PROTOCOL

Study Title	A Phase I/II Multicenter Study Evaluating the Safety and Efficacy of Allogeneic GDA-201 Natural Killer Cells in Patients with Relapsed/Refractory B Cell Non-Hodgkin Lymphoma
Brief Title	Evaluation of Safety and Efficacy of GDA-201 NK Cells in Patients With Relapsed/Refractory B Cell NHL
Clinical Phase	Phase I/II
Product	GDA-201
IND Number	[redacted]
EU Trial Number	2023-503432-41-00
Sponsor	Gamida Cell Ltd. Beit Ofer 5 Nahum Hafzadi Jerusalem 9548401 Israel Tel: 972-2-6595666 Medical Director Roei Mazor, M.D., PhD
Protocol No.	GC P#01.01.050
Amendment	# II
Dated	May 02, 2023

This clinical study will be conducted in accordance with the Sponsor's Standard Operating Procedures (SOPs), this protocol, current Good Clinical Practice (GCP), the Declaration of Helsinki, the provisions of International Conference on Harmonization (ICH) Guidelines, Regulation (EU) No 536/2014 and all local applicable laws and regulations.

CONFIDENTIAL

The information in this document is considered privileged and confidential and may not be disclosed to others except to the extent necessary to obtain Institutional Review Board (IRB)/ Ethics Committee (EC) approval, written informed consent and the approval of local regulatory authorities as required by local law.

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LIST OF ABBREVIATIONS

aGvHD	acute graft-versus-host disease
ACT	adoptive cell therapy
ADC	Antibody-Drug Conjugate
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
BITE	Bispecific T cell Engager
CAR-T	chimeric antigen receptor modified T-cells
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CR	complete response
CRu	complete response/unconfirmed
CSF	cerebrospinal fluid
CT	computed tomography
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DM	diabetes mellitus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose-positron emission tomography
FFPE	Formalin-Fixed Paraffin-Embedded
FL	follicular lymphoma
GCP	good clinical practice
GTD	greatest transverse diameter
GvHD	graft-versus-host disease
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HGBCL	high-grade B-cell lymphoma
HGBCL NOS	high-grade B-cell lymphoma not otherwise specified
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplantation
IDSA	Infectious Diseases Society of America
IRB	institutional review board
IEC	independent ethics committee

ICF	informed consent form
IV	intravenous
LD	lymphodepletion
LN	lymph nodes
mAb	monoclonal antibody
MM	Multiple myeloma
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NAM	nicotinamide
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
NK	natural killer
ORR	overall response rate
PMBCL	primary mediastinal B-cell lymphoma
PD	progressive disease
PET	positron emission tomography
PK	pharmacokinetics
PR	partial response
PT	preferred term
RCT	randomized clinical trial
RP2D	recommended phase II dose
SAE	serious adverse event
SC	Subcutaneous/subcutaneously
SD	stable disease
SLL	small lymphocytic lymphoma
SOC	system organ class
SOE	schedule of events
SPD	sum products of the greatest diameters
SSC	study steering committee
TBili	total bilirubin
ULN	upper limit of normal
UTI	urinary tract infection
WBC	white blood cell

SPONSOR PROTOCOL APPROVAL PAGE

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Clinical Phase	Phase I/II
Protocol Number:	GC P#01.01.050
Amendment Number:	Amendment II
Dated:	May 02, 2023

Approved by:

Medical Director

[redacted]

_____ _____

Signature Date

INVESTIGATOR'S AGREEMENT

Protocol Title: A Phase I/II Multicenter Study Evaluating the Safety and Efficacy of Allogeneic GDA-201 Natural Killer Cells in Patients with Relapsed/Refractory B Cell Non-Hodgkin Lymphoma

Clinical Phase: Phase I/II

Protocol Number: GC P#01.01.050

Amendment Number: Amendment II

Dated: May 02, 2023

I have carefully read the foregoing protocol including all appendices and agree that it contains all the necessary information for conducting the study safely.

I will conduct this study in strict accordance with this protocol and according to the current Good Clinical Practice (GCP) regulations and will attempt to complete the study within the time designated.

I will provide copies of the protocol and all other information relating to pre-clinical and prior clinical experience submitted by the sponsor to all personnel responsible to me who participate in the study. I will discuss this information with them to ensure that they are adequately informed regarding the drug and conduct of the study.

I agree to keep records on all patient information (CRFs, shipment, and all other information collected during the study) in accordance with the current GCP and local regulations.

Principal Investigator's Name	
Signature	
Date	
Institution	

1. STUDY SYNOPSIS

Protocol Number	GC P#01.01.050
Protocol Title	A Phase I/II Multicenter Study Evaluating the Safety and Efficacy of Allogeneic GDA-201 Natural Killer Cells in Patients with Relapsed/Refractory B Cell Non-Hodgkin Lymphoma
Brief Title	Evaluation of Safety and Efficacy of GDA-201 NK Cells in Patients With Relapsed/Refractory B Cell NHL
Principal Investigator:	
Sponsor:	**Gamida Cell** Beit Ofer, 5 Nahum Hafzadi Givat Shaul, Jerusalem, 9548401 Israel
IND Number:	[redacted]
EU Trial Number	**2023-503432-41-00**
Number of Centers	Multicenter (Phase I in US; Phase II in US, Israel, and Europe)
Clinical Phase	Phase I/II
Investigational Product	GDA-201 is an allogeneic cryopreserved natural killer (NK) cell-based therapy derived from donor peripheral blood
Study Duration	Total study duration for individual patients is approximately 13 months from the signing of informed consent to the last visit (one year following the first GDA-201 infusion). The study ends when all patients have completed their last follow-up. Patients who enroll in the long-term follow up sub-study will be followed for an additional 5 years, up to 6 years following the initial GDA-201 infusion.
Study Objectives	The overall study objective is to evaluate the safety and efficacy of cryopreserved, allogeneic GDA-201 in patients with relapsed/refractory B Cell Non-Hodgkin Lymphoma (NHL). Phase I objectives: • Assess the safety of GDA-201 + rituximab as determined by dose limiting toxicities • Determine the maximum tolerated dose (MTD), to be applied as the recommended Phase II dose (RP2D) Phase II objectives:

	• Assess the safety and efficacy of GDA-201 in separate cohorts of patients with follicular lymphoma (FL), or diffuse large B-cell lymphoma (DLBCL) and High grade B cell lymphoma (HGBCL)
Primary Study Endpoints	Primary endpoint- Phase I: • dose-limiting toxicity (DLT) and safety of GDA-201 Primary endpoint: Phase II: • Overall response rate (ORR)
Secondary and Exploratory Study Endpoints	Secondary endpoints: Phase I: • ORR Secondary endpoints: Phase II: • ORR Independent Radiological Review Committee (IRRC) • Duration of response (DOR) (Investigator Assessment) • Progression free survival (PFS) (Investigator Assessment) • Overall survival (OS) (Investigator Assessment) • Safety and tolerability (Investigator Assessment) Exploratory Endpoints [redacted]
Study Hypothesis	Infusion of GDA-201 in patients with relapsed/refractory NHL will be safe and provide a disease response.
Number of Patients	A maximum of 99 patients will be treated as follows: 12-36 patients in the Phase I portion 63 patients (32 in FL cohort and 31 in DLBCL/HGBCL cohort) in the Phase II portion
Inclusion Criteria	1. Patients must have relapsed/refractory FL or DLBCL/HGBCL that has failed conventional therapy defined as follows (for the Phase I dose escalation: patients with marginal zone lymphoma or mantle cell lymphoma are also eligible): a. Lymphoma characterized by current and/or historical expression of CD20 as determined by flow cytometry or immunohistochemistry. b. Received at least 2 prior lines of therapy (at least one of which contained chemotherapy and at least one of which contained an anti-CD20 monoclonal antibody (mAb)).

c. Transplant ineligible patients allowed assuming they meet criterion b.

d. Patients who failed prior chimeric antigen receptor modified T cells (CAR-T) cell therapy or are considered ineligible for CAR-T therapy per the Investigator's discretion are eligible.

e. FL transformed to DLBCL/HGBCL: Must have received at least 1 line of therapy after transformation to DLBCL/HGBCL

2. Patients must have measurable disease as defined by the Lugano response criteria (Cheson et al. 2014) as determined by study investigators. Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy. Baseline disease assessment must be performed after completion of the last line of therapy.
3. Patients must be at least 18 years of age. In Dose level 1 patients must be at least 75 kg.
4. Patients must have Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
5. Patients must have adequate hematologic, hepatic, renal, cardiac and pulmonary function prior to any study treatment defined as:
   a. Absolute neutrophil count (ANC) ≥ 1000/μL
   b. Platelet count ≥ 50,000/μL
   c. Creatinine ≤ 1.5 mg/dL or creatinine clearance ≥50 mL/min
   d. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤ 3 x upper limit of normal (ULN)
   e. Total bilirubin (TBili) ≤ 1.5 x ULN unless patient with a history of Gilbert's syndrome
   f. Cardiac ejection fraction ≥ 45%, no evidence of pericardial effusion as determined by an echocardiography
   g. Baseline oxygen saturation > 92% on room air
   h. No clinically significant pleural effusion

If organ dysfunction is due to lymphoma involvement and not due to prior toxicities the following laboratory parameters are permitted:

   a. Platelet count ≥ 30,000 if due to hypersplenism or disease involvement in marrow
   b. TBili ≤ 3 x ULN if due to hepatic disease involvement
   c. Growth factors are permitted to meet required ANC if cytopenia is due to marrow disease involvement

6. No Class II or greater New York Heart Association Functional Classification criteria (Appendix A) or serious cardiac arrhythmias likely to increase the risk of cardiac complications of cytokine therapy (e.g. ventricular tachycardia, frequent ventricular ectopy, or supraventricular tachyarrhythmia requiring chronic therapy)

	7. Patients must be able to be off systemic corticosteroids (with the exception of physiological steroid replacement therapy) and other immunosuppressive drugs for at least 5 half-lives prior to GDA-201 infusion and up until day 14 post GDA-201 infusion (excluding preparative regimen pre-medications), unless approved by the sponsor. 8. Patients after allogeneic Hematopoietic Stem Cell Transplantation (HSCT) are eligible if they are at least 6 months after the transplant and off all immunosuppressive drugs . 9. Patients after allogeneic HSCT or any other allogeneic cell therapy are eligible without evidence of active Graft-versus-Host Disease (GvHD). 10. No evidence of ongoing neurotoxicity or cytokine release syndrome from prior therapies 11. Sexually active females of childbearing potential and males with partners of childbearing potential must agree to use effective contraception from the time of screening pregnancy test and for at least 4 months after completion of therapy 12. Patient signs the written informed consent after being aware of the nature of the patient's disease and willingly consents to the treatment program after being informed of alternative treatments, potential risks, benefits, and discomforts
Exclusion Criteria	1. Pregnancy, as indicated by a positive serum or urine human chorionic gonadotrophin (HCG) test, or lactation 2. Active bacterial, fungal, or viral infection that is uncontrolled or requiring systemic antimicrobials for management. Simple urinary tract infection (UTI) and uncomplicated bacterial pharyngitis are permitted if responding to active treatment 3. HIV infection not controlled on therapy, and/or with active viremia (HIV viral load needs to be undetectable), or AIDS defining illnesses. 4. History of acute or chronic active hepatitis B or C infection not documented to be cleared per current Infectious Diseases Society of America (IDSA) guidelines (see Appendix B). Patients at risk for reactivation of HBV infection must be on prophylactic anti-HBV antiviral therapy 5. Patients with active autoimmune disease requiring immunosuppressive therapy. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone and patients with controlled type 1 diabetes mellitus (DM) on a stable insulin regimen may be eligible for this study. 6. History of severe asthma and currently treated with chronic asthma medications (a history of mild asthma requiring inhaled steroids only is eligible) 7. Live vaccine <6 weeks prior to start of therapy 8. Patient with detectable cerebrospinal fluid (CSF) malignant cells, or brain metastases, or with a history of central nervous system (CNS) lymphoma or primary CNS lymphoma, CSF malignant cells or brain

	metastases. Patients with a history of CNS involvement can be included if cleared by magnetic resonance imaging (MRI) and CSF for at least 6 months 9. History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (e.g. cervix, bladder, breast, prostate) unless disease free for at least 2 years 10. Presence of any indwelling line or drain (e.g., percutaneous nephrostomy tube, indwelling foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Dedicated central venous access catheters such as a Port-a-Cath or Hickman catheter are permitted 11. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis per chest imaging at screening. History of radiation pneumonitis in the radiation field (fibrosis) is allowed 12. Known hypersensitivity to any of the study treatments, gentamycin, albumin, DMSO or any other GDA-201 excipient Note: Infusion reactions with rituximab are common. Patients with a history of infusion reactions to rituximab that can be managed with recommended pre-medications should not be excluded 13. Time between previous treatment and first dose of study treatment (rituximab): a. Allogeneic HSCT < 6 months prior to study treatment b. ASCT < 3 months prior to study treatment c. CAR-T < 2 months prior to study treatment d. Major surgery or chemotherapy < 4 weeks prior to study treatment (6 weeks for melphalan) e. Radiation therapy < 2 weeks prior to study treatment f. Monoclonal antibodies including checkpoint blockade < 2 weeks prior to study treatment (does not apply to rituximab). g. Antibody-Drug Conjugates (ADCs) including polatuzumab vedotin and loncastuximab tesirine < 4 weeks prior to study treatment, unless approved by the sponsor h. Targeted therapies, Bispecific T cell Engagers (BiTEs), small molecule inhibitors or any investigational therapy within 5 half-lives of the drug, unless approved by the sponsor
Study Design	This is an open-label, non-randomized, interventional, single group assignment study of GDA-201, an allogeneic cryopreserved NK cell therapy derived from donor peripheral blood, in combination with rituximab, monoclonal anti-CD20 antibody, for patients with relapsed or refractory B Cell non-Hodgkin lymphoma (NHL). Lymphoma characterized by current and/or historical expression of CD20 as determined by flow cytometry or immunohistochemistry.

	The study is divided into a phase I dose escalation phase and a phase II expansion phase. Patients with relapsed or refractory FL or DLBCL/HGBCL (for the Phase I dose escalation: patients with marginal zone lymphoma or mantle cell lymphoma are also eligible) will receive GDA-201 followed by a short course of low-dose interleukin-2 (IL-2). Rituximab will be administered prior to and after GDA-201 infusion <u>Phase I: Dose escalation phase</u> The objective of Phase I is to evaluate the safety of GDA-201 in patients with follicular lymphoma (FL), diffuse large B-cell lymphoma/high grade B-cell lymphoma (DLBCL/HGBCL), marginal zone lymphoma or mantle cell lymphoma. The maximal tolerated dose (MTD) Recommended Phase II Dose (RP2D) will be determined based on dose limiting toxicities (DLT). The starting dose will be 2.5 x 10^7 cells/kg. Patients within each cohort will be assessed for DLTs, and enrollment in each cohort will continue to occur sequentially until a MTD is reached. DLTs are defined as one of the following within the first 28 days of the first dose of GDA-201, as assessed by CTCAE v 5.0. Acute GvHD is assessed according to the Consensus Conference on Acute GvHD grading (Przepiorka et al. 1995): • Steroid refractory Grade II acute GvHD • Grade III or IV acute GvHD • Grade 4 infusion reaction • Grade 4 or 5 related adverse event (AE) • Grade 3 or above cardiac, central nervous system or pulmonary adverse event • Any Grade 3 or above non-hematologic adverse event that does not resolve to Grade 2 or below within 72 hours, with the exception of renal or hepatic adverse events which may take up to 7 days to resolve • Treatment emergent ≥Grade 3 autoimmune disorder • Grade 3 or above allergic reaction that does not recover to Grade 2 or below within 24 hours • Grade 4 cytopenia lasting beyond Day 42 (the 28-day DLT observation period will be extended to confirm). The first 3 patients enrolled at each dose level will be staggered to allow monitoring of each patient for DLTs for 28 days following the first GDA-201 infusion. Thus, patients may be added to each dose level cohort after the preceding patient in the cohort has been observed for a minimum of 28 days. Dose escalation to the subsequent level can occur following discussion with the

Study Steering Committee (SSC) after the last patient on the current cohort has been observed a minimum of 28 days.

