN **OR** direct bilirubin ≥ULN for subjects with total bilirubin levels > 1.5× ULN
Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)	>2.5 × ULN (> 5 × ULN for subjects with liver metastases)
* Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks ** Creatinine clearance should be calculated per institutional standard.	

Prior Therapy

14. Prior radiotherapy within 2 weeks of start of study intervention. Subjects must have recovered from all radiation-related toxicities and not require corticosteroids (up to 4 mg/day dexamethasone or equivalent will be allowed provided dose is stable for at least 30 days prior first SUPLEXA dose and remains stable throughout the trial), and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.
15. Transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (CSF) (including granulocyte CSF [GCSF], granulocyte-macrophage CSF [GMCSF], or recombinant erythropoietin) within 4 weeks prior to baseline.
16. Any vaccines (live, attenuated, inactivated or research vaccines) within 30 days of dosing with study intervention (refer to Section 6.8.1 for prohibited vaccines).

Prior/Concurrent Clinical Study Experience

17. Participation in another clinical study of an investigational agent during the 2 weeks of this study's screening period.

    Note: Subjects participating in an observational study are an exception to this criterion and may qualify for the study with Sponsor approval.

    Note: Subjects who have entered the follow-up Period of an investigational study may participate if 14 days have elapsed since the last dose of the previous investigational agent before blood is drawn for this study.

Other Exclusions

18. < 6 months life expectancy at the local site Investigator judgement.
19. Pregnant or breastfeeding female subjects within the projected duration of the study, starting with the first screening visit through 120 days after the last dose of study intervention.

5.3 SCREEN FAILURES

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

Individuals who do not meet the criteria for participation in this study for reversible reasons may be rescreened. A new subject number will be assigned upon rescreening. For more details on specific indications refer to the SUPLEXA IB.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol.

6.1 STUDY INTERVENTION ADMINISTERED

ARM Name	**Active**
Primary Intervention Name	SUPLEXA therapeutic cells (referred to as SUPLEXA throughout)
Type	Autologous cellular therapy comprised of ex vivo activated autologous PBMC comprised predominantly of NK, NKT, γδ T cells, and T cells of both CD8-positive and CD4-positive types stored in cryogenic media.
Dose Formulation	PlasmaLyte with 28 mM glucose, 3.5% human serum albumin, 50% EZ-CPZ (a proprietary cryopreservative medium) and 10% dimethyl sulfoxide
Unit Dose Strength	Billion cells
Dosage Level(s)	Each subject in each cohort will receive a target 2.5 billion SUPLEXA cells (range 1.3 to 3.1 billion cells) per infusion of 100 mL of cryogenic preservative solution.
Route of Administration	IV
Administration instructions	Administer weekly (QW) ±2 days for the first 3 weekly infusion and thereafter weekly with a range of -1 day to +7 days. For prophylactic pre-treatment, refer to Section 6.8.1. Thaw a SUPLEXA IV infusion bag. Into the SUPLEXA IV infusion bag, slowly transfer approximately 250 mL (250 grams) of diluent PlasmaLyte (±20% is within the acceptable range; i.e., 200-300 grams or mLs). Allow the fluid to transfer by gravity. Infuse each individual bag's full volume within 60 minutes into the subjects. Where doses of 2 bags (5B cells) is given the same process and time is used. Thus, infusion of 2 bags is within 2 hours (120min). Subjects may ambulate after infusion is complete. For the first 3 weekly infusions:

ARM Name	Active
	• The first 3 subjects in each cohort will be monitored closely at the clinic for at least 6 hours after each of the first 3 weekly infusions and be contacted by phone on a daily basis (weekdays) between weekly infusions for up to 5 days post the 3rd treatment. • After the first three subjects , any subject receiving SUPLEXA will require a minimally 90minute (+/- 30min) post infusion observation and will be monitored for any AEs and immediate post infusion reaction(s). Refer to Pharmacy manual for detailed administration instructions.
Sourcing	Autologous SUPLEXA therapeutic cells are manufactured, labelled, stored, and distributed by selected Contract Manufacturing Organisation.
Packaging and Labelling	Packaging and labelling will be per local regulations.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only subjects led in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorized site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the relevant pharmacy manual.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable; this is an open-label study.

6.4 STUDY INTERVENTION COMPLIANCE

Study intervention will be administered at the study site in the presence of the Investigator or designee, as per the SoA (Section 1.3).

A record of the dose of SUPLEXA administered to each subject must be maintained and reconciled with study intervention and compliance records. Minimally, drug start and stop date and time, including dates for drug delays will also be recorded in the electronic case report form (eCRF).

6.5 DOSE LIMITING TOXICITY CRITERIA

A DLT is defined as the occurrence or start of any of the events listed below during the treatment of the first 3 subjects in each cohort that are assessed as related to study intervention (SUPLEXA) by the Investigator or the Sponsor. An AE should not be considered as a DLT if it can reasonably be attributed to underlying disease, disease progression, concomitant medications, or other extraneous causes. Worsening of pre-existing medical illness could be due to study intervention and should not be excluded from consideration as a DLT.

The first 15 subjects will be assessed for DLT. For each subject, the DLT assessment period will comprise of 2 parts as follows (Refer to Figure 5):

- The first DLT assessment period – 1 week after the first dose (prior to administration of the second dose).
- The second DLT assessment period - 1 week after the second dose (prior to the administration of the 3rd dose)

Subjects who withdraw before the end of the DLT assessment period for reasons other than DLTs will be replaced.

All toxicities will be graded by the local site Investigator using National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) v5.0.

The following will be considered DLTs:

Haematologic:

1. Grade 4 neutropenia lasting for ≥7 days.
2. Febrile neutropenia is defined as ANC <1000/mm^3 with a single temperature of 38.3ºC (101°F) or a sustained temperature of 38ºC (100.4°F) for >1 hour.
3. Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia associated with clinically significant bleeding.
4. Grade 4 anaemia unless there is an alternative explanation e.g., bleeding, etc.

Non-haematologic:

1. ≥ Grade 3 non-haematologic toxicity, except for the following Grade 3 events that are considered either not an adverse event or events that could be managed with standard of care:
   a) Grade 3 inflammatory reaction attributed to a local anti-tumour response (e.g., inflammatory reaction such as pain, irritation, or localized rash at sites of metastatic disease, lymph nodes, etc.).
   b) Grade 3 fatigue lasting ≤ 3 days.
   c) Grade 3 diarrhea, nausea, or vomiting lasting ≤3 days without or with use of anti-emetics or anti-diarrheals per standard of care.
   d) Grade 3 rash and/or pruritis without use of corticosteroids or anti-inflammatory agents per standard of care.

2. Any Grade 3 or Grade 4 non-haematologic laboratory value if:
   a) Clinically significant medical intervention is required to treat the subject and does not resolve within 72 hours, or
   b) Potential drug-induced liver toxicities with laboratory parameters as described below
      – ≥ Grade 3 and above elevation in ALT or AST if an alternative explanation other than the study intervention is not available.
      – ≥ Grade 3 and above elevation of total bilirubin of any duration if an alternative explanation other than the study intervention is not available.
      – Grade 2 elevation AST/ALT with concurrent elevation of total bilirubin >2 ×ULN or INR >1.5 ×ULN if an alternative explanation other than the study intervention is not available.

6.5.1 Dose Modifications and Individual Stopping Rules due to DLT

All eligible subjects are planned to receive a minimal cumulative dose of approximately 7.5 billion cells of SUPLEXA administered as target of 2.5 billion cells per individual SUPLEXA doses. The first 3 doses will be administered at least 1 week apart (unless delayed due to DLTs as described below) at Day 1 (baseline), Week 1 and Week 2.

During the study, the cumulative dose of study intervention will not be modified unless triggered by rules governing DLT (as described below); that is, subjects experiencing a DLT which does not resolve within 3 weeks or 2 DLTs may only receive 1 or 2 infusions, each 2.5 billion cells (for these subjects, cumulative dose may range between 2.5 billion cells to 5.0 billion cells.

The DSMB will convene to review all available data collected during the DLT assessment period(s) including Investigator's impressions and provide an additional layer of oversight. The DSMB will make recommendations to the Sponsor on enrolment modifications.

The rules below will apply independently to the solid tumours and haematologic malignancies in parallel and for each subject in the study.

1. Enrol a subject and administer 1st dose on Day 1. Assess for DLTs during the first DLT assessment period (1 week post 1st infusion).
   a) No DLT, continue to 2nd dose at Week 1 (Day 8) – refer to item 2 below,
   b) Subject experienced a DLT (per DLT criteria in Section 6.5) and the is event resolved within 3 weeks to baseline levels (Grade 1 or lower)?
      i) Yes, continue to 2nd dose – refer to item 2 below
      ii) No, permanently discontinue study intervention and subject will continue to be followed-up as part of the study (unless withdraw consent and start other anti-cancer therapies) as described in Section 7.2.
2. Administer 2nd dose. Assess for DLTs during the 2nd DLT assessment period (1 week post 2nd infusion)
   a) No DLT, continue to 3rd dose – refer to item 3 below

b) Subject experienced a DLT (per DLT criteria in Section 6.5)

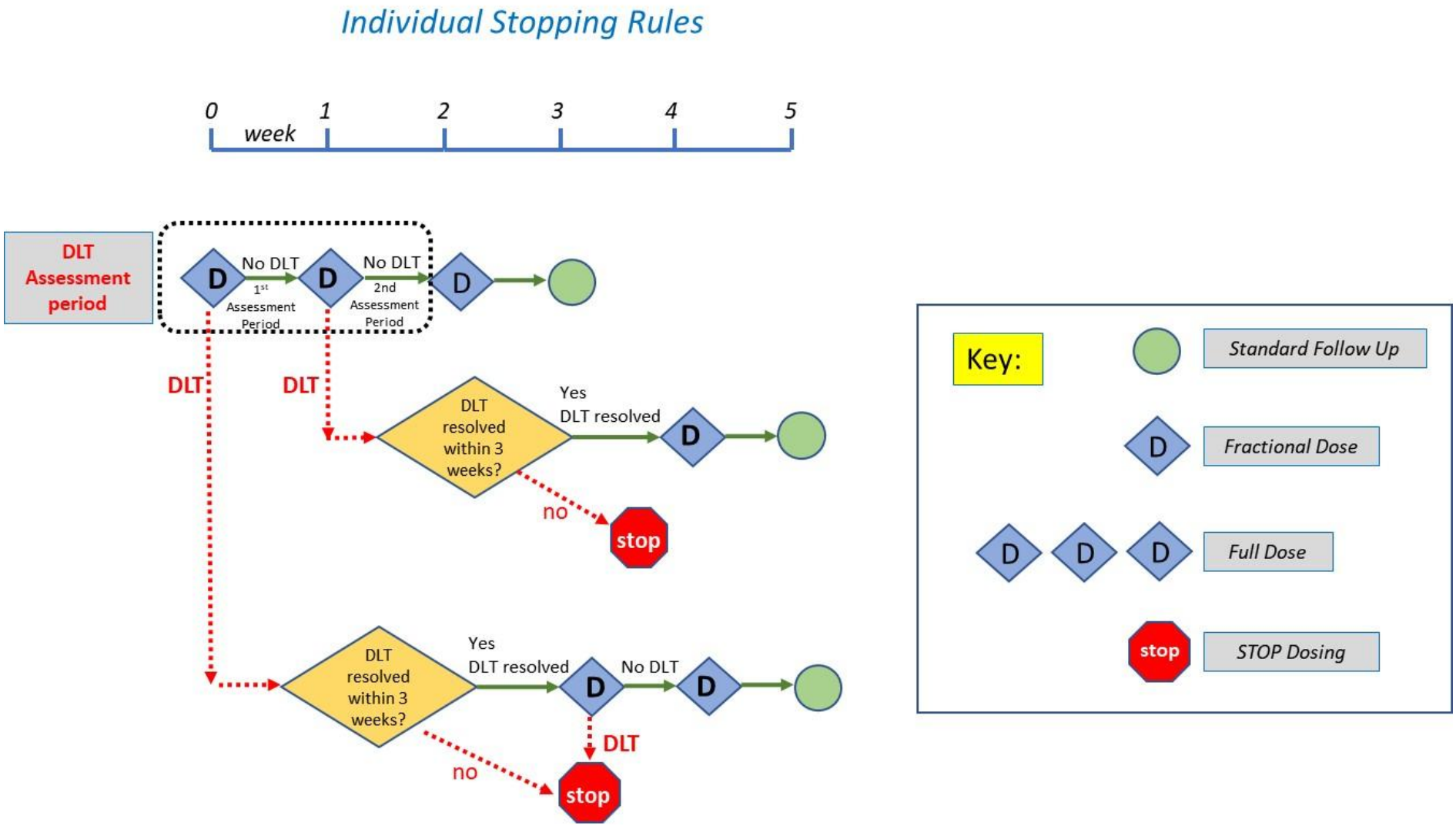
i) If first occurrence of DLT and the event resolved within 3 weeks to baseline levels (Grade 1 or lower)?

- Yes, continue to 3rd dose – refer to item 3 below
- No, permanently discontinue study intervention and subject will continue to be followed-up as part of the study (unless withdraw consent and start other anti-cancer therapies) as described in Section 7.2.

ii) If second occurrence of DLT in the same subject, permanently discontinue study intervention and subject will continue to be followed-up as part of the study (unless withdraw consent and start other anti-cancer therapies) as described in Section 7.2.

3. Administer 3rd dose and follow-up subject per SoA (Section 1.3).

Figure 5: Individual DLT Stopping Rules and Dose Modification of Study Intervention



Abbreviations: D = dose; DLT = dose limiting toxicities; S = stop

6.6 TOXICITY MANAGEMENT

Guidelines for toxicity management associated or possibly associated with SUPLEXA are located in the appendices for:

- CRS toxicity (Appendix 6, Section 10.7)
- TLS toxicity (Appendix 7, Section 10.8)

6.7 TREATMENT OF OVERDOSE

Any overdose of study intervention is unlikely given the premade doses, but should they occur must be recorded in the eCRF including quantity of the excess dose and the duration of the overdose. AEs associated with an overdose or incorrect administration of study intervention should be recorded in the AE eCRF. An overdose will not be considered an SAE unless the outcome of the overdose meets seriousness criteria.

For this study, any dose of study intervention greater than the number of cells in a given infusion bag will be considered an overdose as will any administration greater than specified in a particular dose reduction cohort.

In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

6.8 CONCOMITANT GENERIC THERAPY

Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving within 4 weeks before the first dose of study intervention through 24 weeks after the last dose of study intervention must be recorded along with:

- Name of medication/therapy (generic name)
- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Concomitant medications administered 24 weeks after the last dose of study intervention should be recorded for SAEs.

Concomitant medications necessary for the health and well-being of the subject and that do not interfere with study assessments are permitted during the study at the Investigator's discretion. All treatments that the Investigator considers necessary for a subject's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. This includes the use of appropriate medications for the treatment of AEs and/or concurrent illnesses under the direction of the Investigator. All medications must be recorded in the source and on the appropriate eCRFs. Start of new medications of any type (over the counter or prescription) during the study however is strongly discouraged as it can be deemed confounding.

Concurrent use anti-androgen therapies subjects with prostate cancer and anti-estrogen therapies for subjects with breast cancer is allowed. Bisphosphonate IV (i.e., zoledronic acid) or denosumab subcutaneous (SC) therapy must be initiated prior or within the first 60 days of the first administration of the study intervention. Oral bisphosphonate may be initiated at any point in the study for the treatment of osteoporosis.

Concurrent use of continued targeted therapies and immune checkpoint inhibitor therapies (e.g., anti-PD-1, anti-PD-L1 or anti-CTLA4) may be allowed provided the subject was on a stable dose for at least 3 months prior to enrolment and had at least a stable disease response.

Concurrent use of dexamethasone (up to 4 mg/day) may be allowed provided the subject was on a stable dose for at least 30 days.

The Sponsor's Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1 Prophylaxis

For cytotoxic chemotherapies, allopurinol administration is recommended 24 hours prior to initiation of treatment with SUPLEXA because of the immediate action of the cytotoxic chemotherapy. For cellular therapies however, cells require at least a day to migrate out of the circulation to the tumour bed and synchronous tumour lysis will be delayed. Therefore, allopurinol will be administered concomitantly with each SUPLEXA dose, and between doses as directed by the investigator.

The following pretreatment regimen is suggested, although a different regimen based on local standard of care/ institutional practices is permitted: Approximately 1 hour (60 min ± 15 min) before each SUPLEXA infusion, all subjects will receive single administration of:

- Acetaminophen 1000 mg PO (for potential fever)
- Diphenhydramine 12.5 mg PO (for potential rash)
- Allopurinol 100 mg (IV or PO) (for potential tumour lysis syndrome in subjects who are at intermediate risk for TLS; refer to Figure 6). This should be followed, unless the investigator determines continued oral dosing of allopurinol is required.

6.8.2 Prohibited Medications and Treatment

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study intervention may be required. The Investigator should discuss any questions regarding this with the Sponsor's Medical Monitor. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the subject's primary physician. However, the decision to continue the subject on study intervention requires the mutual agreement of the Investigator, the Sponsor, and the subject. Subjects who, in the assessment of the Investigator, require the use of any of the prohibited treatments for clinical management should be removed from the study.

The following medications are excluded from concomitant use for all subjects during the study:

- Vaccines:

- Live vaccines including, but are not limited to measles, mumps, rubella, varicella/zoster, yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine.
- Attenuated vaccines, e.g., FluMist®
- Inactivated vaccines, e.g., COVID-19 vaccine; Please also refer to Section 10.9 (Guidance to Address Global Health Emergencies)
- Research vaccines, including any investigative COVID-19 vaccine studies

Note: Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed.

- Concurrent use of immunostimulatory agents, including but not limited to IFN-α, IFN-γ, or interleukin 2 (IL-2) with study intervention, during the entire study.
- Any investigational agent, other than SUPLEXA.
- Immunosuppressive anticancer therapies (chemotherapy, radiation therapy, biological therapy or immunotherapy which are not specified in this protocol) or approved by the Sponsor will be excluded. Herb supplements that are used for the treatment of the malignancy under the study are not allowed.
  Note: Palliative radiation therapy for pain management or for symptomatic solitary lesion if not new lesion may be allowed at the Investigator's discretion.

  Note: Surgery to bone lesion to prevent the risk of fracture will be allowed.
- Concurrent use of immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, or methotrexate.

6.8.3 Rescue Medications and Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating Investigator.

7 STOPPING RULES, DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT WITHDRAWAL FROM THE STUDY

7.1 STUDY STOPPING RULES

Enrolment in this study will be stopped at any time for safety reasons.