Dosing Cohorts

Dose Level	Dose*
1	$2.5x10^7$ cells/kg
2	$5x10^7$ cells/kg
3	$1x10^8$ cells/kg
4	$2x10^8$ cells/kg

*Based on dosing tables for GDA-201 product bags, allowing a maximal deviation of 33% from the intended dose.

Phase II expansion phase

The objective of the Phase II expansion cohort is to evaluate the safety and efficacy of GDA-201 in two patient cohorts, FL and DLBCL/HGBCL.

<table>
<tr><td>Study Treatments</td><td>The following table summarizes the overall treatment regimen.

<table><tr><th>Component</th><th>Dose</th><th>Days</th></tr><tr><td>Rituximab</td><td>[redacted]</td><td>-10, -3, +14*</td></tr><tr><td>Lymphodepletion (LD)</td><td>[redacted]</td><td>-5, -4, -3</td></tr><tr><td>GDA-201</td><td>[redacted]</td><td>0, +2</td></tr><tr><td>Interleukin-2</td><td>[redacted]</td><td>0, +2, +4.</td></tr></table>* The last rituximab dose may be administered +/- 2 days</td></tr>
<tr><td>Statistical Considerations</td><td><u>Design and Sample size considerations:</u>

The Phase I portion of the study is a conventional 3 + 3 design with four sequential dose cohorts. The first cohort will start at the 2.5x 10^7 cells/kg dose level. If all cohorts are completed, 24 patients will have been treated with a maximum of 6 patients per cohort. The goal is to determine the recommended phase II dose (RP2D) during the phase I portion of the study. Phase I patients who are not evaluable for DLT may be replaced.

At the discretion of the study sponsor, after the dose escalation phase across the four dose levels is complete, up to an additional 12 patients may be treated to further characterize the DLT and safety profiles by histology (follicular lymphoma or DLBCL/HGBCL) at one or two dose levels prior to the phase II expansion. This will be designated as “backfilling” a cohort in order to ensure that the cohort enrolls a minimum of 3 patients per histology. With the addition of the additional patients enrolled in backfilled cohorts, the MTD and/or RP2D may be determined. The RP2D may be different by histology (follicular lymphoma or DLBCL/HGBCL).

For each cohort in the Phase II portion of the study, a Simon’s optimal 2-stage design will be employed based on the ORR (CR or PR) endpoint.
• In the FL cohort, 11 patients will be enrolled in the first stage. If ≥3 patients achieve ORR, it will continue to enroll an additional 21 patients in the second stage for a total of 32 patients in the cohort. At the end of stage 2, if ≥10 out of the 32 patients achieve ORR, it is considered promising for further evaluation. This design has 80% power to test the null hypothesis of 20% response rate against the alternative hypothesis of 40% with a 1-sided type 1 error rate not exceeding 0.075
• In the DLBCL/HGBCL cohort, 14 patients will be enrolled in the first stage. If ≥3 patients achieve ORR, it will continue to enroll an additional 17 patients in the second stage for a total of 31 patients in the cohort. At the end of</td></tr>
</table>

stage 2, if ≥8 out of the 31 patients achieve ORR, it is considered promising for further evaluation. This design has 80% power to test the null hypothesis of 15% response rate against the alternative hypothesis of 33% with a 1-sided type 1 error rate not exceeding 0.075

Phase II patients who are not evaluable for response may be replaced. Patients who have at least one efficacy evaluation following GDA-201 infusion will be considered evaluable for response.

Safety Analysis

The data emerging from this study will be reviewed periodically by the SSC and recommendations will be provided to the sponsor.

Ongoing safety assessment guidelines will be used to monitor the following events, and alert the SSC. A safety alert will be triggered if one of the following criteria is met:

1. Any death not related to disease progression
2. Grade 4 or above cardiac, CNS or pulmonary DLT in 2 subjects, that is at least possibly related to GDA-201
3. Any DLT occurring in Dose level 1
4. Grade 5 adverse event that is probably or directly related to GDA-201
5. Grade III-IV acute GvHD crossing the thresholds based on a Bayesian continuous monitoring model detailed in 12.6.

If an alert occurs, accrual to the study will be temporarily halted. The SSC will consider the data in depth and make recommendations to the sponsor.

All adverse events (AEs) will be coded to a system organ class (SOC) and a preferred term (PT) based on the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or later.

Patient incidence of all adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation of treatment, and fatal AEs will be tabulated by SOC and PT.

The number and percent of patients reporting AEs will be evaluated overall and by dose level and will also be tabulated by severity and relationship to study treatment. The severity of each AE will be graded using The Common Terminology Criteria for Adverse Events (CTCAE) v 5.0 or later criteria.

For the Phase I portion of the study, DLTs (if any) will be summarized by dose and will be listed separately.

Changes in laboratory values and vital signs will be summarized with descriptive statistics. Use of concomitant medications, levels of GDA-201 cells in blood and incidence of anti-HLA antibodies will also be summarized.

Efficacy Analysis

	The primary analysis for efficacy will be based on the cohort-specific efficacy evaluable analysis population. Sensitivity analyses may include pooling additional patients treated in phase I at the same dose level. The ORR endpoint is defined as the incidence of either a complete response or a partial response (PR) by the Lugano response criteria as determined by the study investigators. All patients that do not meet the criteria for an objective response by the analysis cutoff date will be considered non-responders. For the ORR endpoint, the Clopper-Pearson 85% and 95% confidence intervals (CIs) will be calculated. Confidence intervals adjusting for the 2-stage nature of the design may also be provided. Duration of response (DoR) will be calculated among responders (CR and PR). The Kaplan-Meier method will be used to estimate median DoR and the confidence intervals. Patients who continue to respond at the time of the analysis will be censored at the last assessment of response. Progression-free survival (PFS) is measured from the date of first GDA-201 dose until the date when progressive disease (PD) is first observed per the Lugano response criteria as determined by the study investigators, or death from any cause, whichever is earlier. Patients without PD or death will be censored at the last available tumor assessment. PFS will be summarized using the Kaplan-Meier method. Overall survival (OS) is measured from the date of first GDA-201 dose until death. Patients who are alive will be censored at the last known alive date. OS will be summarized using the Kaplan-Meier method. Sensitivity analyses of the ORR and PFS based on the assessments by the IRRC will also be provided.
Role of Study Steering Committee (SSC)	The SSC will provide oversight of the study. Recommendations of the SSC will be based on an ongoing assessment on the safety and efficacy of the treatment regimen. Based on those assessments the SSC may make any of the following recommendations: • Dose escalation to the next cohort • Add patients to the current cohort • Dose modification • Determination of the MTD • Proceed from Phase I to Phase II of the study • Proceed to Stage II in each cohort of the Phase II • Stop enrollment for one or both cohorts Additional roles for the SSC include recommendations for: • Modifying or removing LD for all patients or for one cohort • Safety monitoring throughout the study

Figure 1: Study Design Schema

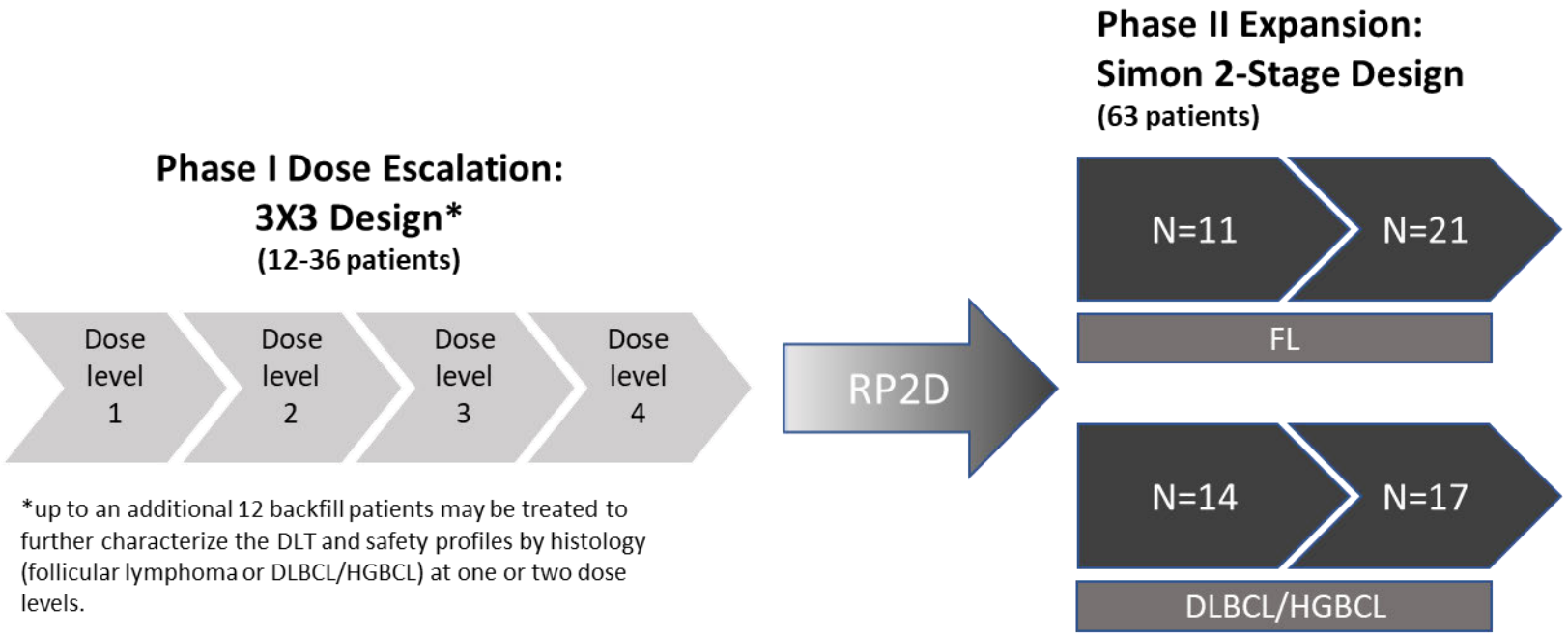


Figure 2: Patient Treatment & Follow-up Schema

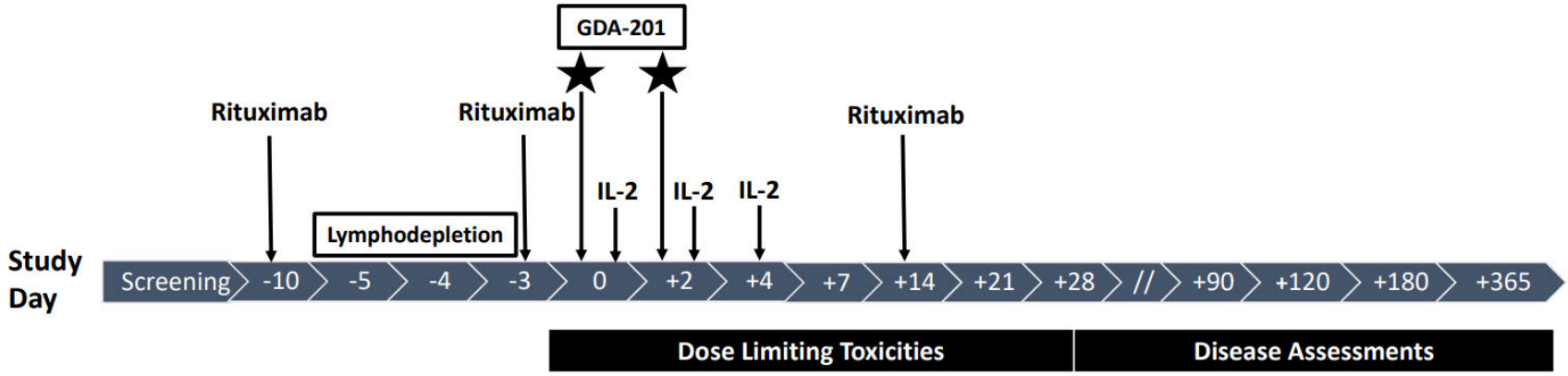


Table 1: Schedule of Events

		Days Pre/Post GDA-201 Infusion																		
	Screening (within 28 days prior to study treatment on Day -10)	-10	-5	-4	-3	0	2	4	7 ±1	14 ±2	21 ±2	28 ±2	42 ±4	56 ±4	70 ±4	90 ±7	120 ±14	180 ±14	270 ±14	365 ±14
Written Informed Consent[1]	x																			
Eligibility Criteria[2]	x																			
Medical History	x[21]																			
Disease Assessment	x											x				x		x		x
Positron emission tomography (PET)/CT[3]	x[4]											x				x		x		x
Tumor biopsy[10]	x[24]																			
Physical Examination[5]	x	x	x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
AE assessment		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Weight	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Height	x																			
Vital signs[6]	x	x	x	x	x	x[9]	x[9]	x	x	x	x	x	x	x	x	x	x	x	x	x
ECOG performance status	x	x	x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Previous cancer treatment history	x																			
Concomitant medications[7]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hematology (CBC differential)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry[8]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
B2 microglobulin	x											x	x	x	x	x	x	x	x	x
Ferritin		x				x			x	x	x									x
Allelic level HLA Typing (HLA-A, B, C, DRB1)	x																			
GDA-201 Central Laboratory Sampling[20]		x				x	x	x	x	x		x				x				

		Days Pre/Post GDA-201 Infusion																		
	Screening (within 28 days prior to study treatment on Day -10)	-10	-5	-4	-3	0	2	4	7 ±1	14 ±2	21 ±2	28 ±2	42 ±4	56 ±4	70 ±4	90 ±7	120 ±14	180 ±14	270 ±14	365 ±14
Anti-donor HLA testing[11]	x													x		x				
CRP		x				x			x	x	x									
Serum or urine beta HCG (females) [12]	x	x[23]																		
GvHD Assessment	x[13]								x	x	x	x				x		x		x
Electrocardiogram (ECG)	x					x[17]	x[17]	x[17]												
Echocardiogram (ECHO)	x[14]																			
Bone marrow biopsy or aspirate (if previously positive)	x[15]															x[15]				
Lymphodepletion (LD)[16] Cyclophosphamide Fludarabine			x	x	x															
GDA-201[18]						x	x[22]													
Rituximab		x			x					x[19]										
IL-2						x	x	x												

[1] Signed consent is required prior to performing any protocol specific tests, procedures or treatments that are not part of the standard site practice. The ICF signature can be obtained earlier than 28 days prior to study treatment

[2] All eligibility criteria must be met before LD commences

[3] If the PET-CT is not of high resolution for accurate disease assessment, the scan must be repeated within 7 days

[4] Baseline PET CT of the neck, chest, abdomen and pelvis: PET-CT performed following the patient's last line of therapy and prior to signing the consent may be used for confirmation of eligibility. If PET CT is performed > 28 days prior to the initiation of study treatments or if patient receives any anti-cancer therapy between screening and LD chemotherapy, the PET-CT scan must be repeated to establish a new baseline. PET CT should be performed as close to enrollment as possible

[5] Lumbar puncture and cerebrospinal fluid (CSF) examination only for patients with new or suspicious neurological findings suggestive of CNS involvement, as deemed clinically appropriate by the investigator.