The study includes DLT Stopping rules (refer to Section 6.5.1). In addition, enrolment and treatment with SUPLEXA will be temporarily suspended for any of the following reasons pending review and recommendations from the DSMB:

- Any death that is not due to disease progression within 30 days after receiving SUPLEXA will result in a hold of further enrolment, until an investigation into the cause of death is performed by DSMB. If it is determined that the death was not related to the study intervention, then enrolment may restart. If the relationship between SUPLEXA infusion and death is not clear, or it appears that the death may be related to study intervention, enrolment will be held until further review. Refer to Section 8.3.7.
- The occurrence of two ≥ Grade 4 DLTs in 2 study subjects.
- At least 3 cases of ≥Grade 3 of the following events assessed as related to study intervention:
  - Immunological related events
  - CRS
  - TLS

Suspension of the study will entail stopping the enrolment of new subjects and maintaining enroled subjects in the study. Suspension of the study will not entail cessation of dosing in subjects who did not complete the 3-dose administration unless so directed by the regulatory agencies or advised by the DSMB and agreed to by the Sponsor. The suspension will remain in effect until the case(s) and supporting information have been discussed between the Sponsor and the DSMB and the relevant regulatory agencies, if applicable, with a decision made to either resume the study or stop the study. If a decision is made to stop the study, all subjects will immediately discontinue dosing with study intervention and will undergo a follow-up visit as specified in the SoA.

The DSMB will review safety data at regular intervals, and can recommend, in its judgment, halting the study for any substantial imbalance in AEs. Sponsor additionally reserves the right to stop the study at any time for any reason. The regulatory health authorities and Australian Human Research Ethics Committee (HREC) will be notified in the event the study is stopped.

7.2 DISCONTINUATION OF STUDY INTERVENTION

In some instances, it may be necessary for a subject to permanently discontinue study intervention. Please also refer to stopping rules described in Section 7.1.

A subject must permanently discontinue study intervention if they meet one of the following individual stopping rules:

- Any Grade 4 life threatening events assessed as related to study intervention.
- ≥Grade 3 immunological-related event assessed as related to study intervention (refer to Section 7.2.1)

A subject may also discontinue study intervention for reasons including but not limited to:

- Adverse event
- Lost to follow-up
- Non-compliance with study drug
- Physician decision
- Pregnancy (refer to Section 7.2.2)
- Progressive disease
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal by subject
- Death

Permanent discontinuation of study intervention does not mean withdrawal from the study, and the subject will be encouraged to remain in the study, complete the ET visit and then continue to complete all study visits as per the SoA, including all follow-up visits.

For subjects who have discontinued study intervention due to reasons other than disease progression, tumour assessment will be continued at the protocol-specified schedule until documented disease progression or initiation of subsequent anticancer therapy or until 24 months after the last dose of study intervention.

The primary reason for discontinuation from study intervention should be documented on the appropriate eCRF.

7.2.1 Immunological effects: Action and Follow-Up Assessment

SUPLEXA impact on normal tissues is a theoretical concern but one which was not observed in nonclinical studies conducted in the organoid PDX or xenograft or PDX animal models. A subject experiencing an immunological event of CTCAE Grade 3 or greater will permanently discontinue study intervention.

7.2.2 Pregnancy

A subject must permanently discontinue study intervention if they become pregnant but will advance to the post-treatment observational component of this study. See Appendix 4 (Section 10.4) and Section 8.3.5 for additional details.

7.3 Subject Withdrawal from the Study

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the Investigator or at the institution.

A subject may withdraw from the study for reasons including but not limited to:

- Withdrawal by subject
- Initiation of prohibited medications (anti-cancer treatment)

- Lost to follow-up
- Study terminated by Sponsor
- Death

At the time of withdrawal from the study, if possible, an ET visit should be conducted, as shown in the SoA (Section 1.3). The subject will be permanently discontinued both from the study intervention and from the study at that time.

If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the study, he/she/they may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.4 LOST TO FOLLOW UP

A subject will be considered lost to follow-up if he/she/they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she/they will be considered to have withdrawn from the study.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).
- Some visits/study procedures may be done remotely via virtual visits (telemedicine) or at home health visits. Refer to Appendix 6 (Section 10.9) and Study Reference Manual for more details

8.1 EFFICACY ASSESSMENTS

Planned time points for all efficacy assessments are provided in the SoA (Section 1.3).

8.1.1 RECIST v1.1 (Solid Tumours Cohort only)

Objective response to treatment with SUPLEXA will be evaluated using RECIST v1.1 (Eisenhauer, 2009) as described in Appendix 5 Section 10.5. Radiographic imaging will be assessed locally by the Investigator; refer to Section 10.5.2 for methods of measurements.

8.1.2 Disease Response Assessments (Haematologic Malignancies Cohort only)

Haematologic malignancies (multiple myeloma, lymphoma, and chronic lymphocytic leukemia) disease response will be assessed by the Investigator every 4 weeks (±3 days) per standard of care.

8.2 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.

- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

- Oral, aural, or surface temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse.

8.2.3 Electrocardiograms

- 12-lead ECG will be obtained as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

8.2.4 Clinical Safety Laboratory Assessments

- See Appendix 2 (Section10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- Abnormal laboratories will be classified according to the NCI CTCAE, version 5.0.
- The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. If a laboratory finding is abnormal but not clinically significant (NCS) at baseline, postbaseline laboratory abnormalities will be reported as an AE only if there is worsening compared to baseline.
- The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless documented by the Investigator.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor.
  - If such values do not return to normal/baseline within a period judged reasonable by the Investigator, the aetiology should be identified, and the Sponsor notified.

- All protocol-required laboratory tests, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.2.5 Performance Status

ECOG Performance Status (Solid Tumours Cohort)

The Eastern Cooperative Oncology Group (ECOG) Performance Status will be used to assess subject's performance status (Table 2).

Table 2: Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	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	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	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Karnofsky Performance Status (Haematologic malignancies Cohort)

Karnofsky performance status scale will be performed at screening to assess subject's functional impairment, ranging from 100 to 0, in increments of 10, where 100 is normal health and 0 is death (Table 3). To be eligible to participate in this study, subjects must have a Karnofsky performance status of ≥60%. This scale was shown to be valid in assessing geriatric population (Crooks, 1991).

Table 3: Karnofsky Performance Status

Able to carry on normal activity and to work; no special care needed.	100	Normal; no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance but is able to care for most of their personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

8.3 ADVERSE EVENTS (AEs), SERIOUS ADVERSE EVENTS (SAEs), AND OTHER SAFETY REPORTING

AEs will be classified according to the NCI CTCAE, version 5.0.

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Appendix 3 (Section 10.3).

AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the subject to discontinue the study intervention (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 1.3).

Table 4 below summarizes the different observation periods for AEs, and SAEs.

Table 4: Adverse Event Reporting Periods and Reporting Timelines to the Sponsor

Type of Event	Adverse Event	Serious Adverse Event
Reporting period	From first dose of the study intervention until 30 days after the last dose of study intervention discontinued or before initiation of subsequent anticancer therapies, whichever comes first.	From consent until 30 days after the last dose of study intervention discontinued for all SAEs, and any time after that window if the SAEs are believed to be related to study intervention.
Reporting Timelines to the Sponsor	Entered the clinical database on an ongoing basis.	Within 24 hours.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Medical occurrences that begin before the start of the study intervention but after obtaining informed consent will be recorded on the Medical History section of the eCRF not the AE section, unless the medical occurrence is an SAE.

The Investigator is responsible for ensuring that all AEs are properly captured in the subject's medical records and reported in the eCRF.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, HREC, and Investigators.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the HREC, if appropriate according to local requirements.

8.3.5 Pregnancy

- Details of all pregnancies in female subjects will be collected as outlined in Appendix 4 (Section 10.4).
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female subject pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported.
- The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate, and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.3.6 Disease Progression

Clinical signs or symptoms associated with progression of underlying malignancy are not reported as AEs if they are clearly consistent with the suspected progression of the underlying malignancy. Hospitalization **solely** due to the progression of underlying malignancy should NOT be reported as an SAE. Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study. The site should report clinical signs/symptoms that have met the SAE definition within 24 hours of

learning the event if the aetiology is not clear at the time of the onset. If the subsequent workup has revealed that the reported event is associated with progression of underlying malignancy, the follow-up information should be submitted, and event term should be updated to the cause that led to the hospitalization instead of disease progression. For example, if a subject is hospitalized with shortness of breath that is determined to be associated with worsening of pleural effusion during the subsequent workup, pleural effusion could be used an event term instead of disease progression. SAE that has been reported should not be deleted from the database if the event is determined to be associated with disease progression with subsequent workups.

If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

8.3.7 Death Events

All death events will require completion of a death data collection page within the eCRF.

Timelines for reporting of death events are identical to the requirements for SAE reporting. (Appendix 3, Section 10.3). Events resulting in death will be an SAE regardless of association to disease progression (Section 8.3.6). Death is an outcome and should not be reported as an event term. The event that leads to the death should be reported as the SAE term.

8.4 PHARMACODYNAMICS AND CORRELATIVE BIOMARKERS

Whole blood will be collected during study as specified in the SoA and the study-specific Laboratory Manual. The main objective is to characterize the immune phenotype and function of the subject PBMC before each SUPLEXA administration by PBMC composition and cytokine levels in peripheral blood samples, as well as immunophenotyping (e.g., PBMC profiling, cytokine, and tumour pharmacodynamics marker assessment). Additional, chronological blood samples will also be evaluated as above.

Samples may be stored at a facility selected by the Sponsor, to enable downstream batch analysis, to the maximum limit permitted according to local regulations following subject's last visit for the study.

Residual blood samples may be stored for identification of factors or profiles that correlate with measures of response to study intervention.

For more details on the procedures, please refer to the study-specific Laboratory Manual.

9 STATISTICAL CONSIDERATION

9.1 SAMPLE SIZE DETERMINATION

Approximately 60 subjects will be enroled with a cap of about 8 subjects per individual tumour type (e.g., melanoma, breast, prostate, lung, haematological malignancies, etc.). If promising anti-tumour activity coupled with acceptable safety is observed, overall sample size and/or cap per tumour type may be expanded.

9.2 POPULATION FOR ANALYSES

For purposes of analysis, the following populations are defined:

Population	Description
DLT evaluable Population	All subjects who receive at least 1 dose of study intervention and experience a DLT.
Safety Analysis Set	All subjects who receive at least 1 dose of study intervention.
Response Evaluable Population	All subjects who receive at least 1 dose of study intervention and have measurable disease at baseline and at least one post-baseline tumour assessment per RECIST v1.1.

9.3 STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the Sponsor. The SAP may modify the plans outlined in the protocol; however, any major modifications will also be reflected in a protocol amendment. The SAP will be finalized before database lock and will describe the analysis populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. The SAP will supersede this section of protocol in the event of divergence. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.1 General

Statistical analyses will be performed using SAS® v9.4 or higher (SAS Institute, Cary NC, USA) and all analysis will be described in the SAP finalized before database lock.

The standard summary statistics for continuous variables are sample size (n), mean, standard deviation (SD), median, minimum, and maximum. The standard summary statistics for categorical variables are frequencies and percentages. Time to event variables will be summarized using the Kaplan-Meier method. Where confidence limits are appropriate, the confidence level will be 95% (two-sided), unless otherwise stated.

Individual data (including relevant derived variables) will be presented by parameter in listings. Results of statistical analyses, descriptive summary statistics and supportive listings will also be presented.

9.3.2 Efficacy Analysis

Solid Tumour Cohort

The secondary endpoint of ORR will be defined as the proportion of subjects with BOCR of either a CR or PR as assessed by the Investigator using RECIST v1.1 in the Response Evaluable Population as both unconfirmed or confirmed status. ORR will be reported as a proportion along with the corresponding 2-sided 95% Clopper-Pearson exact CI.

A sensitivity analysis of the primary endpoint will be performed in the Response Evaluable Population.

Other secondary and exploratory endpoints are defined as follows for the whole cohort or analysed by tumour type:

Secondary

- TTP will be defined as the time from the first dose of study intervention to the first documented date of disease progression.

Exploratory

- DOR will be defined as the time from the first date of objective response (CR or PR) to the first documented date of disease progression or the date of death due to any cause, whichever occurs first. Only subjects with a CR or PR will be included.
- TTR will be defined as the time from the first dose of study intervention to the first date of objective response (CR or PR). Only subjects with a CR or PR will be included.
- CBR will be defined as the proportion of subjects with a CR or PR or SD at 6 months.
- PFS will be defined as the time from the first dose of study intervention to the first documented date of disease progression or the date of death due to any cause, whichever occurs first.
- OS will be defined as the time from the first dose of study intervention to the date of death due to any cause.
- Biomarker change from baseline with time as % and absolute.

Main analyses of the above response-related endpoints will be performed in the Efficacy Evaluable Population using Investigator-assessed response. Sensitivity analyses of the above response-related endpoints may be performed in the Response Evaluable Population using Investigator-assessed response. If response is also assessed by BICR, further sensitivity analyses of the above response-related endpoints may be performed using BICR-assessed response.

CBR will be analysed in a similar manner as the primary endpoint of ORR.

Time-to-event endpoints (DOR, TTR, PFS, TTP, and OS) will be summarized using Kaplan-Meier estimates. If estimable, median, 25th, and 75th percentiles and associated 95% CIs will be presented. A Kaplan-Meier curve will also be generated for each time-to-event endpoint. For time-to event endpoints, censoring rules will be applied as follows. DOR will be censored at the last tumour assessment date. PFS and TTP will be censored at the last tumour assessment date

for subjects with post-baseline assessment (s). OS will be censored at the last known date alive for subjects.

Haematologic malignancies Cohort

Statistical analyses will be descriptive and graphical in nature. If sample size permits, complete remission will be summarized descriptively using Kaplan-Meier medians and quartiles.

9.3.3 Safety and Tolerability Analysis

Safety outcomes will be analysed at the end of each study intervention period as well as over the course of the entire study.

The safety assessment will be based on the frequency of adverse events, on the observation of clinically significant abnormalities of laboratory values, concomitant medication use, vital signs, and physical examination data in the Safety analysis set.

Adverse events: Overall AE as well as AE classified by system organ class and preferred terminology according to the Medical Dictionary for Regulatory Activities (MedDRA) will be summarized. Additionally, AE will be summarized by severity and relation to study intervention. SAEs and AEs leading to discontinuation will also be summarized.

Other safety data: These data will be summarized by presenting the proportions of subjects with clinically significant abnormalities or changes from baseline values. Laboratory data will be presented in data listings and summarized.

9.3.4 Other Analyses

Additional details for pharmacodynamics and biomarker exploratory analyses will be described in the SAP finalized before database lock.

9.3.5 Interim Analysis

Open label study and no interim analysis is planned.

9.3.6 Data Safety Monitoring Board (DSMB)

The DSMB, a specific independent committee for the study with external representation composed of at least 3 members and include experts in the field of oncology and clinical studies, or biostatistics. Other members may be invited as needed. The DSMB will regularly monitor overall safety on an unblinded basis, as well as general aspects of study conduct, to ensure that the benefits and risks of study participation remain acceptable.

The DSMB will evaluate all relevant toxicity data and confirm that the principal investigator is reporting all serious, unexpected, or other related toxicities to the regulatory authorities.

During the conduct of the study, the DSMB will periodically be asked to advise the Sponsor regarding modification, continuation, or discontinuation of the study based on the review of the study safety data. Efficacy data will not be provided to the DSMB.

Details on the composition of the DSMB, meeting structure, schedule, and procedures, the content and format of DSMB reports, and other relevant details will be determined in consultation with DSMB members and detailed in a separate DSMB charter.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and Ethical Considerations

10.1.1.1 Regulatory Requirements

The Sponsor, Alloplex Australia Pty. Ltd., is the legal Australian Sponsor for the study and will fulfil the obligations that this role entails. The Sponsor shall, to the extent required by the applicable laws and regulations, interact with TGA in connection with this study. The planned regulatory pathway for this study is through the Clinical Trial Notification (CTN) scheme. Aside from approval by the HREC and notification of the TGA no other regulatory approval will be required.

10.1.1.2 Ethical Conduct of the Study

This study will be conducted in accordance with the principles of the current Declaration of Helsinki (Recommendations guiding Medical Doctors in Biomedical Research Involving Human Subjects) and with the NHMRC National Statement on Ethical Conduct in Research Involving Humans (2007, including current updates, 2018). The conduct of the study will be in accordance with the Integrated Addendum to International Council for Harmonisation (ICH) E6 (R1), Guideline for GCP E6 (R2) adopted by TGA (2000), annotated with comments by the TGA (2018).

This study will be conducted under a protocol reviewed and approved by an HREC at each site and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks. At each study site, the study will be overseen by an Investigator who, prior to study start at the site, will have read, and agreed understanding of the protocol requirements and will agree to conduct the study in accordance with the above.

10.1.1.3 Ethics Review

The final study protocol, including the final version of the PICF, must be approved, or given a favourable opinion in writing by an HREC as appropriate. The Investigator must submit written approval to the Sponsor before he or she can enrol any subject/subject into the study.

The Investigator is responsible for informing the HREC of any amendment to the protocol in accordance with local requirements. In addition, the HREC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the HREC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the HREC with reports of any reportable serious adverse drug reactions from any other study conducted with the study intervention. The Sponsor will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the HREC according to local regulations and guidelines.

10.1.1.4 Sponsor and Investigator Obligations

Investigator Obligations

The Investigator and study staff are responsible for maintaining a comprehensive filing system of all study-related (essential) documentation. These include, but are not limited to: HREC correspondence, study intervention accountability logs, and curricula vitae of all personnel participating in the study. These files must be suitable for inspection at any time by the Sponsor, Clinical Research Associate, and/or applicable regulatory authorities.

Protocol Amendments

Neither the Investigator nor the Sponsor will modify or alter this protocol without the agreement of the other. All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant HREC for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the study subjects. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

Protocol Deviations

Should any protocol deviation occur, it must be reported to the Clinical Research Associate (CRA) as soon as is reasonably practical. The deviation and the reason for its occurrence must be documented, reported to the relevant HREC (if required), and included in the study report.

10.1.2 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

The Investigator(s) will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time without prejudice. The subject should be given the opportunity to ask questions and allowed time to consider the information provided before voluntarily signing the written PICF.

The subject's signed and dated informed consent must be obtained before conducting any study procedures. The subjects will be informed of their rights to privacy but will be made aware that the study data will be submitted to the Sponsor and possibly to drug regulatory authorities for review and evaluation. They will be informed also that the CRA may inspect their medical records to verify the accuracy and completeness of the study records and results.

The acquisition of informed consent should be documented in the subject's medical records, as required by the Integrated Addendum to ICH E6(R1), GCP E6(R2), annotated with comments by the Australian Therapeutic Goods Administration (2018) and the NHMRC National Statement on Ethical Conduct in Human Research (2007, including current updates, 2018), and the PICF

will be signed and personally dated by the subject and by the person who conducted the informed consent discussion (not necessarily an Investigator).

The Investigator must maintain the original, signed PICF. A copy of the signed PICF must be given to the subject or legal representative. The date that informed consent was signed will be recorded on the eCRF.

10.1.4 Data Protection

- Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate HREC members, and by inspectors from regulatory authorities.