[6] Vital signs including blood pressure, heart rate, oxygen saturation, and temperature

[7] Including any cancer treatments, if applicable

[8] Blood chemistry must include (at a minimum): serum creatinine, TBili, alkaline phosphatase, AST, ALT, LDH and magnesium

[9] Including respiratory rate assessment on Days 0 and 2

[10] Tumor biopsy is mandatory within 4 months prior to study treatment. A biopsy performed more than 4 months prior to study treatment can be approved at the sponsor's discretion. Tumor biopsy is not mandatory if it is prohibitive from a patient safety perspective, per investigator discretion.
[11] Anti-donor HLA testing for phase I patients only
[12] β-HCG pregnancy test (serum or urine) on all women of child-bearing potential
[13] For patients after any allogeneic cell therapy or HSCT
[14] An ECHO performed following the patient's last chemotherapy treatment or cellular therapy and within 28 days prior to signing the consent may be used for confirmation of eligibility
[15] As clinically indicated
[16] Before LD commences, the criteria in Section 6.2.4 (LD) must be met. If these criteria are not met, then conditioning LD must be delayed until these events are resolved
[17] ECG should be obtained prior to IL-2 administration
[18] Before GDA-201 infusion commences, the criteria in Section 6.2.2 (Investigational product treatment) must be met. If these criteria are not met, then GDA-201 infusion must be delayed until these events are resolved
[19] Rituximab may be administered +/- 2 days
[20] Blood draws for GDA-201 central laboratory assays [redacted] needs to be taken at the beginning of the study visit, before the administration of any medications, study drugs, etc.
[21] Any event after written informed consent has been obtained and prior to study treatment initiation should be recorded as medical history unless the event is directly related to a screening procedure, in such case it would be considered an AE/SAE and documented on the AE/SAE eCRF.
[22] The second infusion day may not be required based on dose and subject's weight.
[23] Serum or Urine beta HCG to be done and results should be obtained before rituximab is given to the patient.
[24] Optional for patients who consent for this assessment: [redacted], see section 7.1.7.

2. INTRODUCTION

2.1. Overview

2.1.1. Non-Hodgkin Lymphoma

Non-Hodgkin Lymphomas (NHL) are a heterogeneous group of lymphoproliferative disorders originating in B-lymphocytes. T-lymphocytes or natural killer (NK) cells (NK/T-cell lymphomas are very rare). In 2022 an estimated 80,470 people were diagnosed with NHL in the US and there were approximately 20,250 deaths due to the disease. NHL is the seventh leading cause of new cancers cases among men and women, accounting for 4.2% of new cancer cases and 3.3% of cancer-related deaths (Siegel et al. 2022). In prospectively collected data from the National Cancer Database, diffuse large B-cell lymphoma (DLBCL; 32%), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL; 19%), follicular lymphoma (FL; 17%), marginal zone lymphoma (MZL;8%), mantle cell lymphoma (MCL; 4%) and peripheral T-cell lymphoma not otherwise specified (PTCL-NOS; 2%) were the major subtypes of NHL diagnosed in the United States between 1998 and 2011(Al-Hamadani et al. 2015)(Al-Hamadani et al. 2015).

The incidence of NHL increased dramatically between 1970 and 1995 and has moderated since the mid1990s. Much of this increase has been attributed to the human immunodeficiency virus (HIV) epidemic and the development of acquired immunodeficiency virus (AIDS) related NHL. However, much of the increase in incidence has been observed in patients in their sixth and seventh decades and has paralleled a major decrease in mortality from other causes. The median age of individuals with NHL has risen in the last two decades(Groves et al. 2000)(Groves et al. 2000).

Patients with NHL commonly receive chemoimmunotherapy as initial treatment, and radiation therapy may be added if patients have early-stage disease. Most patients respond well to treatment, but relapses are frequent and additional therapies including stem cell transplant are often needed.

2.1.1.1. Treatment of Diffuse Large B-cell Lymphoma / High Grade-cell Non-Hodgkin Lymphoma (DLBCL/HGBCL)

The standard approach for patients with advanced-stage DLBCL/HGBCL is treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy . This approach is supported by randomized controlled trials in patients both older and younger than 60 years. The addition of rituximab to CHOP chemotherapy improved both event-free and overall survival compared with CHOP chemotherapy alone (Feugier et al. 2005; Habermann et al. 2006). For patients who do not respond to first-line therapy, high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) represents a second option for cure(NationalComprehensiveCancerNetwork. 2020; Tilly et al. 2015). However, for patients who either relapse after or are not eligible for SCT due to refractory disease or frailty, treatment outcomes are poor (Crump et al. 2017). Furthermore, even if some patients are eligible for transplant, very few actually benefit from this treatment (Crump et al. 2017). Response rates to subsequent therapies range from 10–35% in most cases (Crump et al. 2017; Coleman et al. 2008; Wiernik et al. 2008; Wang et al. 2019). In an international, multicohort

retrospective non-Hodgkin lymphoma (NHL) research study that retrospectively evaluated outcomes in patients with refractory DLBCL (SCHOLAR-1)(Crump et al. 2017), it was found that for patients with refractory DLBCL, the objective response rate was 26% (CR rate, 7%) to the next line of therapy, and the median overall survival was 6.3 months. Taken as a whole these outcomes confirm the need for novel treatments for relapsed/refractory DLBCL.

More recently, axicabtagene ciloleucil, tisagenleucel and lisocabtagene maraleuce anti-CD19 CAR-T cell therapies have been approved by Food and Drug Administration (FDA) for the treatment of adult patients with relapsed refractory DLBCL, high-grade B-cell lymphoma (HGBL) and transformed FL. In 3 multicenter trials CAR-T treatment of aggressive B-cell lymphomas resulted in an overall response rate (ORR) of 59%-84% and CR rates of 43%- 61%. (Neelapu et al. 2017; Schuster S 2017; Abramson J 2017)(Neelapu et al. 2017; Schuster S 2017; Abramson J 2017)Despite these encouraging results the toxicities related to CAR-T cell therapy remain a significant problem. There are two main categories of toxicity: cytokine release syndrome (CRS) and neurotoxicity, which can be accompanied by organ damage (renal failure, cardiac dysfunction, liver dysfunction, etc.). The vast majority of CAR-T cell related toxicities resolve within a few weeks, but these potential complications can be life threatening and, in certain circumstances, lead to death(Brudno and Kochenderfer 2016; Neelapu et al. 2018; Lee et al. 2014)(Brudno and Kochenderfer 2016; Neelapu et al. 2018; Lee et al. 2014).

2.1.1.2. Treatment of Follicular (FL) Non-Hodgkin Lymphoma

The anti-CD20 antibody rituximab has changed the management of FL, and there has been an overall improvement in the survival of patients with FL since the incorporation of rituximab into treatment of this disease (Fisher et al. 2005). Rituximab as a single agent has been compared with watchful waiting in patients with low disease burden and has been found to be associated with improved progression-free survival as well as improved quality of life (Ardeshna et al. 2014). Overall, asymptomatic patients are commonly observed, while patients with a low burden of disease or modest symptoms are treated with rituximab, often with a maintenance strategy after initial dosing has been completed.

Allogeneic stem cell transplant is sometimes considered for patients with FL as part of frontline treatment. Although this approach may potentially lead to a cure for a subset of patients, the significant treatment-related mortality associated with this approach commonly results in this modality being utilized in patients with relapse.

Approximately 20% of patients with FL progress within the first 24 months after first-line therapy with R-CHOP. Relapse within 24 months is predictive for shorter OS. However, many of these cases have primary refractory disease or transformed histology. For example, the PRIMA study found among patients with histopathologically confirmed relapse 20% with histologic transformation.

Not all relapses need to be automatically, immediately treated unless there is evidence of a high tumor burden(Brice et al. 1997; Ardeshna et al. 2003). Widely used regimens are single-agent rituximab, R-CHOP, RCVP (Rituximab, Cyclophosphamide, Vincristine and Prednisolone), RFM (Rituximab, Fludarabine, and Mitoxantrone), or BR (Bendamustine and Rituximab) depending on the 1st-line therapy and duration of response after initial treatment. Patients with relapse occurring after 24 months of last treatment have favorable outcome and can be re-challenged with the initial protocol. Radiation is also an option in selected patients with localized relapse.

Obinutuzumab plus bendamustine has recently been approved as another option for rituximab-refractory patients. The phase III GADOLIN study randomized 396 patients to either six cycles of obinutuzumab with bendamustine followed by obinutuzumab maintenance for 2 years or bendamustine alone. The median event-free survival was significantly better with obinutuzumab (26.8 vs 13.2 months) (Sehn et al. 2016). With extended follow-up, recently updated results of the study showed significant improvement of OS (median OS not reached vs 53.9 months; HR 0.67) in favor of obinutuzumab(Cheson et al. 2018)(Cheson et al. 2018).

CAR-T therapy has been investigated in indolent lymphomas as well. A study with 14 relapsed/refractory patients with FL demonstrated CR in 10/14 (71%). Of note, 89% of responding patients had maintained the response after median follow-up time of 2.5 years(Schuster et al. 2017). More recently Novartis reported a positive Phase 2 in August 2020 of Kymriah in R/R FL. Yescarta (Gilead) was approved for FL in March 2021.

2.1.1.3. Salvage Therapies for DLBCL/HGBCL and FL

Taken as a whole, while there are a number of therapeutic options available for patients with FL and DLBCL/HGBCL the prognosis of patients with relapsed/refractory NHL who are not eligible for high dose chemotherapy and autologous stem cell transplantation (ASCT) is poor, and relapse after ASCT portends an even worse prognosis(Tonn et al. 2013; Childs and Berg 2013)(Tonn et al. 2013; Childs and Berg 2013). The addition of rituximab to standard salvage regimens such as ICE (Ifosfamide, Carboplatin and Etoposide) or DHAP (Dexamethasone, High dose Cytarabine and Cisplatin) significantly increases responses; however, the responses are lower in patients who have already received rituximab as a part of their initial regimen. Conventional salvage regimens generally result in substantial morbidity, especially in patients over the age of 60 years and the goals of those treatments is usually palliative. There is therefore a need for alternative therapies that can provide durable responses without the attendant toxicities of current approved regimens.

2.2. Gamida Cell Nicotinamide (NAM) Technology

2.2.1. Background to NK Cells

NK cells, defined by the cell surface marker phenotype CD3-/CD56+, play a critical role in immunosurveillance and immune activation against abnormal cells. Unlike T cell activation, NK cells do not require the prior sensitization to a specific tumor antigen for the recognition and killing of malignant cells. Upon activation, NK cells have the ability to induce tumor apoptosis and are also essential in modulating adaptive immune responses through production of chemokines and cytokines such as interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α). Due to their innate ability to eliminate tumor cells, infusion of NK cells represents an attractive approach to immunotherapeutic treatment of patients with cancers. Moreover, specialized tumor specific antibodies can bind with high affinity specific targets on tumor and NK cells simultaneously, bringing them in close proximity, and facilitate triggering of the killing cascade. Therefore, NK cell therapies can also provide a platform for antibody-dependent cellular cytotoxicity (ADCC), for broad applicability and efficient treatment of refractory tumors.

Despite preliminary evidence of NK cell activity demonstrated in some patients with leukemia, clinical results with previous NK therapies have been disappointing. The insufficient numbers of NK cells among peripheral blood mononuclear cells (PBMCs) and the limited ability of

adoptively transferred NK cells to proliferate *in vivo*, as well as to home to, and be retained in the tumor microenvironment, likely plays a role in their limited efficacy to date. Proliferation of NK cells in culture using human serum and stimulating cytokines (IL-2, IL-15, IL-21) has been well documented in the scientific literature. However, most reports show a modest increase in number of cells and demonstrate a need for additional stimuli for proliferation(Childs and Carlsten 2015).

An important challenge, therefore, in advancing the clinical application of NK cells is to deliver an appropriate dose of cells that will display increased homing, retention and proliferation activities upon *in vivo* infusion, while maintaining their cytotoxic capacity.killing activity(Childs and Carlsten 2015).

2.2.2. Nicotinamide (NAM) based technology

NAM is a nicotinamide adenine dinucleotide (NAD) precursor, inhibitor of NAD-consuming enzymes, which can balance NAD catabolism. As such, NAM is a master regulator of NAD-related signaling pathways, NAD-dependent metabolic pathways, histone acetylation and ribosylation. It also modulates energetic response pathways, energy homeostasis, resistance to cellular stress and maintenance of mitochondrial membrane potential(Son et al. 2013). NAM was also demonstrated to decrease loss of function of CD34+ cells expanded in culture and enhance migration and homing activities of *ex vivo* expanded cells(Peled et al. 2012). It was therefore hypothesized, that NK cells expanded in culture with NAM will display enhanced functionality.

In a clinical study, patients undergoing myeloablative allogenic HSCT with cord blood- derived CD34+ cells cultured with NAM (omidubicel) demonstrated prompt and durable engraftment(Horwitz et al. 2019).

Early preclinical studies show that NK cell cultures, stimulated with IL-15 and NAM, augment tumor cytotoxicity and cytokine (TNF-α and IFN-γ) secretion. Unlike the known changes induced in NK cell cultures with cytokines, NK cells expanded with NAM maintained expression of activating and inhibitory receptors, [redacted]

NAM cultured NK cells demonstrated better retention in the bone marrow, spleen and peripheral blood of irradiated NSG mice, as well as increased *in vivo* proliferation.

These findings were mechanistically supported by a substantial increase in CD62L (L-selectin) expression in cultures treated with NAM. CD62L is pivotal for NK cell trafficking to the BM and lymph nodes (LN) and their homeostatic proliferation (Juelke et al. 2010). CD62L receptor expression is known to be down regulated following expansion in culture, thus hindering the ability of NK cells to be recruited into the tumor microenvironment and tumor bearing LN. The up-regulation of CD62L on NK cells may result in high affinity binding to endothelial cells expressing CD62L binding proteins, which would improve NK cell homing from the circulation into the BM and secondary lymphoid tissues. This could enhance the ability of adoptively transferred NK cells to mediate anti-tumor effects against hematological malignancies such as multiple myeloma (MM), leukemia and lymphoma.

[redacted]

[redacted]

GDA-201 is an allogeneic cryopreserved NK cell therapy derived from donor peripheral blood. Nonclinical studies demonstrated that *ex vivo* expansion of NK cells with NAM increases NK cytotoxicity *in vitro* against multiple tumor cell lines and upregulates CD62L, which enhances its migration potential to tumor sites. In the current study, GDA-201 will be evaluated for the treatment of patients with relapsed or refractory NHL, administered in conjunction with rituximab.

In order to enable multi-site clinical trials, optimize treatment access to patients and create an off-the-shelf therapy, a cryopreserved formulation of GDA-201 was developed. Studies of NK cells cryopreserved [redacted] showed a comparable outcome *in vitro* in the viability, phenotyping (CD16 and CD62L surface expression) and function (cytotoxicity killing and ADCC) of GDA-201.

2.2.3. Summary of previous human study

2.2.3.1. Investigator-sponsored Trial MT2015-46

In a separate clinical study, GDA-201, a cell therapy consisting of fresh NK cells, with similar functionality as cryopreserved GDA-201, was being investigated under [redacted] in a single-center investigator-sponsored study at the University of Minnesota, study MT2015-46, "A Phase I Trial Testing NAM Expanded Haploidentical or Mismatched Related Donor Natural Killer (NK) Cells Followed by a Short Course of IL-2 for the Treatment of Relapsed/Refractory Multiple Myeloma and CD20+ Non-Hodgkin Lymphoma."

Study MT2015-46 is a phase I dose-finding study with an expansion phase. The primary objective of the study was to determine the maximum tolerated dose (MTD) of GDA-201 in combination with disease specific monoclonal antibody (mAb) (elotuzumab or rituximab) in patients with relapsed/refractory MM or CD20-positive NHL, respectively. Up to three dose levels of GDA-201 were tested. Dose limiting toxicity was defined as any grade 4 or greater suspected adverse reaction within 24 hours after cell infusion or Grade III or IV acute Graft-versus-Host Disease (aGvHD) within 28 days after the first cell infusion.

Secondary objectives included safety, disease response, and persistence of donor NK cells in patient.

2.2.3.2. Treatment regimen

Donor apheresis was collected and manufacturing of GDA-201 was initiated approximately two weeks prior to infusion. The first day of GDA-201 infusion is designated as Day 0.

On Day -5, patients commence a course of lymphodepletion (LD) consisting of fludarabine [redacted] mg/m^2 IV and cyclophosphamide [redacted] mg/m^2 IV once a day for 3 doses.

Patients were treated with disease-specific monoclonal antibody (mAb) therapy on Days -10, -3 and +11. Patients with MM received elotuzumab 10 mg/kg IV, and patients with NHL receive

rituximab 375 mg/m^2 IV, with appropriate premedications and monitoring per the respective package inserts.

GDA-201 was administered on Day 0 and Day +2. Patients were premedicated with acetaminophen [redacted]mg PO and/or diphenhydramine[redacted] mg PO before and 4 hours after the infusion. corticosteroids were to be avoided fromDay -3 through Day +14.

Interleukin-2 (IL-2) [redacted] was administered subcutaneously (SC) on Day 0, Day +2, and Day +4.

GDA-201 doses in the phase I dose-finding portion of study MT2015-46 are outlined in Table 2. Enrollment began at dose level 1 with cohorts of 2 patients without regards to NHL or MM diagnosis. An increase in dose level was not to occur until at least one patient assigned to a dose level completed the Day 28 follow-up.

Table 2: GDA-201 Dose Cohorts in Study MT2015-46

Dose Cohort	**TNC[a] dose Dose 1 Day 0**	**TNC dose Dose 2 Day +2**	**TNC dose Dose 1+2**
1	1 x 10^7/kg	1 x 10^7/kg	2 x 10^7/kg
2	5 x 10^7/kg	5 x 10^7/kg	10 x 10^7/kg
3	1 x 10^8/kg	1 x 10^8/kg	2 x 10^8/kg

[a] TNC: total nucleated cells

The expansion phase of Study MT2015-46 was to enroll 10 patients with each diagnosis (MM or NHL) treated at the MTD identified in the phase I dose-finding portion of the study.

The study was amended in February 2019 to allow retreatment with GDA-201 of patients with stable disease (SD) or response. The treatment regimen is similar to that of initial treatment including use of disease specific mAb, timing of the GDA-201 cell infusions, and IL-2, however LD is not to be re-administered if retreatment with GDA-201 takes place within 100 days of the first dose, and may be eliminated or reduced to two days if retreatment takes place after Day +100.

2.2.3.3. Study Results MT2015-46

Study MT2015-46 was open to enrollment October 18, 2017 and enrollment completed on August 15, 2022. 35 patients were treated with GDA-201. Seventeen patients have received the maximum target dose [redacted]

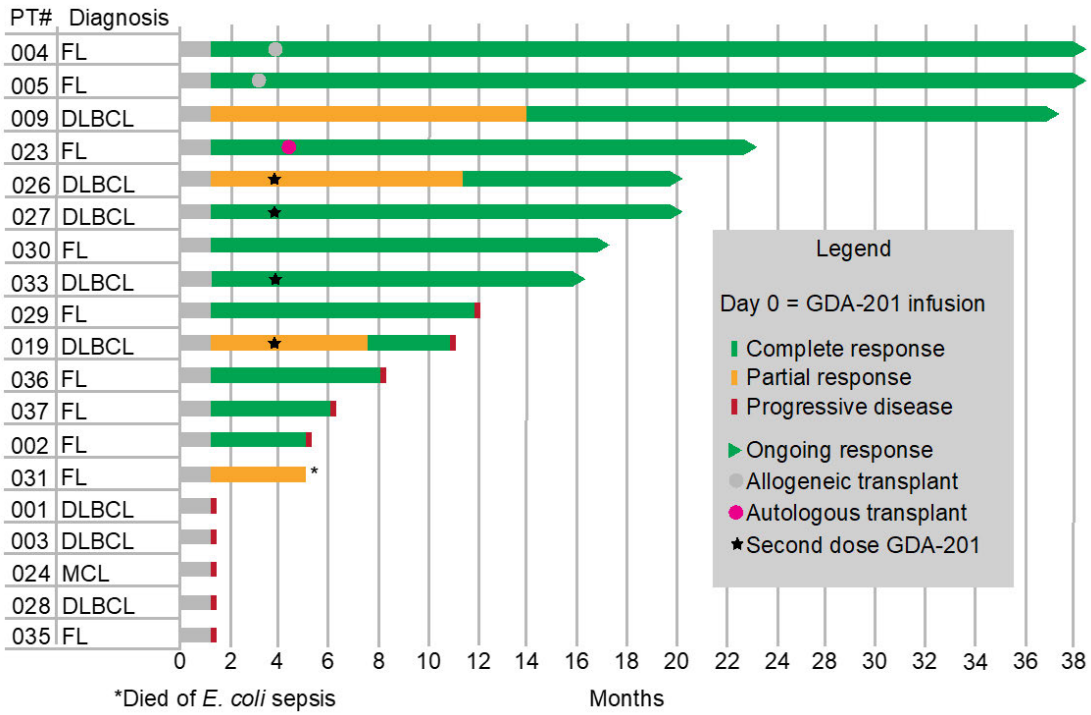
No DLTs were observed in patients treated at any of the three dose cohorts tested.. The most common CTCAE v 5.0 Grade 3 and 4 AEs were neutropenia and thrombocytopenia, febrile neutropenia, leukopenia and hypertension. All events were transient. There were no neurotoxic events, confirmed cytokine release syndrome (CRS), graft vs host disease (GvHD) or marrow aplasia. One patient died within 30 days of enrollment from RSV resulting in complicated pneumonia and E-coli sepsis with renal failure.

Of the 35 patients treated, 16 had MM and 19 had NHL (10 follicular, 2 transformed, 6 diffuse large cell lymphoma, 1 mantle cell lymphoma).

Among 19 NHL patients evaluable for response an ORR of 74% and a CR rate of 68% were recorded. All responding patients exhibited a clinical response within 28 days post-GDA-201 infusion. Four NHL patients received a second dose of GDA-201 without additional lymphodepleting chemotherapy. Two patients (one with FL and one with DLBCL) showed a further deepening of response from PR to CR. The median duration of response was 16 months (range 5-36 months). Progression-free survival (PFS) at 1 and 2 years were estimated at 50% (95% CI = 27-69%) and 35% (95% CI = 14-58%), respectively. Two patients underwent HSCT and one had autologous HSCT for consolidation. After censoring for the transplant, the PFS at 2 years was 19% (95%CI 2-51%) and overall survival (OS) at 2 years was 73% (CI = 43-89%).

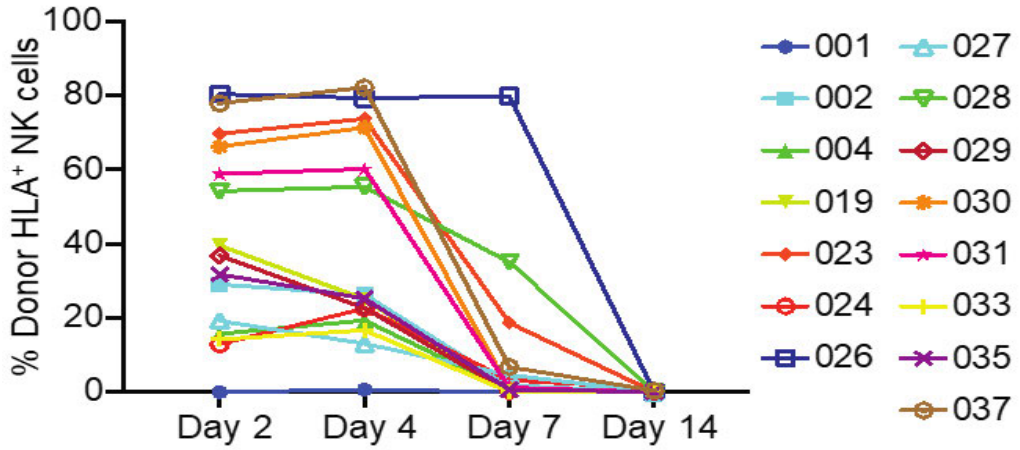
Clinical efficacy data in patients are illustrated in the Swimmer's Plot below (Figure 3), in which the duration of response is plotted for individual patients.

Figure 3: Responses of NHL Patients in Study MT2015-46



Persistence of GDA-201 in patients treated with fresh GDA-201 in Study MT2015-was explored using flow cytometry detecting donor-HLA-specific CD56+ CD3- cells in peripheral blood. Preliminary results from 15 patients (Figure 4) demonstrated the persistence of donor GDA-201 in peripheral blood up to day 7-10 (day 7 range 2-55% donor cells), as well as enhanced *in vivo* proliferation (median Ki67 99%).

Figure 4: Percentage of Donor-HLA-positive NK cells in peripheral blood in Study MT2015-46 (n=15)



2.3. Overall Risk Benefit

The use of NK cells may offer a promising tool for immunotherapy in patients with various relapsed and/or refractory hematologic malignancies. The infusion of allogeneic NK cells could elicit a potent anti-tumor activity via natural cytotoxicity, cytokine stimulated cytotoxicity, and ADCC, when infused in combination with a tumor-targeting antibody. Based on the available nonclinical data with cryopreserved GDA-201, and the preliminary clinical results of the GDA-201 in its fresh formulation, the *ex vivo* expansion of NK cells in the presence of NAM can enable the clinical application of GDA-201 cells that will display antitumor activity.

This study aims to assess the safety and efficacy of GDA-201 infusion in patients with relapsed and/or refractory B Cell NHL, in conjunction with rituximab. In addition to the potential functional and quantitative advantages of GDA-201, the study aims to evaluate the use of cells derived from unrelated donors, with no requirement for HLA matching with the patient. This approach could broaden the access of patients to a potentially effective treatment for a severe life-threatening disease by providing an off-the-shelf therapy.

The risk-benefit relationship has been carefully considered in the preparation of the study protocol. Patients entered onto this trial have failed prior therapies and have limited therapeutic options for the treatment of their lymphoma. The study shall be discontinued in the event new findings indicate a relevant increase in risk or deterioration of the risk-benefit relationship.

2.4. Rationale for Study Design & Dosages

2.4.1. Study Population

GDA-201 is intended for the treatment of hematological cancers expressing CD20 on the cell surface. This includes aggressive, fast growing lymphomas, such as high grade B cell lymphoma and DLBCL and indolent, slow growing lymphomas like follicular lymphoma (FL). It is not currently planned to include other B cell cancers in which only a small percentage of the tumor cells express the antigen on their cell surface (Hodgkin's Lymphoma, Acute Lymphoblastic Leukemia (ALL), multiple myeloma), high grade lymphomas (e.g. Burkitt's Lymphoma), or Chronic Lymphocytic Leukemia (CLL) with extensive peripheral disease.

Eligible patients have relapsed or refractory lymphoma following at least 2 prior lines of therapy (at least one of which contained chemotherapy and at least one of which contained an anti-CD20 monoclonal antibody (mAb)).

Patients who failed prior CAR-T cell therapy or are considered ineligible for CAR-T therapy per the Investigator's discretion are eligible. As such, the Investigator may determine that patients are eligible for the study if they are not considered to be candidates for CAR-T therapy due to their primary disease status, comorbidities or other considerations.

2.4.2. Dosage GDA-201

This is a phase I/II study which seeks to determine the safety and efficacy of cryopreserved, allogeneic GDA-201 with rituximab, when given with LD and followed by a short course of low-dose IL-2, in patients with relapsed/refractory B Cell NHL.

In a previous phase 1 study, (Bachanova 2020) doses between [redacted] cells/kg given over two separate infusion days were associated with 74% ORR and DLT was not observed. It is expected that safety and efficacy will be observed in this study at the same dosage levels. However, several modifications have been introduced to GDA-201 production in order to enable immediate treatment access to patients and create an off-the-shelf therapy. [redacted] The sourcing of cells for GDA-201 has also been modified from haploidentical related donors to unrelated allogeneic donors. Therefore it will be important to confirm safety as part of current study.

As such, dose escalation will start with a GDA-201 dose of 2.5 x 10^7 cells/kg, and will be escalated to a maximal dose of 2 x 10^8 cells/kg, consistent with the doses assessed in the previous study. Patients in each dose level will be dosed according to the closest available GDA-201 bag size, allowing for deviations up to 33% from the intended dose.

2.4.3. Host Conditioning

The Adoptive Cell Therapy (ACT) process can be subdivided into 3 steps: host conditioning, cell transfer, and post-transfer cell support. The host conditioning step can include multiple components – LD, IL-2 administration and in NHL, rituximab administration. Despite the widespread use of conditioning regimens, it is unclear if all of the components are necessary and how they should be administered. In the previous University of Minnesota trial (MT2015-46) all of these components were employed prior to administration of GDA-201 cells. The resulting high response rate observed was notable. However, utilization of host conditioning regimens is associated with significant toxicity and the need for hospitalization. Equally as significant there has never been a randomized clinical trial (RCT) evaluating the contribution of LD and host conditioning to ACT. While it is desirable to modify and or delete some of these conditioning components, it is also possible they are necessary to achieve similar response rates in the current study. The hope is that some or all of those components are not necessary. Therefore, a host conditioning regimen is included as part of the current study but may be modified or deleted following review by the SSC. The rationale for each of the Host Conditioning components is summarized below.