10.1.5 Dissemination of Clinical Study Data

- A CSR will be developed by the Sponsor at completion of data analysis. This report will be a clinical and statistical integrated report, according to the ICH E3 guidelines.
- Sponsor will register the study and post study results regardless of outcome on a publicly accessible website (e.g., *clinicaltrials.gov*) in accordance with the applicable laws and regulations.

10.1.6 Data Quality Assurance

- All subject data relating to the study will be recorded on printed or electronic eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, HREC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site 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.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator per ICH-GCP and local regulations or institutional policies. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7 Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

10.1.8 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of subjects.

The first act of recruitment is the first site open and will be the study start date.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor, else study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

- Failure of the Investigator to comply with the protocol, the requirements of the HREC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the HREC(s), the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject(s) and should assure appropriate subject therapy and/or follow-up.

10.1.9 Publication Policy

The publication policy for this study is located within the Clinical Study Agreement with the Investigator and/or Institution.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The clinical laboratory tests detailed in Table 5 will be performed by a central laboratory at timing/frequency detailed in the SoA (Section 1.3)
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report

Table 5: Clinical Safety Laboratory Tests

Hematology	
White blood cell count (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils – absolute and %)	Red blood cell (RBC) RBC Indices: MCV, MCH, %Reticulocytes
Haemoglobin	Haematocrit
Platelet count	
Clinical Chemistries[a]	
Electrolytes: Sodium, Potassium, CO_2 or bicarbonate, Chloride, Calcium, Magnesium, Phosphorus, Liver function: Alkaline Phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), Total Bilirubin Renal function: Blood Urea Nitrogen, Creatinine, Creatine Kinase, calculated Creatinine Clearance Cockcroft-Gault Other: Albumin, lactate dehydrogenase (LDH), non-fasting Glucose, uric acid, lactate dehydrogenase, total protein, total cholesterol, and triglycerides	
Urinalysis	
Basic Urinalysis (dipstick, including macroscopic appearance, bilirubin, blood, colour, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen;	Full urinalysis (dipstick plus microscopic evaluation) to be performed only at the Screening and End of Study visits). A reflex microscopic urinalysis should be performed if the result of the urinalysis is abnormal or at the discretion of the PI or delegate.
Other Study-Specific Laboratory Assessments	
Serum and urine human chorionic gonadotropin (hCG) pregnancy test Syphilis screening test (rapid plasma regain)	**Serology** HIV antibody, hepatitis B surface antigen (HBsAg), hepatitis C virus antibody or HCV RNA (qualitative)

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a subject or clinical study subject, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations (Medically important):

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, 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 dependency or drug abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF within 24 hours of Investigator/site awareness of the event.
- It is **not** acceptable for the Investigator to send photocopies of the subject's medical records to the Sponsor in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all subject identifiers, except for the subject number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

AE severity will be evaluated by the Investigator in accordance with the NCI CTCAE v5.0[1]. For AEs that are not adequately addressed in the NCI CTCAE, the Investigator should classify the intensity of the AE using the following guidelines:

- Grade 1: Mild: Aware of sign or symptom, but easily tolerated; no intervention needed
- Grade 2: Moderate: Discomfort enough to cause interference with usual activity, minimal non-invasive intervention indicated (e.g., short course of antibiotics)
- Grade 3: Severe: Medically significant but not immediately life-threatening; incapacitation with inability to work or do usual activity
- Grade 4: Life-threatening: Refers to an event in which the subject was at risk of death at the time of the event, as judged by the Investigator; urgent/emergent intervention indicated. This category should not be used for an event that hypothetically might have caused death if it were more severe.
- Grade 5: Fatal outcome.

It will be left to the Investigator's clinical judgment to determine whether an AE is of sufficient severity to require the subject's removal from treatment or from the study. A subject may also voluntarily withdraw consent from treatment due to what she/he perceives as an intolerable AE. If either of these situations arises, the subject should be strongly encouraged to undergo an end-of-study assessment and be under medical supervision until symptoms cease or the condition becomes stable. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.

[1] Please refer to the CTCAE v5 published on November 2017 at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf .

- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The Investigator may change his/her opinion of causality considering follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Causality Categories:

- **Related**: An event is considered related if there is a reasonable possibility of causal association between the study intervention and the event. This means there is evidence to suggest a causal relationship between the study intervention and the AE. The AE follows a reasonable temporal sequence from the time of study intervention administration and follows a known response to the study intervention and cannot be reasonably explained by other factors such as the subject's clinical state or other therapeutic interventions, or concomitant drugs administered to the subject.
- **Not related**: The available evidence support that the event is related to other factors such as the subject's clinical state, therapeutic interventions or concomitant drugs administered to the subject.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject die during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology, if available.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available and within 24 hours of Investigator/site awareness. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to the Sponsor's Medical Monitor by telephone. • Contacts for SAE reporting is provided in the SAE form.

10.4 APPENDIX 4: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

10.4.1 Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

2. Premenarchal
3. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to a medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.

Postmenopausal female

- A postmenopausal state is defined as having had no menses for 1 year without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 1 year of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2 Contraception Guidance

Male Subjects

Male subjects are eligible to participate if they agree to the following from informed consent, during the treatment period and for 90 days after the last dose of study intervention:

- Refrain from donating sperm

PLUS, either**:**

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception/barrier as detailed below
  - Agree to use a male condom

Female Subjects

- A female subject is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
  - Is not a woman of childbearing potential (WOCBP)

OR

  - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), preferably with low user dependency (see table below), at least 28 days prior to 1st screening visit, during the intervention period, and for 60 days after the last dose of study intervention, and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The Investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
  - A WOCBP must have negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) within 72 hours prior to receiving the first administration of study intervention and a negative urine pregnancy test on Baseline before first administration of study intervention. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test is required, and results must be negative.
  - If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required, and results must be negative. In such cases, the subject must be excluded from participation if the serum pregnancy result is positive.

Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

Table 6: Contraception Methods Acceptable for this Study

Highly Effective Methods[a] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation
• Intrauterine device (IUD)
• ParaGurad Intrauterine hormone-releasing system (IUS) (non-hormonal)[b]
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
Highly Effective Methods[a] That Are User Dependent
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*
Other Methods
• Diaphragm (must be used with another contraceptive method)

[a] Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study.

10.4.3 Collection of Pregnancy Information

Male subjects with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate

form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of foetal status (presence or absence of anomalies) or indication for the procedure.

Female Subjects who become pregnant

- The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a subject's pregnancy.
- The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported to the Sponsor as an SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered related to the study intervention by the Investigator will be reported to the Sponsor. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

10.5 APPENDIX 5: SUMMARY OF RESPONSE EVALUATION CRITERIA IN SOLID TUMOURS (RECIST) V1.1

10.5.1 RECIST v1.1

Disease response will be evaluated using the RECIST v1.1 by the Investigator at timepoints specified in the SoA. The following summarizes the process for selecting baseline measurable lesions and deriving the appropriate response at subsequent imaging time points. For specific details related to the response criteria please refer to the published RECIST v1.1 (Eisenhauer, 2009).

Evaluation of Tumour Burden at Subsequent Assessments

Please refer to the SoA for the timing of subsequent imaging assessments.

Target Lesions:

Target lesions are measured at every subsequent assessment and an overall SOD is calculated. Target lesions are assessed as Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), or Not All Evaluated (NAE) at every time point based on the calculated SOD.

Target Assessment	Evaluation Definition
Complete Response (CR)	CR is declared if **ALL** of the following are true for target lesions: • The disappearance of all non-nodal target lesions • Any pathological lymph nodes must have a reduction in short axis to <10 mm.
Partial Response (PR)	PR is declared if there is a decrease of at least 30% in the SOD of target lesions compared to the baseline SOD of target lesions.
Progressive Disease (PD)	PD is declared if **ANY** of the following are true for target lesions: • SOD of all target lesions increases at least 20% compared to the smallest SOD recorded from any prior assessment NOTE: In addition to the relative increase at least 20%, the sum must also demonstrate an absolute increase of at least 5 mm. ***OR*** • The appearance of one or more new lesions.
Stable Disease (SD)	SD is declared if target lesion assessment does not meet criteria for PR, PD, or CR.

Non-Target Lesions:

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed qualitatively at subsequent assessments. Non-target lesions are assessed as CR, PD, non-CR/non-PD (NCNP), or NAE at every time point.

Non-Target Assessment	Evaluation Definition
Complete Response (CR)	CR is declared if **ALL** of the following are true for non-target lesions: • Disappearance of all non-target lesions and normalization of tumour marker level. • All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non-PD (NCNP)	NCNP is declared when persistence of one or more non-target lesion(s) and/or the maintenance of tumour marker level above the normal limits is observed.
Progressive Disease (PD)	PD is declared if **ANY** of the following are true for non-target lesions: • *Unequivocal Progression* of existing non-target lesions. NOTE: Unequivocal Progression of non-target disease is defined as an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesion(s) is usually not sufficient to quality for unequivocal progression. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease should therefore be extremely rare. ***OR*** • The appearance of one or more new lesions.

New Lesions:

The determination of new lesions should be unequivocal and not be attributable to differences in the scanning technique, change in modality, or findings thought to represent something other than tumour. This is particularly important when the subject's target lesions show PR or CR.

A lesion identified at a subsequent time point in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. This underscores the importance of scanning all anatomical locations that are suspected to contribute to disease burden at baseline.

Bone metastases:

Evaluation of response in subjects with bone-only disease will be performed by MRI (preferred modality) per modified MDA criteria (Table 7). CT scans should only be performed when MRI is contraindicated (cases of bypass for example).