2.4.3.1. Lymphodepleting (LD) Chemotherapy

Lymphodepleting chemotherapy is used with other cellular therapy regimens in order to prolong persistence of cells and increase efficacy. Studies in mice and humans have suggested that the effectiveness of ACT therapy can be improved by lymphodepleting the host prior to cell infusion(Dudley et al. 2002; Dudley et al. 2008). Several mechanisms have been proposed for this beneficial effect. Previous studies shown that LD removes endogenous lymphocytes functioning as cellular sinks for homeostatic cytokines and allows free cytokines to induce survival and proliferation of adoptively transferred cells(Gattinoni et al. 2005). Utilization of LD has been incorporated into approved CAR-T therapies and have primarily employed chemotherapy with cyclophosphamide and fludarabine(Neelapu et al. 2017; Schuster et al. 2019)(Neelapu et al. 2017; Schuster et al. 2019).

Whether LD will be necessary as part of allogenic NK cell therapy is unknown. LD has been incorporated into the majority of clinical trials exploring the use of NK cells in hematologic malignancies(Liu et al. 2021). It was noted in one study that LD resulted in endogenous cytokine release and that elevated levels of IL-15 were associated with improved clinical response(Bachanova et al. 2018).(Bachanova et al. 2018)

2.4.3.2. IL-2 Administration

It has been shown that freshly isolated, resting NK cells are generally less lytic as compared to NK cells primed via various strategies(Bryceson et al. 2006). Although NK cells do not require immunologic priming, certain conditions have been shown to lower their threshold of activation and enhance antitumor immunity. Cytokines such as IL2 and IL15 provide not only a proliferative signal to NK cells, but also enhance function(Woan and Miller 2019).

Clinical protocols of ACT infusing *ex vivo* expanded tumor-infiltrating lymphocytes (TIL) or T-cell receptor (TCR) engineered peripheral blood T cells have employed the concomitant administration of IL-2. It is usually administered intravenously at the highest tolerated dose every 8 h in an inpatient hospital setting to support expansion and function of the adoptively transferred cells(Rosenberg et al. 2008). This dosing regimen results in a high peak of exposure along with associated acute toxicities of a short duration that is designed to activate the IL-2 receptor(Charych et al. 2017). There have been attempts at decreasing the toxicity and improving the pharmacokinetics (PK) of IL-2 by lowering the doses and administering subcutaneously (SC), but it is unclear if the benefit is maintained compared to high dose IL-2(Chapuis et al. 2012). Given the higher activity of GDA-201 cells it is possible a lower and less toxic dose of IL-2 will be sufficient.

2.4.3.3. Rituximab Administration

NK cells are a well described mediator of rituximab induced tumor lysis(Mentlik James, Cohen, and Campbell 2013). NK cells have the capacity to mediate ADCC upon recognition of the Fc segment of IgG bound to cell surfaces. This antigen-specific NK cell targeting mechanism appears to play an important role in tumor eradication by several therapeutic tumor specific monoclonal antibodies (mAb), such as trastuzumab, rituximab, and elotuzumab. In patients with NHL, the addition of rituximab enhances NK cell mediated ADCC against CD20-positive NHL cells.

Administration of rituximab several days prior to administration of GDA-201 has the added potential of depleting circulating B-lymphocytes which permits greater targeting of the

lymphoma cells. Previous studies of rituximab have documented a dose-dependent, rapid, and specific B cell depletion (Maloney et al. 1994).

3. STUDY OBJECTIVES, HYPOTHESIS & STUDY ENDPOINTS

3.1. Objectives

3.1.1. Study Hypothesis

The overall study objective is to evaluate the safety and efficacy of cryopreserved, allogeneic GDA-201, when given with lymphodepleting chemotherapy and followed by a short course of low-dose IL-2, in patients with relapsed/refractory B Cell NHL

3.1.2. Study Objectives

Phase I objectives:

- Assess the safety of GDA-201 + rituximab as determined by dose limiting toxicities
- Determine the maximum tolerated dose (MTD), to be applied as the recommended Phase II dose (RP2D)

Phase II objectives:

- Assess the safety and efficacy of GDA-201 in separate cohorts of patients with FL and DLBCL/HGBCL

3.2. Study Endpoints

3.2.1. Primary Endpoints

- Primary endpoint- Phase I:
  - DLT and safety of GDA-201
- Primary endpoint: Phase II:
  - Overall response rate (ORR)

3.2.2. Secondary Endpoints

- Secondary endpoints: phase I:
  - ORR
- Secondary endpoints: Phase II:
  - ORR Independent Radiological Review Committee (IRRC)
  - Duration of response (DOR). (Investigator Assessment)
  - Progression free survival (PFS). (Investigator Assessment)
  - Overall survival (OS) (Investigator Assessment)
  - Safety and tolerability (Investigator Assessment)

3.2.3. Exploratory Endpoints

- [redacted]

[redacted]

4. STUDY POPULATION

4.1. Number of Patients

- A maximum of 99 patients will be treated as follows:
  - 12-36 patients in the Phase I portion
  - 63 patients (32 in FL cohort and 31 in DLBCL/HGBCL cohort) in the Phase II portion

4.2. Eligibility Criteria

4.2.1. Inclusion Criteria

1. Patients must have relapsed/refractory FL or DLBCL/HGBCL that has failed conventional therapy defined as follows (for the Phase I dose escalation: patients with marginal zone lymphoma or mantle cell lymphoma are also eligible):
   a. Lymphoma characterized by current and/or historical expression of CD20 as determined by flow cytometry or immunohistochemistry.
   b. Received at least 2 prior lines of therapy (at least one of which contained chemotherapy and at least one of which contained an anti-CD20 monoclonal antibody (mAb)).
   c. Transplant ineligible patients allowed assuming they meet criterion b.
   d. Failed prior CAR-T cell therapy or are considered ineligible per the Investigator's discretion.
   e. FL transformed to DLBCL/HGBCL: Must have received at least 1 line of therapy after transformation to DLBCL/HGBCL
2. Patients must have measurable disease as defined by the Lugano response criteria (Cheson et al. 2014) as determined by study investigators. Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy
3. Patients must be at least 18 years of age. In Dose level 1 patients must be at least 75 kg.
4. Patients must have ECOG performance status 0 or 1
5. Patients must have adequate hematologic, hepatic, renal, cardiac and pulmonary function prior to any study treatment defined as:
   a. Absolute neutrophil count (ANC) ≥ 1000/µL
   b. Platelet count ≥ 50,000/µL
   c. Creatinine ≤ 1.5 mg/dL or creatinine clearance ≥50 mL/min
   d. Serum ALT or AST ≤ 3 x upper limit of normal (ULN)
   e. Total bilirubin (TBili) ≤ 1.5 x ULN unless patient with a history of Gilbert's syndrome
   f. Cardiac ejection fraction ≥ 45%, no evidence of pericardial effusion as determined by an echocardiography
   g. Baseline oxygen saturation > 92% on room air

h. No clinically significant pleural effusion

If organ dysfunction is due to lymphoma involvement and not due to prior toxicities the following laboratory parameters are permitted:

a. Platelet count ≥ 30,000 if due to hypersplenism or disease involvement in marrow

b. Total bilirubin (TBili) ≤ 3 x ULN if due to hepatic disease involvement

c. Growth factors are permitted to meet required ANC if cytopenia is due to marrow disease involvement

6. No Class II or greater New York Heart Association Functional Classification criteria (Appendix A) or serious cardiac arrhythmias likely to increase the risk of cardiac complications of cytokine therapy (e.g. ventricular tachycardia, frequent ventricular ectopy, or supraventricular tachyarrhythmia requiring chronic therapy)
7. Patients must be able to be off systemic corticosteroids (with the exception of physiological steroid replacement therapy) and other immunosuppressive drugs for at least 5 half-lives prior to GDA-201 infusion and up until day 14 post GDA-201 infusion (excluding preparative regimen pre-medications), unless approved by the sponsor.
8. Patients after allogeneic HSCT are eligible if they are at least 6 months after the transplant andoff all immunosuppressive drugs.
9. Patients after allogeneic HSCT or any other allogeneic cell therapy are eligible if there is no active Graft-versus-Host Disease (GvHD)
10. No evidence of ongoing neurotoxicity or cytokine release syndrome from prior therapies
11. Sexually active females of childbearing potential and males with partners of childbearing potential must agree to use effective contraception from the time of screening pregnancy test and for at least 4 months after completion of therapy
12. Patient signs the written informed consent after being aware of the nature of the patient's disease and willingly consents to the treatment program after being informed of alternative treatments, potential risks, benefits, and discomforts

4.2.2. Exclusion Criteria

1. Pregnancy, as indicated by a positive serum or urine human chorionic gonadotrophin (HCG) test, or lactation
2. Active bacterial, fungal, or viral infection that is uncontrolled or requiring systemic antimicrobials for management. Simple urinary tract infection (UTI) and uncomplicated bacterial pharyngitis are permitted if responding to active treatment
3. HIV infection not controlled on therapy, and/or with active viremia (HIV viral load needs to be undetectable), or AIDS defining illnesses.
4. History of acute or chronic active hepatitis B or C infection not documented to be cleared per current Infectious Diseases Society of America (IDSA) guidelines (see Appendix B). Patients at risk for reactivation of HBV infection must be on prophylactic anti-HBV antiviral therapy
5. Patients with active autoimmune disease requiring immunosuppressive therapy. Patients with a history of autoimmune-related hypothyroidism on a stable dose of

thyroid replacement hormone and patients with controlled type 1 diabetes mellitus (DM) on a stable insulin regimen may be eligible for this study

6. History of severe asthma and currently treated with chronic asthma medications (a history of mild asthma requiring inhaled steroids only is eligible)
7. Live vaccine <6 weeks prior to start of therapy
8. Patient with detectable CSF malignant cells, or brain metastases, or with a history of central nervous system (CNS) lymphoma or primary CNS lymphoma, CSF malignant cells or brain metastases. Patients with a history of CNS involvement can be included if cleared by magnetic resonance imaging (MRI) and CSF for at least 6 months
9. History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (e.g. cervix, bladder, breast, prostate) unless disease free for at least 2 years
10. Presence of any indwelling line or drain (e.g., percutaneous nephrostomy tube, indwelling foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Dedicated central venous access catheters such as a Port-a-Cath or Hickman catheter are permitted
11. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis per chest imaging at screening. History of radiation pneumonitis in the radiation field (fibrosis) is allowed
12. Known hypersensitivity to any of the study treatments, gentamycin, albumin, DMSO or any other GDA-201 excipient
    Note: Infusion reactions with rituximab are common. Patients with a history of infusion reactions to rituximab that can be managed with recommended pre-medications should not be excluded
13. Time between previous treatment and first dose of study treatment (rituximab):
    a. Allogeneic HSCT < 6 months prior to study treatment
    b. ASCT < 3 months prior to study treatment
    c. CAR-T < 2 months prior to study treatment
    d. Major surgery or chemotherapy < 4 weeks prior to study treatment (6 weeks for melphalan)
    e. Radiation therapy < 2 week prior to study treatment
    f. Monoclonal antibodies including checkpoint blockade < 2 weeks prior to study treatment (does not apply to rituximab)
    g. Antibody-Drug Conjugates (ADCs) including polatuzumab vedotin and loncastuximab tesirine < 4 weeks prior to study treatment, unless approved by the sponsor
    h. Targeted therapies, Bispecific T cell Engagers (BiTEs), small molecule inhibitors or any investigational therapy within 5 half-lives of the drug, unless approved by the sponsor

5. PATIENT ENROLLMENT & DOSE LEVEL ASSIGNMENT

5.1. Written Consent

Written consent must be obtained prior to the performance of any research related tests or procedures.

5.2. GDA-201 Cell Dose Level Assignment

Up to 4 dose levels of GDA-201 cells will be tested in this study followed by the expansion cohort. Assignment of the dose level will be provided by the sponsor or designee. This is an open label study with no blinding or randomization. In Phase I, patients will be assigned to the currently enrolling GDA-201 dose level without regards to underlying disease. In Phase II patients will be non-randomly assigned to either the FL or DLBCL/HGBCL cohort based on their underlying disease.

5.2.1. Patients Who Do Not Begin Study Treatment

If a patient signs consent and is later found not able to begin the first dose of study treatment, for whatever reason, the patient will be removed from study. The patient will be considered a screen/baseline failure and the reason for removal from study will be clearly indicated. Patients will be allowed to re-screen. The patient will be replaced to fulfill study enrollment requirements.

5.3. Patient Enrollment

Once all screening assessments are completed and the patient's eligibility is confirmed, study treatment can begin. Patient enrollment is defined as receiving the first dose of rituximab (Day -10).

6. STUDY TREATMENT

This is an open-label, non-randomized, interventional, single group assignment study of GDA-201, an allogeneic cryopreserved NK cell therapy derived from donor peripheral blood, in combination with rituximab, monoclonal anti-CD20 antibody, for patients with relapsed or refractory B Cell non-Hodgkin lymphoma (NHL).

The study is divided into a phase I dose escalation and a phase II expansion study.

Patients with relapsed or refractory FL or DLBCL/HGBCL will receive GDA-201 followed by a short course of low-dose interleukin-2 (IL-2) (for the Phase I dose escalation: patients with marginal zone lymphoma or mantle cell lymphoma are also eligible). Rituximab will be administered prior to and after GDA-201 infusion (see Figure 1 for the study schema).

6.1. Treatment Plan

6.1.1. Phase I: Dose Escalation

The objective of Phase I is to evaluate the safety of GDA-201 for patients with FL, DLBCL/HGBCL, marginal zone lymphoma or mantle cell lymphoma. The MTD will be determined based on DLTs.

As outlined in Table 3 , the starting dose will be 2.5 x 10^7 cells/kg.
Safety within each cohort will be assessed by the incidence of DLTs (see Section 11.2 for DLT definitions) over an observation period of 28 days. For the first 3 patients enrolled at each dose level, a 28-day staggering interval of DLT free observation period is required to be completed before treating a subsequent patient in the same dose level cohort. Dose escalation to the next dose level can only proceed after the third patient has completed a 28-day DLT free observation period and following discussion with the SSC.

Table 3: Dosing Cohorts

Dose Level	Dose*
1	2.5x10^7 cells/kg
2	5x10^7 cells/kg
3	1x10^8 cells/kg
4	2x10^8 cells/kg

*Based on GDA-201 dosing table allowing for a maximal 33% deviation from the intended dose (Table 5).