Table 7: Modified MD Anderson (MDA) Criteria for Bone Metastases+

Response Category	Criteria
Complete Response	Normalization of Signal intensity on MRI
	Complete sclerotic fill-in of lytic lesions or normalization of bone density on CT*
Partial Response	Osteoblastic flare – Interval visualization of lesions with sclerotic rims or new sclerotic lesions in the setting of other signs of PR and absence of progressive bony disease
	≥50% decrease in measurable lesions on MRI
	≥50% decrease in measurable lesions or ≥50% subjective decrease on ill-defined lesions on CT*
Progressive disease	≥25% increase in size of measurable lesions on MRI
	≥25% increase in size of measurable lesions or subjective increase in the size of ill-defined lesions on CT*
	New bone metastasis
Stable disease	No change
	<25% increase or <50% decrease in size of measurable lesions
	<25% subjective increase or <50% subjective decrease in size of ill-defined lesions
	No new bone metastasis

*CT only to be performed if MRI is contraindicated

+Measurements are based on the sum of a perpendicular, bidimensional measurement of the greatest diameters of each individual lesion

Source: (Costelloe, 2010)

Table 8: Overall Time Point Response Assignment at Subsequent Assessments

Once the Target-Lesion, Non-Target Lesion, and New Lesion Assessments have been completed for a subsequent imaging assessment, an Overall Time Point Response may be assigned.

Target Lesion Assessment	Non-Target Lesion Assessment	New Lesion Assessment	Overall Time Point Response
CR	CR	No	CR
CR	NCNP	No	PR
CR	NAE	No	PR
PR	NCNP or NAE	No	PR
SD	NCNP or NAE	No	SD
NAE	NCNP	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR - Complete Response, PR - Partial Response, SD - Stable Disease, PD - Progressive Disease, NCNP - Non-CR/Non-PD, NAE - Not All Evaluated, NE - Not Evaluable

10.5.2 Radiographic Imaging as Basis for Methods of Measurement

- Computed tomography (CT) and Magnetic resonance imaging (MRI): CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumours of the chest, abdomen, and pelvis. Head and neck tumours and those of extremities usually require specific protocols. See RECIST v1.1. guidelines for additional specifications on CT and MRI measurements.
- Chest X-ray: Chest CT is preferred over chest x-ray; particularly when progression is an important endpoint, since CT is more sensitive.
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is a concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- Endoscopy and Laparoscopy: The utilization of endoscopy and laparoscopy for objective tumour evaluation is not advised.
- Tumour Markers: Tumour markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response when all lesions have disappeared.
- Cytology and Histology: These techniques can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumour types such as germ cell tumours).

The same imaging modality should be used throughout the study for a given subject.

Details concerning all of the above methods of measurement can be obtained in the RECIST v1.1. guidelines.

10.6 APPENDIX 6: MODIFIED RECIST V1.1 FOR IMMUNE-BASED THERAPEUTICS

Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the measured size of a target lesion, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST v1.1 in many respects but have been adapted to account for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression but rather a favorable inflammation of the tumor.

Unlike RECIST v1.1, iRECIST requires the confirmation of progression on a subsequent scan and uses the terms iUPD (immune unconfirmed progression) and iCPD (immune confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD.

For target lesions, iCR, iPR, and iSD can all be assigned after iUPD has been documented, as long as iCPD was not confirmed (Table 9). iUPD is defined by RECIST v1.1 criteria for progressive disease; iUPD can be assigned multiple times as long as iCPD is not confirmed at the next assessment. Progression is confirmed in the target lesion category if the next imaging assessment after iUPD (4–8 weeks later) confirms a further increase in sum of measures of target disease from iUPD, with an increase of at least 5 mm. However, the criteria for iCPD (after iUPD) are not considered to have been met if CR, PR, or SD criteria (compared with baseline and as defined by RECIST v1.1) are met at the next assessment after iUPD. The status is reset (unlike RECIST v1.1, in which any progression precludes later CR, PR, or SD). iCR, iPR, or iSD should then be assigned; and if no change is detected, then the timepoint response is iUPD.

The assessment of non-target lesions at each timepoint follows similar principles. iUPD (but not iCPD) can have been documented before iCR or when the criteria for neither CR nor PD have been met (referred to as non-iCPD/non-iUPD) and can be assigned several times, as long as iCPD was not confirmed. iUPD is defined by RECIST v1.1 criteria; however, iUPD can be assigned multiple times as long as iCPD is not confirmed at the next assessment. Progressive disease in the non-target lesion category is confirmed if subsequent imaging, done 4–8 weeks after iUPD, shows a further increase from iUPD. The criteria for iCPD are not judged to have been met if RECIST v1.1 criteria for complete response or non-iCR/non-iUPD are met after a previous iUPD. The status is reset (unlike RECIST v1.1) and iCR, or non-iCR/non-iUPD is assigned; if no change is detected, the timepoint response is iUPD.

iCPD is confirmed if further increase in tumour burden, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued increase in tumour burden (from iUPD) where RECIST v1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions
  - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
  - Continued unequivocal progression in non-target disease with an increase in tumour burden
  - Increase in size of previously identified new lesion (s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new

lesions) or additional new lesions.

- RECIST v1.1 criteria are met in lesion (target or non-target) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR or iCR if those criteria are met compared to baseline). The prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as immune overall response (iOR) providing that iCPD is not documented at the next assessment after iUPD.

The event date to be used for calculation of progression-free survival (iPFS) should be the first date at which progression criteria are met (i.e., the date of iUPD) provided that iCPD is confirmed at the next assessment. If iUPD occurs, but is disregarded because of later iSD, iPR, or iCR, that iUPD date should not be used as the progression event date.

Table 9 iRECIST Time Point iResponse

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

				unequivocal) and /or • size or number of new lesions previously identified
Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on o increase in size or number of new lesions previously identified

TP = time-point; NT = non-target, T = target; NL = new lesions; iUPD = unconfirmed immune PD; iCPD = confirmed immune PD; SOM = sum of measures. iCR – immune complete response; iPR – immune partial response; iSD – immune stable disease

* Using RECIST v1.1 principles. If no PSPD occurs, RECIST v1.1 and iRECIST categories for CR, PR and SD would be the same.

** in any lesion category.

*** previously identified in assessment immediately prior to this time point.

Source: (Seymour, 2017a)

10.7 APPENDIX 7: CRS TOXICITY TREATMENT GUIDELINES

Note these as guidelines may require modification based on clinical circumstances of each subject. The investigator should consider both best outcome for the subject and institutional standard of care treatment protocols. As such failure to exactly follow these guidelines is not a protocol deviation or violation as follows:

Cytokine Release Syndrome Grading Assessment (Lee, 2019)	**Corticosteroids**
Grade 1: Symptoms are not life-threatening and require symptomatic treatment only (fever, nausea, fatigue, headache, myalgias, malaise)	• N/A
Grade 2: Symptoms require and respond to moderate intervention: • Oxygen requirement <40% FiO_2 OR • Hypotension responsive to IV fluids or low dose of one vasopressor OR • Grade 2 organ toxicity*	• Vigilant supportive care with careful monitoring of cardiac and other organ function
Grade 2: As above but with **extensive co-morbidities or older age.** **OR** **Grade 3:** Symptoms require and respond to aggressive intervention: • Extensive co-morbidities or older age • Oxygen requirement ≥40% FiO_2 OR • Hypotension requiring high-dose or multiple vasopressors OR • • Grade 3 organ toxicity* or Grade 4 transaminitis	• Administer methylprednisolone 1 mg/kg IV twice daily or equivalent dexamethasone (e.g., 10 mg IV every 6 hours). Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days. • If no improvement, within 24 hours, consider starting tocilizumab or manage as Grade 4 (below)
Grade 4: Life-threatening symptoms: • Requirement for ventilator support OR • Grade 4 organ toxicity* (excluding transaminitis)	• Administer methylprednisolone 1000 mg IV per day for 3 days; if improves, then manage as above. • Consider alternate immunosuppressants if no improvement or if condition worsens.

Source: (Lee, 2019) (EMA, 2018)

10.8 APPENDIX 8: TLS TOXICITY MANAGEMENT

Note these are guidelines that might require modification based on clinical circumstances of each subject and consider institutional standard of care treatment protocols, and failure to exactly follow these guidelines is not a protocol deviation or violation as follows:

Tumor lysis syndrome (TLS) is an oncology emergency that occurs as a result of rapid tumor cell breakdown and the consequent release of massive amounts of intracellular contents, including potassium, phosphate, and uric acid, into the systemic circulation. These metabolic disturbances lead to life-threatening conditions and may cause sudden death if not treated. TLS commonly occurs following initiation of cytotoxic treatment in patients with high-grade lymphomas or acute lymphoblastic leukemia. Spontaneous cases involving both solid and hematologic tumors have also been reported. Rarely, TLS occurs following treatment with irradiation, corticosteroids, hormonal therapy, or biologic therapy. It is necessary to identify subjects at risk for TLS early in order to initiate preventive measures. In the event that preventive measures fail, the clinical parameters and signs of TLS must be understood and recognized so that treatment can begin as soon as possible, as this condition is a significant cause of morbidity and mortality.

When tumor cells are rapidly broken down and their contents released into the extracellular space, the released ions and compounds can cause metabolic disturbances too great to be neutralized by the body's normal mechanisms. The syndrome characterized by these metabolic derangements is known as TLS. TLS can cause life-threatening conditions and even death unless appropriately and immediately treated.