Based on the safety and tolerability of GDA-201 in the first 3 evaluable patients after the first cycle of treatment, escalation to a subsequent dose level or addition of patients to a current dose level will occur based upon the following criteria:

- If there are no GDA-201-related DLTs experienced within 28 days, dose escalation to the subsequent dose level may proceed
- If 1 of 3 patients at a dose level experiences a DLT within 28 days following a single dose of GDA-201, 3 additional patients may be enrolled into the study at the current dose level
- If there are no further DLTs experienced in the 3 additional patients within 28 days following a single dose, escalation to the next dose level may proceed
- If a DLT occurs in ≥ 2 patients in any dose group of 3 to 6 patients within 28 days following a single dose, dose escalation will stop

Additional patients will be treated at the preceding lower dose level, if needed, to have at least 6 patients treated at that dose level. If 6 patients were previously treated, the preceding lower dose level will provisionally be considered the MTD pending any decision to enroll additional patients (up to 12 patients enrolled in backfilled cohorts) at the discretion of the study sponsor to further characterize the DLT and safety profile by histology (follicular lymphoma or DLBCL/HGBCL) prior to phase II expansion.
Patients within each cohort will be assessed for DLTs, and enrollment in each cohort will continue to occur sequentially until a MTD is reached. The MTD will be applied as the recommended Phase II dose (RP2D).

Dose escalation will stop at completion of Dose Level 4 even if the MTD is not identified. At the discretion of the study sponsor, after the dose escalation phase across the four doses is complete, up to an additional 12 patients enrolled in backfilled cohorts may be treated to further characterize the DLT and safety profiles by histology (follicular lymphoma or DLBCL/HGBCL) at one or two dose levels prior to the phase II expansion. This will be designated as “backfilling” a cohort in order to ensure that the cohort enrolls a minimum of 3 patients per histology. With the addition of these backfill patients, the MTD and/or RP2D may be determined. The RP2D may be different by histology (follicular lymphoma or DLBCL/HGBCL).

6.1.2. Phase II: Expansion Phase

The objective of the Phase II expansion cohort is to evaluate the safety and efficacy of GDA-201 in two patient cohorts, FL and DLBCL/HGBCL.

Patients will be treated with GDA-201 at the RP2D along with LD.

The patients will be followed for treatment response by positron emission tomography (PET)-CT at 28 days following the first GDA-201 infusion, and continue to be followed at 90, 180 and 365 days following the initial treatment. All patients will be followed for one year from the first GDA-201 infusion to determine time to relapse and progression free survival.

Patients with either FL or DLBCL/HGBCL will continue to be included in separate cohorts by diagnosis. Each disease group will accrue independently, closing to enrollment once a total of 63 (32 in FL cohort and 31 in DLBCL/HGBCL cohort) evaluable patients are enrolled.

In order to provide optimal patient care and to account for individual medical conditions, investigator discretion may be used in the prescribing of all supportive care drug therapy (i.e. acetaminophen, diphenhydramine, antimicrobials, etc.).

6.2. Treatment Regimen

The following table summarizes the overall treatment regimen that will be employed:

Table 4: Study Treatment Plan

Component	Dose	Days
Rituximab	[redacted]	-10, -3, +14*
Lymphodepletion (LD)**	[redacted]	-5, -4, -3
GDA-201	[redacted]	0, +2
Interleukin-2	[redacted]	0, +2, +4.

* The last rituximab dose be administered +/- 2 days

** LD chemotherapy dose adjustments will be permitted according to local institutional guidelines and with sponsor approval.

Administration of GDA-201 and other study treatments should follow the schedule outlined in this section .

6.2.1. Rituximab

- Will be administered with appropriate pre-medications and monitoring per the package insert
- A ±2-day window is permissible for the last rituximab dose (Day 14)
- **NOTE:**
  - Biosimilars may be used
  - SC administration is **NOT** permitted

6.2.2. Investigational Product GDA-201

Before GDA-201 infusion commences, the following criteria must be met. If these criteria are not met, then GDA-201 infusion must be delayed until these events resolve.

- No evidence or suspicion of infection. Patient must not be receiving systemic anti-microbials for the treatment of an active infection within 48 hours prior to GDA-201 infusion (prophylactic use of anti-microbials is allowed)
- No clinically evident changes in bone marrow, renal, hepatic, pulmonary or cardiac function since screening
- Creatinine clearance is at or above limits set in eligibility criteria
- No acute neurological toxicity > grade 1 (with the exception of peripheral neuropathy)

- In addition, if any of the following are known to occur, the GDA-201 infusion may need to be delayed. Contact the Study Medical Monitor before GDA-201 infusion commences for guidance:
  - CRP is ≥100 mg/L
  - Temperature is ≥ 38.0°C within 48 hours prior to GDA-201 infusion. Unexplained fever requires pan-culture, respiratory viral panel, chest CT scan and any additional symptom-directed workup to rule out occult infection
  - WBC count of ≥ 20,000/µL within 48 hours prior to GDA-201 infusion
  - If the GDA-201 infusion is delayed > 2 weeks, lymphodepleting chemotherapy may need to be repeated. In all cases of GDA-201 infusion delays, contact the Study Medical Monitor for guidance
- Each GDA-201 treatment will be given over two infusion days: Day 0 and Day +2. Depending on the patient's weight, GDA-201 may be given only on Day 0. For the Phase I, both infusion days and 24 hours subsequent follow up will be performed during an inpatient stay
- The 2nd GDA-201 infusion day will be performed if all toxicities from 1st infusion day decrease to ≤ CTCAE grade 2
- GDA-201 is provided in cryobags. See Table 5 for the GDA-201 dosing table per patient weight – note that patients may require one or more GDA-201 bags per infusion day to complete their treatment according to the assigned dose level
- On each day of GDA-201 infusion:
  - Pre-medications: Patients should be pre-medicated with acetaminophen/paracetamol [redacted] mg PO and/or diphenhydramine [redacted] mg PO before starting GDA-201 infusions and 4 hours ±30 minutes after completing the GDA-201 infusions (note that this dose will also provide the pre-medication for IL-2 dosing)
  - See Sections 8.4 and 8.5 (Handling and Preparation of GDA-201; and Administration) and the product handling manual for GDA-201 preparation and infusion instructions.
  - The infusion rate of GDA-201 should not exceed [redacted]
  - Infuse GDA-201 within **2 hours from dilution to end of infusion**
  - A minimal interval of **1 hour is required from the start of infusion of the first bag, to the start of infusion of the subsequent bag**, to ensure the minimal infusion time according to the endotoxin limit [redacted]
- The GDA-201 cells are intended to be infused by gravity without additional support (examples of additional support are the use of a volumetric pump or a syringe push).
- GDA-201 should be given with blood infusion set with filter [redacted]
- **Hydration** will be administered per institutional guidelines. Any elevation of daily metabolic monitoring will be treated with more aggressive hydration, while being attentive to fluid overload

Follow-up after GDA-201 Infusion

Patients on the Phase I will be hospitalized to receive treatment with GDA-201 followed by a 24 hour post infusion observation period. Patients should not be discharged from the hospital until all GDA-201-related non-hematological toxicities return to ≤ Grade 1. Patients may be discharged with non-critical and clinically stable or improving toxicities (e.g., renal insufficiency) even if > Grade 1, if deemed appropriate by the investigator. Patients should remain hospitalized for ongoing GDA-201 -related fever, hypotension, hypoxia, or if deemed necessary by the treating investigator.

Table 5: GDA-201 Dosing Table

		Number of GDA-201 Bags to be Infused[1]			
		Day 0		**Day 2**	
Dose Level[2]	**Patient Weight (kg)**	[redacted]	[redacted]	[redacted]	[redacted]
Dose Level 1: 2.5 x 10^7 cells/kg	Up to 75	Not Applicable[5]			
	75 and above	1			
Dose Level 2: 5 x 10^7 cells/kg	Up to 75	1			
	75 and above	1		1	
Dose Level 3: 1 x 10^8 cells/kg	Up to 60	1		1	
	60 to < 90		1	1	
	90 and above		1		1
Dose Level 4: 2 x 10^8 cells/kg	Up to 60		1		1
	60 to < 90		2		1
	90 and above		2		2

1. Depending on the patient's weight, GDA-201 may be given only on Day 0.
2. Dose level is assigned according to the actual infused dose. Deviations up to 33% from the intended dose level are acceptable to accommodate the closest GDA-201 bag size.
3. [redacted]
5. No dosing is feasible due to maximal allowed deviation from intended dose of 33%

6.2.3. Interleukin-2

- IL-2 will be given subcutaneously (SC) at [redacted]
- For patients weighing < 45 kilograms, the IL-2 will be given at [redacted]
- Pre-medication with acetaminophen/paracetamol [redacted] mg PO and diphenhydramine [redacted] mg PO/IV before the IL-2 dose and 4 hours after each dose

of IL-2 is recommended *(note that this dose can also provide the post-medication for GDA-201 dosing)*

- On days of GDA-201 cell infusion, IL-2 will be administered no sooner than 4 hours after GDA-201 administration has been completed
- For the Phase I, the first two doses will be administered as part of the hospitalization for the GDA-201 cell infusion. The 3rd IL-2 dose may be given as an outpatient
- If the patient has experienced grade 2 or greater GDA-201 infusion related toxicity on Day 0 or Day +2, the dose of IL-2 may be held for up to 48 hours. If the toxicity resolves to grade 1 or better within 48 hours, IL-2 may be given with all planned doses to be given; however the administration of remaining dose(s) must be at least 24 hours apart
- If IL-2 cannot be started within 48 hours after the Day 0 GDA-201 infusion, no IL-2 will be given and the patient will be replaced, but remain evaluable for primary and secondary endpoints
- Instructions for dilution and administration of IL-2 can be found in Appendix G.

6.2.4. Lymphodepleting (LD) Chemotherapy

Before LD commences, the following criteria must be met. If these criteria are not met, then lymphodepleting chemotherapy must be delayed until these events resolve.

- No evidence or suspicion of infection
- No clinically evident changes in bone marrow, renal, hepatic, pulmonary or cardiac function since screening
- Creatinine clearance is at or above limits set in eligibility criteria
- No acute neurological toxicity > Grade 1 (with the exception of peripheral neuropathy)
- In addition, if any of the following are known to occur, a delay in lymphodepleting chemotherapy may be required. Contact the Study Medical Monitor before lymphodepleting chemotherapy commences for guidance
  - WBC count of ≥ 20,000/µL within 48 hours prior to lymphodepleting chemotherapy
  - CRP is ≥100 mg/L
  - Temperature is ≥ 38.0° C within 48 hours prior to lymphodepleting chemotherapy. Unexplained fever requires pan-culture, respiratory viral panel, chest CT and any additional symptom- directed workup to rule out occult infection
  - If any other screening assessments or procedures are repeated between enrollment and the start of lymphodepleting chemotherapy and results are outside the eligibility criteria

The 3 day lymphodepleting regimen of fludarabine and cyclophosphamide will be administered in accordance with the below daily dosing instructions.

- Fludarabine [redacted] mg/m^2 is administered as a 0.5 to 1-hour intravenous (IV) infusion once a day for 3 doses beginning on Day -5
- Cyclophosphamide [redacted] mg/m^2 is administered as a 1 to 2-hour IV infusion once a day for 3 doses on Day -5
- IV hydration with 700-1000 mL of 0.9% NaCl given prior to cyclophosphamide on the days of infusion. An additional 700-1000 mL of 0.9% NaCl at the completion of the cyclophosphamide infusion guidelines

- Dosing is based on body surface area calculation (BSA) unless actual body weight (ABW) is > 150% above ideal body weight (IBW), in which case the dose should be computed using adjusted body weight. LD chemotherapy dose adjustments will be permitted according to local institutional guidelines and with sponsor approval.
- Patients should be instructed to drink plenty of liquids during and for 24 hours following the chemotherapy (approximately 2 liters/24 hours). In general patients should be kept well-hydrated but closely monitored to prevent fluid overload
- Mesna is a detoxifying agent used to inhibit hemorrhagic cystitis induced by chemotherapy. The active ingredient mesna is a synthetic sulfhydryl compound designated as sodium-2-mercaptoethane sulfonate with a molecular formula of C2H5NaO3S2
    - Mesna should be administered per institutional guidelines. Refer to the most recent version of the package insert for specific details surrounding the administration of mesna
- Patients are to receive allopurinol 300 mg PO daily, unless known allergy, continuing until Day +7 or as clinically indicated
- Patients are to receive antimicrobial prophylaxis:
    - Anti-viral therapy with acyclovir 400 mg PO twice daily.
    - Anti-PCP prophylaxis is recommended - Sulfamethoxazole-Trimethoprim x 2/week until Day 60
    - Antibiotic and antifungal prophylaxis is recommended: levofloxacin 250mg/day begin Day 0 (give only if ANC < 1000); fluconazole 100mg/day begin Day 0 (continue until ANC > 1000)

6.2.5. Concomitant Therapy for Symptom Management

Medications may be administered for the management of symptoms associated with the administration of GDA-201, IL-2 and Rituximab as needed. These might include analgesics, anti-emetics, anti-histamines, diuretics, anti-anxiety medications, and medications for pain management, including narcotic agents.

NOTE: Systemic corticosteroids: Given the profound deleterious effects of systemic corticosteroids on NK function, they are to be avoided from 5 half-lives prior to GDA-201 infusion through Day +14. It is advised to refrain from systemic corticosteroids use up to Day 90 unless clinically indicated. P**hysiological steroid replacement therapy is permitted.**

6.2.6. Concomitant Medications

During screening and throughout the study, patients may take only stable doses of medications for chronic conditions that are not specifically excluded by the protocol. The Medical Monitor should be consulted by the Investigator if there are any concerns about what constitutes a stable dose or what is a chronic condition.

7. STUDY VISITS AND PROCEDURES

7.1. Study Procedures

7.1.1. Informed Consent

Before a patient's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the patient after adequate explanation of the study design, anticipated benefits and the potential risks. Patients should sign the most current IRB/IEC approved ICF prior to any study specific activity or procedure is performed.

The consent process and the patient's agreement or refusal to participate in the study is to be documented in the patient's medical records. If the patient agrees to participate, the ICF is to be signed and personally dated by the patient and by the person who conducted the informed consent discussion. The original signed ICF will be retained in accordance with institution policy and IRB/IEC requirements with a copy of the ICF provided to the patient.

All patients who are enrolled into the study should be re-consented with any updated version of the IRB/IEC approved ICF if relevant to their participation in the study.

7.1.2. Demographic Data

Demographic data will be collected as per country and local regulations and guidelines. Where applicable, demographic data will include sex, year of birth, race, ethnicity, and country of enrollment to study their possible association with patient safety and treatment effectiveness.

7.1.3. Medical and Previous Cancer Treatment History

Relevant medical history prior to the start of AE reporting will be collected. Relevant medical history is defined as data on the patient's concurrent medical condition that would be typically shared in a referral letter. All findings will be recorded in the CRFs.

In addition to the medical history, all history related to the patient's disease, treatment and response to treatment will be collected and must date back to the original diagnosis.

For patients who are being referred from another clinic or institution to the participating research center, copies from the patients chart should be obtained.

7.1.4. Physical Exam, Vital Signs and ECOG Performance Status

Physical exams will be performed during screening and at times noted in the Schedule of Event (SOE). Changes noted in subsequent exams when compared to the baseline exam will be reported as an AE.

During GDA-201 administration/hospitalization, vital signs including blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature will be monitored before, during and

after each GDA-201 infusion and then routinely according to standard of care. If the patient has a fever (temperature >38.2°C), vital signs will be monitored more frequently as clinically indicated.

Performance status as measured by the ECOG scale will be performed to quantify the patient's general well-being and ability to perform activities of daily life.