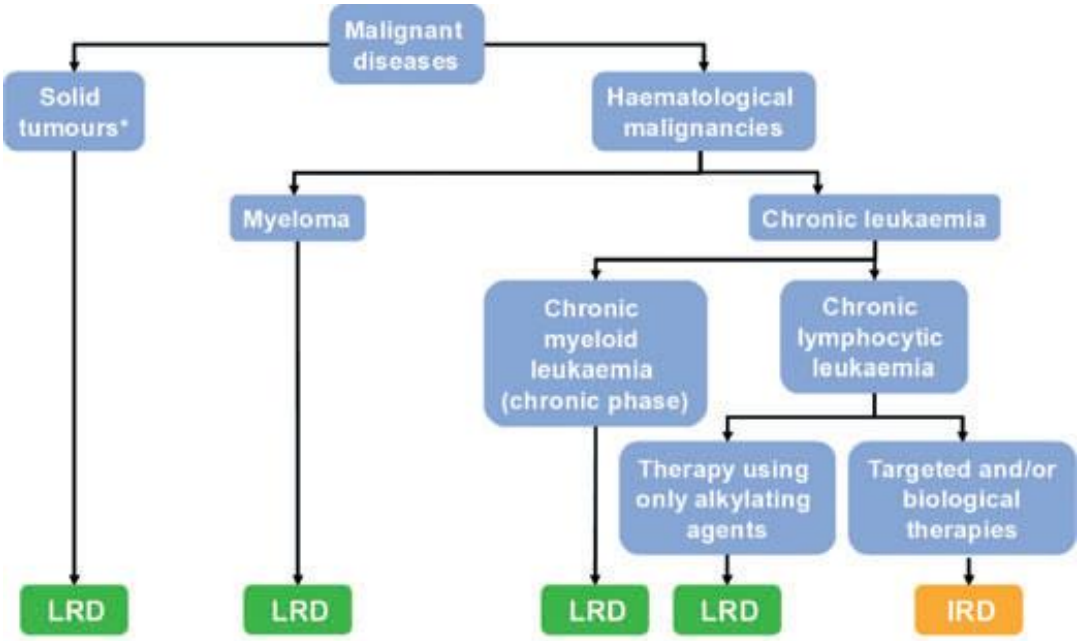
The Cairo-Bishop definition provided specific laboratory criteria for the diagnosis of TLS, as well as a grading system for describing the degree of severity of TLS (Cairo, 2010). Laboratory TLS is defined as any two (or more) of the following abnormalities:

- Serum uric acid level ≥ 8 mg/dL, or 25% increase from baseline.
- Serum potassium level ≥ 6 mmol/L, or 25% increase from baseline.
- Serum phosphate level ≥ 6.5 mg/dL in children and ≥ 4.5 mg/dL in adults, or 25% increase from baseline.
- Serum calcium level ≤ 7 mg/dL, or 25% decrease from baseline.

All these abnormalities must occur within 7 days after the dosing with SUPLEXA.

Table 10 provides recommendation for prevention and treatment of TLS according to the subject's risk level as shown in Figure 6. Investigator should consider institution standard of care treatment protocols. Subjects will likely need to be aggressively hydrated with IV fluids. The target diuresis is at least 100 to 200 mL/hour (similar to the prophylaxis rate). Loop diuretics or mannitol may be used in conjunction with aggressive fluid-loading to promote aggressive diuresis. Furosemide can be used for this purpose in dosages of 20 to 100 mg IV every 4 to 8 hours or as an IV infusion of 10 to 20 mg/hour. Allopurinol, urate oxidase, and possibly urinary alkalinization all have a role in management. Ultimately, dialysis may also be needed, especially if a subject exhibits severe or refractory acute renal failure and/or symptoms from the metabolic derangements.

Figure 6: TLS risk assessment of solid tumours, myelomas and chronic leukaemias



*Bulky, solid tumours, sensitive to chemotherapy, such as neuroblastomas, germ-cell tumours and small-cell lung cancer are

Source: (Cairo, 2010)

Abbreviation: LRD, low risk disease; IRD, intermediate risk disease

Table 10: Recommendation for Prevention and Treatment of Tumour Lysis Syndrome

Risk Level	Low-risk disease	Intermediate-risk disease	High-risk disease
Diagnostic measures	• No specific measures	• Daily monitoring of laboratory abnormalities before and during the first 7 days of anticancer therapy	• At least twice daily monitoring of laboratory abnormalities before and during the first 7 days of anticancer therapy
Preventive measures	• Moderate hydration is recommended	• Vigorous hydration • Keep urinary output >100 mL/h • Treatment with allopurinol or febuxostat should be started at least 24 hours before initiation of anticancer therapy and should be continued till normalization of uric acid levels and signs of large tumour burden are absent	• vigorous hydration • Keep urinary output >100 mL/h • Single dose 6 mg of rasburicase. Repeat doses, as necessary. in case of contraindication treatment with febuxostat
Treatment of established tumour lysis syndrome	• Admission to intensive care unit with continuous cardiac monitoring and monitoring of laboratory abnormalities every 4–6 hours • early nephrology consultation to estimate the indications for renal replacement therapy • Correction of electrolyte abnormalities • vigorous hydration, keep urinary output >100 mL/h • Single dose 6 mg of rasburicase. Repeat doses as necessary. In case of contraindication, treatment with febuxostat		

Source: (Alakel, 2017)

10.9 APPENDIX 9: GUIDANCE TO ADDRESS GLOBAL HEALTH EMERGENCIES AND POTENTIAL IMPACT ON THE CLINICAL STUDY

As of March 12, 2020, a coronavirus disease 2019 (COVID-19) pandemic has been declared by the World Health Organization, leading to implementation of extensive measures by healthcare systems globally to limit viral spread, with potential impact on conduct of clinical studies (because subjects/healthcare workers are in self-isolation/quarantine, there is limited access to public places, including hospitals, and health care professionals are committed to critical tasks).

Based on guidelines issued by global regulatory authorities ((Health Canada, 03 April 2020; MHRA, 22 April 2020; Australian Government, 2020; EMA, April 2020; FDA, March 2020)), the actions listed below are being implemented in this protocol to address potential disruptions to study conduct secondary to COVID-19 infection or control measures. These actions are to assure the safety of study subjects, maintain compliance with good GCP, and minimize the risks to study integrity.

Informed Consent

- If written consent by the study subject is not possible (for example because of physical isolation due to COVID-19 infection), consent could be given orally by the study subject.
- Study subjects and the person obtaining consent could sign and date separate informed consent forms
- In case a written informed consent cannot be obtained at the clinical site, electronic informed consent can be obtained remotely. Alternatively, the consent form may be sent to the subject or the subject's legally authorized representative by facsimile or e-mail, and the consent interview may then be conducted by telephone when the subject or subject's legally authorized representative can read the consent form during the discussion.
- If re-consent is necessary for the implementation of **new urgent changes in study conduct** (mainly expected for reasons related to COVID-19 or important safety issues for other trials), alternative ways of obtaining may include contacting the study subject via phone or video-calls and obtaining oral consents, to be documented in the study subjects' medical records, supplemented with e-mail confirmation.
- The informed consent procedure to remain compliant with the study protocol as well as local regulatory requirements. All relevant records should be archived in the Investigator's site master file. A correctly signed and dated informed consent form should be obtained from the study subjects later, as soon as possible.

Study Visits and Procedures

- COVID-19 screening procedures that may be mandated by the health care system in which a clinical study is being conducted do not need to be reported as an amendment to the protocol even if done during clinical study visits. The Investigator in consultation with the Sponsor will decide if it is in the best interest of COVID-positive subjects to remain in the study.
- In the case of missed visits due to COVID-19 (or other public health emergencies) related reasons:
  - The site should make every effort to contact the study subject to confirm and document the reason for the missed visit, and at minimum evaluate AEs/SAEs, and concomitant medications in order to assess subject safety.

  - The study subject should continue to collect the daily diary responses on the diary.

- To maintain the integrity of the study, if study subjects cannot access a clinical study site, alternative methods of collecting study procedures may be considered where possible and in certain situations, with Sponsor approval:
  - A local laboratory may be used to collect laboratory samples as required by the protocol. Local analysis can be used for safety decisions. In addition, local laboratory can be used for study endpoints if samples drawn at the local laboratory cannot be shipped to the central laboratory. If a local laboratory is used, applicable lab ranges and laboratory certification should be provided to the Sponsor.
  - According to site business continuity plans, home visits may be used to collect laboratory samples and assessments as required by the protocol.
  - In cases where a subject is continuing to receive study intervention but COVID-19 pandemic-related circumstances preclude a visit to the investigative site, remote visits (e.g., virtual visits by telemedicine or phone contact) will be allowed for relevant study procedures while maintaining subject's privacy, as would be done for a clinic visit.
  - Alternate imaging centres may be used; this depends on whether the protocol-specified procedures are related to eligibility criteria, safety evaluations, or endpoint assessments.
  - For missed assessments for primary and secondary endpoints, please discuss these situations with the Sponsor for approval. In certain situations, with prior approval, other options, or delayed visits, can be considered.

Monitoring and Audits

- Certain Sponsor oversight responsibilities, such as monitoring and quality assurance activities need to be re-assessed and temporarily, alternative proportionate mechanisms of oversight may be required. On-site audits will be avoided or postponed, and if permitted under local regulations, physical distancing restrictions should apply.
- Cancelling or postponing of on-site monitoring visits and extending of the period between monitoring visits will be allowed.
- To the extent on-site monitoring remains feasible, it should consider national, local and/or organizational social distancing restrictions.
- Centralized monitoring can be considered for data acquired by electronic data capture systems (e.g., eCRFs, central laboratory or ECG / imaging data, etc.) that are in place or could be put in place provides additional monitoring capabilities that can supplement and temporarily replace on-site monitoring through a remote evaluation of ongoing and/or cumulative data collected from study sites, in a timely manner.
- Off-site monitoring can be conducted and will include phone calls, video visits, e-mails, or other online tools to discuss the study with the Investigator and site staff. Remote monitoring should be focused on review of critical study site documentation and source data. These activities could be used to get information on the clinical study progress, to exchange information on the resolution of problems, review of procedures, study subject status as well as to facilitate remote site selection and Investigator training for critical study procedures.

COVID-19 Vaccination

- Various vaccines for COVID-19 have been approved worldwide.
- Cancer patients, as part of the standard of care at their institution/country, receive COVID-19 vaccine(s) in addition to anti-cancer therapy, including cytotoxic chemotherapy. This is supported by various published guidelines such as ASCO (https://www.asco.org/asco-coronavirus-resources/covid-19-patient-care-information/covid-19-vaccine-patients-cancer) and ESMO (https://www.esmo.org/covid-19-and-cancer/covid-19-vaccination).
- The Sponsor does not have specific data regarding any possible interaction between the COVID-19 vaccines and SUPLEXA and has no evidence or rationale to suggest SUPLEXA alters the vaccine's efficacy or increases the vaccine's toxicity. However, given the uncertainty of the combination of this FIH product and COVID-19 vaccinations, COVID-19 vaccinations are not allowed within 30 days prior to enrolment through 30 days after last infusion SUPLEXA infusion.

Risk Mitigation

- The Sponsor will continually assess whether the limitations imposed by the COVID-19 public health emergency on protocol implementation pose new safety risks to study subjects, and whether it is feasible to mitigate these risks by amending study processes and/or procedures.

10.10 APPENDIX 10: GLOSSARY

Abbreviation Term	Description
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BICR	blinded independent central review
BOCR	best overall confirmed response
CAR-T	chimeric antigen receptor T cells
CBC	complete blood count
CBR	clinical benefit rate
cGMP	current Good Manufacturing Practice
CPI	checkpoint inhibitor
CR	complete response
CrCl	creatinine clearance
CRS	cytokine release syndrome
CSF	colony stimulating factors
CT	computed tomography
CTCAE	common terminology criteria for adverse events
CTL	cytotoxic CD8-positive T lymphocytes
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DLT	dose limiting toxicities
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report forms
ENLiST	ENgineered Leukocyte STimulator
EOS	end of study
ET	early termination
FIH	first in human
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate

Abbreviation Term	Description
HBsAg	hepatitis B virus surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HREC	Australian Human Research Ethics Committee
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
DSMB	Independent Data Monitoring Committee
IFN	interferon
IHC	immunohistochemistry
IL	interleukin
INR	international normalized ratio
iRECIST	Immune related RECIST
IV	intravenous
LDH	lactate dehydrogenase
LLN	lower limit of normal
mAbs	monoclonal antibody
MDA	Modified MD Anderson
MedDRA	medical dictionary for regulatory activities
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
MTD	maximum tolerated cumulative dose
NAE	not all evaluated
NCI	National Cancer Institute
NCNP	RECIST assessment of non-CR/non-PD
NCS	not clinically significant
NE	not evaluable
NHMRC	National Health and Medical Research Council
NIH	National Institute of Health
NK	natural killer
NKT	natural killer T cells

Abbreviation Term	Description
NLR	neutrophil/lymphocyte ratio
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PD-1	programmed death-1
PDX	patient derived xenografts
PFS	progression-free survival
PICF	participant information sheet and informed consent form
PO	per os (by mouth)
PR	partial response
PT	prothrombin time
QW	once per week
RECIST	response evaluation criteria in solid tumours
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
TCR	T cell receptor
TGA	Australian Therapeutic Goods Administration
TIL	tumour infiltrating lymphocytes
TLS	tumour lysis syndrome
TNF	tumour necrosis factor
TTP	time to progression
TTR	time to response
ULN	upper limit of normal
WOCBP	women of childbearing potential

10.11 APPENDIX 11: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC). Prior amendments are provided in this section in chronological order.

Amendment 1.0; 09 November 2021

Overall Rationale for the Amendment:

Summary of Changes (in order of appearance)

Section Number and Name	Description of Change	Rationale for Change
1.1 Synopsis (Overall Design) 4.1.2 Treatment Period	• Clarify staggering procedure • Clarify determination for treatment extension	• To align with Study Schema and for clarity • Per request of HREC
1.3 Schedule of Activities 6.8.1 Prophylaxis	• Clarify reason and timing of treatment prophylaxis	• Per request of HREC
2.3.1 Risk Assessment 6.6 Toxicity Management 10.6 CSR Toxicity Treatment Guidelines 10.7 TLS Toxicity Management	• Cross reference to CRS and TLS toxicity treatment guidelines which were added (Appendices 6 and 7) • For TLS, clarify summary of risk	• Per request of HREC
5.2 Exclusion Criteria	• Add exclusion of subject at high risk for developing TLS	• As a safety precaution
5.2 Exclusion Criteria 10.2 Appendix 2 Clinical Safety Laboratories	• Delete exclusion criteria relating to coagulation • Delete coagulation parameters form laboratory tests	• As biopsies will not be collected as part of this study no need to measure coagulation
7.1 Study Stopping Rules	• Add a study stopping criteria associated with DLTs • Clarify language around study stopping criteria	• Per request of HREC
8.4 Pharmacodynamics and Correlative Biomarkers	• Moved text on disease biomarkers under this section and delete immunogenicity which is not assessed	• For consistency and clarity
General	• Minor administrative changes and clarifications made throughout the protocol (e.g., blood volumes collected) • Correct typographical errors, hyperlinks/cross-references, style, and formatting (not tracked). • Align across protocol sections. • Update glossary (not tracked). • Update header	• For consistency and clarity • Alignment across documents

Amendment 1.1; 30 November 2021

Overall Rationale for the Amendment:

Summary of Changes (in order of appearance)

Section Number and Name	Description of Change	Rationale for Change
.1 Synopsis (Overall Design) 1.3 Schedule of Activities 4.1.2 Treatment Period 6.1 Study intervention administered	• Update procedures for subject safety monitoring post each infusion (3 hours at clinic post infusion and 24 hours each infusion) • Clarify that subjects who qualify for 3 additional weekly SUPLEXA infusions (Optional Treatment Extension period), will undergo similar evaluations as during the Treatment period • Update the SoA to incorporate above changes	• For clarity • Per request of HREC
General	• Correct typographical errors, hyperlinks/cross-references, style, and formatting (not tracked). • Align across protocol sections. • Update protocol section numbering, including adding Appendix 10 (protocol amendment history) • Update footer with version and date	• For consistency and clarity • Alignment across protocol

Amendment 1.2; 25December 2021

Overall Rationale for the Amendment:

Summary of Changes (in order of appearance)

Section Number and Name	Description of Change	Rationale for Change
1 Synopsis (Overall Design) 1.3 Schedule of Activities 4.1.2 Treatment Period 6.1 Study intervention administered	• Update procedures for subject safety monitoring post infusion for the first 3 subjects in each cohort and subsequent subjects • Update the SoA to incorporate above changes	• Per request of HREC
1.3 Schedule of Activities 3. Objectives and Endpoints (exploratory) 8.4 Pharmacodynamics and correlative biomarkers	• Delete assessment of disease biomarkers (CEA and PSA)	• Additional samples are not required as analysis will be done in the exploratory assessments
General	• Correct typographical errors, hyperlinks/cross-references, style, and formatting (not tracked) • Align across protocol sections • Update protocol section numbering • Update footer with version and date	• For consistency and clarity • Alignment across protocol

Amendment 2; 18 May 2022

Overall Rationale for the Amendment:

Summary of Changes (in order of appearance)

Section Number and Name	Description of Change	Rationale for Change
1.1 Synopsis 1.2 Study Schema 1.3 Schedule of Activities 4.1 Overall Study Design	• Extend screening to 35 days	• For logistic reasons (Administrative Amendment #01)
1.1 Synopsis 1.3 Schedule of Activities 4.1 Overall Study Design 6.1 Study Intervention Administered	• Specify assessments during the observation period post SUPLEXA administration	• For clarity and to align with File Note dated 17 January 2022
1.1 Synopsis 4.1 Overall Study Design	• Update enrolment process beyond the first 3 subjects in each cohort	• For manufacturing and logistical reasons
1.3 Schedule of Activities 6.8.1 Prophylaxis	• Clarify that prophylactic measures listed in the protocol are recommended; site can follow standard of care.	• To allow flexibility without compromising patient safety, premedication's according to institutional practices will be permitted (Administrative Amendment #04)
6.1 Study Intervention Administered	• Update administration instruction	• For alignment with the SUPLEXA therapeutic manual. Dilution range of SUPLEXA was widen from 200-300mL to facilitate dilution at the clinical site as PlasmaLyte is not available in Australia in 250mL bags units. The range has been validated through preclinical experiments and makes no difference to SUPLEXA cell viability. (Administrative Amendment #03)
8.2.2	• Update method(s) for collected temperature	• Based on clinical site standard practice (Administrative Amendment #02)
10.6 Appendix 6: CRS Toxicity Treatment Guidelines	• Clarify CRS toxicity treatment guidelines	• For clarity (File Note dated 11 February 2022)
General	• Correct typographical errors, hyperlinks/cross-references, style, and formatting (not tracked) • Align across protocol sections • Update protocol section numbering • Update footer with version and date	• For consistency and clarity • Alignment across protocol

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