7.1.5. Cardiac Function

Each patient's cardiac function, as measured by Left Ventricular Ejection Fraction (LVEF), will be assessed during the screening period to confirm study eligibility. No evidence of clinically significant pericardial effusion as required by eligibility will also be confirmed. Both LVEF and pericardial effusion will be assessed prior to study enrollment by ECHO (MUGA also acceptable). An ECHO performed following the patient's last chemotherapy treatment and within 28 days prior to signing the consent may be used for confirmation of eligibility.

A 12-lead ECG will also be performed during the screening period.

7.1.6. Disease Response Assessment

Patients will be evaluated for disease response by the site investigator at times indicated in the SOE. Disease assessments will be evaluated per the Lugano response criteria) Flow cytometric, molecular or cytogenetic studies will not be used to determine response.

Baseline PET-CT scans of the neck, chest, abdomen and pelvis, along with the appropriate imaging of all other sites of disease are required. Patients will have their first post GDA-201 infusion planned PET-CT tumor assessment 28 days following the GDA-201 infusion and at regular intervals as highlighted in the SOE during the post treatment follow-up.

Post GDA-201 administration disease assessments will be used to determine the time when progressive disease (PD) occurs. Patients with symptoms suggestive of disease progression should be evaluated for progression at the time symptoms occur even if it is off schedule as per the SOE.

A bone marrow aspirate and/or biopsy should be performed only when the patient had bone marrow involvement with lymphoma prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment. The bone marrow aspirate and/or biopsy must show no evidence of disease by morphology, or if indeterminate by morphology, it must be negative by immunohistochemistry to assign a CR to treatment.

7.1.7. Laboratory

The below samples will be collected at the time points indicated in the SOE. Additional samples (e.g., blood, urine, CSF, tissue, etc) may be collected as needed for further safety testing.

Local laboratory analysis:

- Tumor biopsy
- Optional for patients who consent for this assessment: [redacted]
- Complete Blood Count with Differential
- Chemistry panel must include (at the minimum): serum creatinine, total bilirubin (TBili), alkaline phosphatase, AST, ALT, LDH and magnesium.
- C-reactive protein (CRP)
- Ferritin
- B2 microglobulin
- Allelic level HLA typing
- Anti-donor HLA-testing
- Serum or urine beta HCG for females of childbearing potential. If the screening pregnancy test is positive, the patients should not be enrolled. If a standard of care pregnancy test is collected during the course of the study, and the result is positive, the investigator should contact the Study Medical Monitor for instructions. If a female partner of a male patient becomes pregnant during the conduct of the study, it must be reported by contacting the Study Medical Monitor for instructions

Central laboratory analysis:

- Blood draws for GDA-201 central laboratory assays [redacted] for will be collected according to the SOE and shipped to a central laboratory for processing. The blood draw needs to be taken at the beginning of the study visit, before the administration of any medications, study drugs, etc.
- [redacted]

7.2. Study Visits

7.2.1. Study Duration

The total duration of participation for each patient is approximately 13 months. The main study will be considered complete when the last patient enrolled has completed the last protocol

required follow-up visit. Patients who enroll in the long-term follow up sub-study will be followed for an additional 5 years, up to 6 years following the initial GDA-201 infusion.

The patients will be followed for treatment response by PET-CT at 28 days following the first GDA-201 infusion, and continue to be followed at 90, 180and 365 days following the initial GDA-201 treatment. All patients will be followed for one year from the first GDA-201 infusion to determine time to relapse and progression free survival.

Should the patient fail to return to the clinic for a scheduled protocol specific visit, sites will need to make 2 attempts by a combination of telephone and mail (if applicable) to contact the patient. Sites must document both attempts to contact the patient. If a patient does not respond within 1 month after the second contact the patient will be considered lost to follow-up and no additional contact will be required.

At any time during the study period, if a patient fails to achieve SD, PR or CR, or progresses following a response, or begins another cellular therapy treatment for his/her disease, the patient's post treatment assessment will be recorded and he/she will be followed for SAEs through 30 days following the last dose of study treatment and then for survival through one year after the first GDA-201 infusion.

7.2.2. Screening

The screening period begins from the date the patient signs the IRB/IEC approved informed consent form (ICF) and continues through commencement of study treatments. Informed consent must be obtained before performing any non-standard of care study specific procedures. Procedures that are part of standard of care are not considered study specific procedures and may be performed prior to obtaining consent and used to confirm eligibility. Confirmation of this data must occur within the time allowance as outlined below and in the SOE.

After written informed consent has been obtained, patients will be screened to confirm study eligibility and participation. Only patients who meet the eligibility criteria listed in Section 4.2 and who commence study treatments will be enrolled in the study. If at any time prior to enrollment the patient fails to meet the eligibility criteria, the patient should be designated as a screen failure on the patient screening log with the reasons for failing screening.

Investigative sites will maintain a log of all screened patients who were reviewed and evaluated for study participation. Information collected on the screening log should include limited information such as the date of screening, date the patient was enrolled or the reason for why the patient failed screening.

The following assessments/procedures are to be completed during the screening period at the time points outlined in the SOE.

- Written Informed Consent
- Eligibility Criteria – All eligibility criteria must be met before LD commences

- Medical history
- Disease assessment - baseline disease assessment must be performed after completion of prior chemotherapy
- GvHD assessment (for patients after allogeneic HSCT or any other allogeneic cell therapy). See Appendix C
- Concomitant medications documentation and previous cancer treatment history
- Physical examination including height and weight
    - Patients with symptoms of CNS malignancy such as new onset severe headaches, neck stiffness, seizures, encephalopathy, cranial nerve deficits, or any focal neurologic findings on physical exam will have lumbar puncture for examination of CSF
- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature
- ECOG performance status
- ECG
- ECHO for LVEF and pericardial effusion assessment
    - An ECHO performed following the patients last chemotherapy treatment and within 28 days prior to signing the consent may be used for confirmation of eligibility
- PET-CT
    - Baseline PET CT of the neck, chest, abdomen and pelvis
        - PET-CT performed following the patients last line of therapy and prior to signing the consent may be used for confirmation of eligibility
        - If PET CT is performed > 28 days prior to the initiation of study treatments or if patient receives any anti-cancer therapy between screening and LD chemotherapy, the PET-CT scan must be repeated to establish a new baseline. PET CT should be performed as close to enrollment as possible
- Laboratories
    - Tumor biopsy is mandatory within 4 months prior to study treatment, unless it is prohibitive from a patient safety perspective, per investigator discretion or unless approved by the sponsor.
    - Optional for patients who consent for this assessment: [redacted]
    - Chemistry panel
    - CBC with differential
    - B2 microglobulin
    - β-HCG pregnancy test (serum or urine) on all women of child-bearing potential
    - Allelic level HLA Typing (intermediate resolution HLA-A, B, C, DRB1)
    - Anti donor HLA Testing
    - Bone marrow biopsy or aspirate (if previously positive) as clinically indicated.
    - Lumbar puncture only for patients with new or suspicious neurological findings suggestive of CNS involvement

- Serious Adverse Event (SAE)/ Adverse Event (AE) reporting since the time of consent and prior to study treatment initiation only if the event is directly related to screening procedure (refer to section 15.2 for Procedures for Adverse Events (AEs) Recording and Reporting)

Re-Screening

Patients who are unable to complete the screening assessments or do not meet the eligibility criteria during the 28-day screening period will be permitted to rescreen one time. If rescreening occurs within 28 days of the initial signing of the informed consent, only the procedure(s)/assessment(s) that did not originally meet the eligibility criteria need to be repeated. All other initial screening procedures/assessments do not need to be repeated. If rescreening occurs more than 28 days from the signing of the initial informed consent, patients must be reconsented (if > 3 months has elapsed) and repeat all expired screening procedures/assessments.

7.2.3. Study Visit Day -10

- Physical examination including weight
- AE assessment
- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature
- ECOG performance status
- Laboratories
  - Chemistry panel
  - CBC with differential
  - Ferritin
  - CRP
  - GDA-201 central laboratory sampling (before rituximab administration)
  - Serum or urine β-HCG pregnancy test (results should be obtained before rituximab is administered).
- Concomitant medications documentation
- Administration of rituximab with appropriate pre-medications and monitoring (refer to Section 6.2.1)
- Serious Adverse Event (SAE) reporting (refer to Section 15.2 for Procedures for Adverse Events (AEs) Recording and Reporting)

7.2.4. Study Visit Day -5, Day -4 and Day -3

Before Lymphodepleting Chemotherapy commences, the criteria in Section 6.2.4 must be met. If these criteria are not met, then LD must be delayed until these events resolve.

- Weight
- AE assessment
- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature
- ECOG performance status
- Laboratories
  - Chemistry panel

  - CBC with differential
- Concomitant medications documentation
- Administration of Lymphodepleting Regimen, consisting of fludarabine and cyclophosphamide for three consecutive days (refer to Section 6.2.4)
- Serious Adverse Event (SAE) reporting (refer to Section 15.2 for Procedures for Adverse Events (AEs) Recording and Reporting)

On Day -5 also add the following:

- Physical Examination

On Day -3 also add the following:

- Administration of rituximab with appropriate pre-medications and monitoring (refer to Section 6.2.1)

7.2.5. Study Visit Day 0

Before GDA-201 infusion commences, the criteria in Section 6.2.2 (Investigational Product Treatment) must be met. If these criteria are not met, then GDA-201 infusion must be delayed until these events resolve.

- Physical examination including weight
- AE assessment
- Vital signs including blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature
- ECOG performance status
- ECG should be obtained before IL-2 administration
- Laboratories
  - Chemistry panel
  - CBC with differential
  - Ferritin
  - CRP (C-reactive protein)
  - GDA-201 central laboratory sampling (before GDA-201 administration)
- Concomitant medications documentation
- Administration of study drug GDA-201 cell infusion, pre-medications and hydration (refer to Section 6.2.2)
- Administration of Interleukin-2 (IL-2) with appropriate pre-medications (refer to Section 6.2.3)
- Serious Adverse Event (SAE) reporting (refer to Section 15.2 for Procedures for Adverse Events (AEs) Recording and Reporting)

7.2.6. Study Visit Day 2

Before GDA-201 infusion commences, the criteria in Section 6.2.2 (Investigational Product Treatment) must be met. If these criteria are not met, then GDA-201 infusion must be delayed until these events resolve.

- Physical examination including weight
- AE assessment

- Vital signs including blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature
- ECOG performance status
- ECG should be obtained before IL-2 administration
- Laboratories
  - Chemistry panel
  - CBC with differential
  - GDA-201 central laboratory sampling (before GDA-201 administration if infused on that day)
- Concomitant medications documentation
- Administration of study drug GDA-201 cell infusion, pre-medications and hydration (refer to Section 6.2.2)
- Administration of Interleukin-2 (IL-2) with appropriate pre-medications (refer to Section 6.2.3)
- Serious Adverse Event (SAE) reporting (refer to Section 15.2 for Procedures for Adverse Events (AEs) Recording and Reporting)

7.2.7. Study Visit Day 4

- Physical examination including weight
- AE assessment
- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature
- ECOG performance status
- ECG should be obtained before IL-2 administration
- Laboratories
  - Chemistry panel
  - CBC with differential
  - GDA-201 central laboratory sampling
- Concomitant medications documentation
- Administration of Interleukin-2 (IL-2) with appropriate pre-medications (refer to Section 6.2.3).
- Serious Adverse Event (SAE) reporting (refer to Section 15.2 for Procedures for Adverse Events (AEs) Recording and Reporting)

7.2.8. Study Visit Day 7

- Physical examination including weight
- AE assessment
- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature
- ECOG performance status
- Laboratories
  - Chemistry panel
  - CBC with differential
  - CRP (C-reactive protein)
  - Ferritin
  - GDA-201 central laboratory sampling
- GvHD Assessment

- Concomitant medications documentation
- Serious Adverse Event (SAE) reporting (refer to Section 15.2 for Procedures for Adverse Events (AEs) Recording and Reporting)

7.2.9. Study Visit Day 14

- Physical examination including and weight
- AE assessment
- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature
- ECOG performance status
- Laboratories
  - Chemistry panel
  - CBC with differential
  - GDA-201 central laboratory sampling
  - Ferritin
  - CRP
- GvHD assessment
- Concomitant medications documentation
- Administration of rituximab with appropriate pre-medications and monitoring (refer to Section 6.2.1)
- Serious Adverse Event (SAE) reporting (refer to Section 15.2 for Procedures for Adverse Events (AEs) Recording and Reporting)

7.2.10. Study Visit Day 21

- Physical examination including and weight
- AE assessment
- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature
- ECOG performance status
- Laboratories
  - Chemistry panel
  - CBC with differential
  - Ferritin
  - CRP
- GvHD assessment
- Concomitant medications documentation
- Serious Adverse Event (SAE) reporting (refer to Section 15.2 for Procedures for Adverse Events (AEs) Recording and Reporting)

7.2.11. Study Visit Day 28

- Physical examination including and weight
- AE assessment
- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature
- ECOG performance status
- Laboratories
  - Chemistry panel
  - CBC with differential
  - B2 microglobulin

  - GDA-201 central laboratory sampling
- GvHD assessment
- Concomitant medications documentation
- PET-CT
- Disease Assessment
- Serious Adverse Event (SAE) reporting (refer to Section 15.2 for Procedures for Adverse Events (AEs) Recording and Reporting)

7.2.12. Study Visit Day 42

- Physical examination including and weight
- AE assessment
- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature
- ECOG performance status
- Laboratories
  - Chemistry panel
  - CBC with differential
  - B2 microglobulin
- Concomitant medications documentation
- Serious Adverse Event (SAE) reporting (refer to Section 15.2 for Procedures for Adverse Events Recording and Reporting)

7.2.13. Study Visit Day 56

- Physical examination including and weight
- AE assessment
- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature
- ECOG performance status
- Laboratories
  - Chemistry panel
  - CBC with differential
  - B2 microglobulin
  - Anti-donor HLA testing
- Concomitant medications documentation
- Serious Adverse Event (SAE) reporting (refer to Section 15.2 for Procedures for Adverse Events (AEs) Recording and Reporting)

7.2.14. Study Visit Day 70

- Physical examination including and weight
- AE assessment
- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature
- ECOG performance status
- Laboratories
  - Chemistry panel
  - CBC with differential
  - B2 microglobulin
- Concomitant medications documentation

- Serious Adverse Event (SAE) reporting (refer to Section 15.2 for Procedures for Adverse Events (AEs) Recording and Reporting)

7.2.15. Study Visit Days 90, 120, 180, 270 and 365

- Physical examination including and weight
- AE assessment
- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature
- ECOG performance status
- Laboratories
  - Chemistry panel
  - CBC with differential
  - B2 microglobulin
  - Ferritin – on day 365 only
  - GDA-201 central laboratory sampling – on Day 90 only
  - Anti-donor HLA testing – on Day 90 only
- Concomitant medications documentation
- Serious Adverse Event (SAE) reporting (refer to Section 15.2 for Procedures for Adverse Events (AEs) Recording and Reporting)

On visit Days 90, 180 and 365 only, also perform:

- PET-CT
- Disease Assessment
- GvHD assessment

On visit Day 90 only, also perform:

Bone marrow biopsy or aspirate (if previously positive) as clinically indicated.

7.2.16. Termination Visit

- Physical examination including and weight
- AE assessment
- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature
- ECOG performance status
- Laboratories
  - Chemistry panel
  - CBC with differential
  - B2 microglobulin
  - Ferritin
- Concomitant medications documentation
- Serious Adverse Event (SAE) reporting (refer to Section 15.2 for Procedures for Adverse Events (AEs) Recording and Reporting)
- PET-CT
- Disease Assessment
- GvHD assessment

7.3. Long Term Follow-Up (LTFU)

Patients enrolled on the study will be offered a separate informed consent for long term follow up. Patients will be enrolled in the long term follow-up sub-study after they have completed the one year study follow up. For these patients, information on the following will be collected:

- Subsequent therapies
- Disease status
- Survival

Assessments may be performed as per the standard of care at individual institutions. Data may be obtained by review of medical records from the clinical center, through the patient's primary care physician, and/or contact by phone at the time points 2 years, 3 years, 4 years, 5 years and 6 years following the initial GDA-201 infusion.

8. STUDY MEDICATION: GDA-201

8.1. Description

GDA-201 is an allogeneic cryopreserved NK cell therapy derived from donor peripheral blood. GDA-201 is supplied in 2 doses:

1. [redacted]

8.2. Manufacturing and Shipping

GDA-201 is an allogeneic cell therapy comprised of NK cells isolated from peripheral blood leukapheresis of individual allogeneic donors. [redacted]

8.3. GDA-201 Supply

Labeling and packaging of GDA-201 is performed according to the relevant Manufacturer's SOP. Cryopreserved GDA-201 is shipped in a cryoshipper equipped with a calibrated data logger. The shipment of GDA-201 will be controlled by the sponsor in order to assure that shipment conditions are appropriately maintained and documented, as detailed in the product handling manual.

Upon arrival at clinical site GDA-201 should be kept [redacted]

8.4. Handling and Preparation of GDA-201

Handling and Preparation of GDA-201 are described in the GDA-201 Product Handling Manual.

GDA-201 should not be irradiated under any circumstances.

Prior to its infusion, GDA-201, its labels, and the related documentation must be identified and checked at the clinical center according to the product handling manual. The clinical center should confirm that GDA-201 was shipped in appropriate conditions and all cryobags are within their shelf life. The related forms must be completed and signed/dated to document this review.

Thawing and dilution of GDA-201 by the clinical site's personnel will be performed immediately prior to infusion. Each GDA-201 cryobag should be separately thawed, diluted and infused according to the product handling manual. Any subsequent GDA-201 cryobag to be infused should not be thawed before confirming the infusion of the preceding GDA-201 bag was completed.

A minimal interval of **1 hour is required from the start of the infusion of the first GDA-201 bag, to the start of the infusion of the subsequent GDA-201 bag**, to ensure the minimal infusion time according to the endotoxin limit [redacted]).

In a brief summary of the preparation process for infusion, the GDA-201 cryobag is removed from liquid nitrogen storage, checked for integrity, and is placed in a [redacted] water bath. As soon as the cells are completely thawed, the bag is removed from the water bath and transferred to a safety grade A cabinet.

[redacted]

8.5. Administration

GDA-201 should be infused via a central venous catheter as per site practice. GDA-201 is intended to be given by gravity without additional support (examples of additional support are the use of a volumetric pump or a syringe push).
GDA-201 should be given with blood infusion set with filter [redacted]

The infusion rate of GDA-201 should not exceed [redacted]. The entire content of the GDA-201 bag should be infused as soon as possible after thaw.

The total duration of each GDA-201 infusion will not exceed 2 hours from dilution to end of infusion.

The process should be repeated for each subsequent GDA-201 bag according to the dosing requirement in section 6.2.2.

GDA-201 contains human blood cells. Follow international and country specific guidelines and local biosafety SOP for handling and disposal to avoid potential transmission of infectious diseases.

9. STUDY STEERING COMMITTEE (SSC)

The data emerging from this study will be reviewed periodically by the SSC. Based on an ongoing assessment on the safety and efficacy of the treatment regimen, the SSC may make any of the following recommendations:

- Dose escalation to the next cohort
- Add patients to the current cohort
- Dose modification
- Determination of the MTD
- Proceed from Phase I to Phase II of the study
- Proceed to stage II in each cohort of the Phase II
- Stop enrollment for one or both cohorts

Additional roles for the SSC include recommendations for:

- Safety monitoring throughout the study
- Modifying or removing LD for all patients or for one cohort, as follows
  - Reduce the LD drug doses for all patients or one cohort
  - Remove use of LD for all patients or one cohort
  - Proceed with patient enrollment with and without LD in parallel (1:1 allocation)
  - Stop enrollment for one regimen
  - Repeat LD for subsequent GDA-201 treatment cycles

  Changes that increase LD dosing for the planned patient population will **not** be implemented without a protocol amendment.

SSC recommendations will be provided to the sponsor. The SSC will include representatives from the Investigators , Medical Monitor and the sponsor.

In the Phase I dose escalation, AEs, clinical laboratory results, cardiac function results, and vital signs will be assessed at least through 28 days following treatment in each cohort in a minimum of three patients to assess DLT. Based on the safety and tolerability of GDA-201 in the first 3 evaluable patients after the first cycle of treatment, escalation to a subsequent dose level or addition of patients to a current dose level will occur. See Section 6.1.1 for details on the criteria for dose escalation and MTD determination.

Throughout the study the SSC will continue to review the study data periodically. If an alert is triggered by the study stopping criteria (see Section 12.6), the SSC will consider the data in depth and make recommendations to the sponsor. It is understood that SSC recommendations to the sponsor are not binding and that the sponsor is the sole party responsible for final decisions regarding modification or continuation of the trial.

10. DISCONTINUATION, TERMINATION OR COMPLETION OF STUDY

10.1. Study Discontinuation

Study interventions, including LD and GDA-201 administration, should be discontinued by the investigator if the investigator believes that it is in best interest of the subject or if any of the following situations occur:

- Disease progression
- Death
- Initiation of another systemic treatment for NHL
- Investigator's decision
- Subject noncompliance / protocol violations
- Study terminated by sponsor
- Subject withdrawal
- Lost to follow-up

10.2. Study Termination

The study can be terminated by the sponsor, Institutional Review Board (IRB) / Ethics Committee or Regulatory Agency at any time.

10.2.1. Subject Withdrawal

A subject may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

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 may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

Sponsor may request subject to be withdrawn.

10.2.2. Lost to follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned

visit schedule and ascertain if the subject wishes to and/or should continue in the study

- Before a subject is deemed lost to follow-up, the sites will need to make 2 attempts by a combination of telephone and mail (if applicable) to contact the patient. Sites must document both attempts to contact the patient.

10.2.3. If a patient does not respond within 1 month after the second contact the patient will be considered lost to follow-up and no additional contact will be requiredStudy Completion

A subject is considered to have completed the main study if:

- followed according to the protocol to the Day 365 visit, or
- disease progression, or
- death, or
- has received a new treatment for NHL (including stem cell transplant)

Subjects who have completed the Day 365 visit can be followed for an additional 5 years in an optional LTFU sub-study.

Subjects who have not completed the main study according to the above list will be followed for SAEs through 30 days following the last dose of study treatment. These subjects will complete a Termination Visit (see section 7.2.16) if possible, and then will be followed for survival through one year after the first GDA-201 infusion. Subjects who consented to the LTFU will be followed for further 5 years in an optional LTFU sub-study.

10.2.4. Termination Visit

11. TERMINATION VISIT WILL INCLUDE ALL RELEVANT STUDY ASSESSMENTS (SEE SECTION 7.2.16) NOT EVALUATED WITHIN 2 WEEKS PRIOR TO THE SUBJECT TERMINATION. **SAFETY EVALUATIONS AND CRITERIA**

11.1. Safety Evaluation and Dose Escalation

Safety will be evaluated by the SSC including Investigators and Medical Monitor. In the Phase I dose escalation, AEs, clinical laboratory results, cardiac function results, and vital signs will be assessed through at least 28 days following the first GDA-201 dose in each cohort in a minimum of three patients to assess DLT. Based on the safety and tolerability of GDA-201 in the first 3 evaluable patients after the first cycle of treatment, escalation to a subsequent dose level or addition of patients to a current dose level will occur.

11.2. Dose-Limiting Toxicity Definition

On discovery, all DLTs should be immediately reported (within 24 hours of knowledge of the event) to Parexel.
DLTs defined as one of the following, within the first 28 days of the first dose of GDA-201, by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v 5.0 (Appendix F). Acute GvHD will be assessed according to the Consensus Conference on Acute GvHD grading ((Przepiorka et al. 1995)Appendix D):

- Steroid refractory Grade II acute GvHD. Steroid refractory GvHD is defined as GvHD that does not respond to at least 1 mg/kg/day or equivalent of prednisone within 7 days of initiating therapy
- Grade III or IV acute GvHD
- Grade 4 infusion reaction
- Grade 4 or 5 related adverse event (AE)
- Grade 3 or above cardiac, central nervous system or pulmonary adverse event.
- Any Grade 3 or above non-hematologic adverse event that does not resolve to Grade 2 or below within 72 hours, with the exception of renal or hepatic adverse events which may take up to 7 days to resolve
- Treatment emergent ≥Grade 3 autoimmune disorder
- Grade 3 or above allergic reaction that does not recover to Grade II or below within 24 hours
- Grade 4 cytopenia lasting beyond Day 42 (the 28-day DLT observation period will be extended to confirm)

11.3. Continuation of Therapy

Patients will continue to receive the same dose level of GDA-201 as assigned at study entry unless dose delay or discontinuation is required to manage toxicities. Intra-patient GDA-201 dose escalation is not allowed. Patients who experience GDA-201 related DLT may continue treatment provided that the toxicity can be controlled and that it resolves to either Grade 1 or baseline.

11.4. Dose Modifications and Discontinuations Due to Toxicity

Patients will be monitored for AEs according to NCI-CTCAE v 5.0 (Appendix F). Toxicities observed and felt to be at least possibly related to GDA-201 will be managed as outlined in Table 6 below.

Table 6: GDA-201 Dose Modifications and Discontinuations for Possibly Related Toxicities

Grade (NCI-CTCAE v 5.0) (Appendix F)	Action related to GDA-201 Infusion	Other Study Treatments (IL-2, Rituximab)
Grade 1 or 2	• No dose reductions or delays	• No change
Grade 3 or 4 during GDA-201 infusion	• Administration of GDA-201 will be discontinued	• Withhold further therapy until symptoms resolve[1, 2]
Grade 3 following completion of GDA-201 infusion(s) (Day 0 and/or Day 2)	• No further GDA-201 infusion(s)	• • Withhold further therapy until symptoms resolve[1, 2]
Grade 4 following completion of GDA-201 infusion(s) (Day 0 and/or Day 2)	• No further GDA-201 infusion(s)	• No further therapy

[1] Grade 3 or 4 toxicities that are considered unlikely or unrelated to GDA-201 should return to at least Grade 2 prior to subsequent GDA-201 administration and other study treatment.

[2] If the patient is judged by the Investigator to be at unacceptable risk, despite not meeting the specifications for a DLT, contact the Medical Monitor to discuss appropriate treatment for the patient on a case-by-case basis.

11.5. Management of Expected Toxicities Associated with GDA-201 Infusion and IL-2

Patients will be monitored for AEs according to the NCI-CTCAE version 5.0 (Appendix F). Toxicities observed and felt to be at least possibly related to GDA-201 will be managed as outlined below. See Appendix E for expected toxicities of rituximab, IL-2 and the lymphodepleting regimen.

11.5.1. Expected Toxicities

11.5.1.1. GDA-201

Toxicities associated with GDA-201 infusion may include:

- fever
- rigors
- changes in blood pressure

- immune mediated toxicity may occur with any cell therapy: cytokine release syndrome, neurotoxicity, macrophage activation syndrome are very rare but could be serious and even fatal

11.5.1.2. Interleukin-2 (IL-2)

Toxicities associated with IL-2 include:

- fever, chills
- skin rash
- fatigue, tiredness
- decreased platelets
- nausea and vomiting
- fluid retention and weight gain
- hypothyroidism
- infection
- abnormal renal function test
- abnormal liver function test

To reduce the intensity of fever and chills, pre-medication with acetaminophen and diphenhydramine before and 4 hours after each dose of IL-2 is recommended. Premedication specifics and dose modifications for unacceptable IL-2 related toxicities are found in Section 6.2.3.

11.5.1.2.1. Hypotension (systolic blood pressure < 90 mm Hg)

IL-2 should be held for hypotension (defined as systolic blood pressure less than 90 mm Hg) if in the presence of any clinically significant symptoms (in the opinion of the treating physician), until the systolic blood pressure reading is stable. If mild dehydration is suspected, an IV fluid bolus may be used per standard of care.

11.5.2. Management of Expected GDA-201 Toxicities

11.5.2.1. Acute Infusion Related Reaction Secondary to the Infusion of Allogeneic GDA-201 Cell Product and Other Study Treatment

Although infusion of donor lymphocytes has not been associated with acute allergic reactions, patients will be closely watched for the occurrence of hypotension, dyspnea and angioedema during and immediately after the infusion.

The GDA-201 infusion will be stopped if a severe infusion related reaction occurs (such as anaphylaxis or acute compromise to a critical organ system).

11.5.2.2. Vascular Leak Syndrome (Systemic capillary leak syndrome)

Neither administration of allogeneic NK cells nor autologous IL-15 activated NK infusions have been associated with vascular leak syndrome in previous experience. Nevertheless, patients will be monitored for weight gain and pulmonary edema during IL-2 administration.

11.5.2.3. Tumor Lysis Syndrome

Tumor lysis syndrome is as a possible risk of any therapy for active hematologic malignancy. All patients (except those with known allergy) are to receive allopurinol 300 mg daily beginning before chemotherapy and continuing until Day +7 or as clinically indicated.

11.5.2.4. Prolonged Marrow Suppression

The lymphodepleting chemotherapy regimen may be associated with pancytopenia. Anemia and thrombocytopenia are expected in all patients receiving LD, who will receive standard supportive transfusion care or as modified based on clinical parameters. Prolonged anemia or thrombocytopenia are not unexpected.

For prolonged neutropenia, recommended management is as follows:

- Days –7 to +14: In the absence of severe, uncontrolled infection, G-CSF or granulocytes should be avoided. If the clinical situation warrants growth factor use, then any remaining IL-2 administration will be stopped.
- At Day +14: If the ANC is <500, G-CSF will be initiated. Begin G-CSF 5 mcg/kg on Day +14 only if ANC < 500 and continue until ANC > 1500 x 2 days.
- Marrow aplasia at Day 35 will trigger a safety assessment by the SSC.

11.5.2.5. Immune Mediated Syndromes

Immunologically mediated syndromes such as cytokine release syndrome (CRS), neurotoxicity (encephalopathy and seizure) or macrophage activation syndrome (MAS) have been rarely observed after NK cell infusion; however, patients will be monitored closely for 28 days including monitoring CRP and ferritin. Treatment of CRS, neurotoxicity and MAS will follow standard guidelines which were developed for chimeric antigen receptor T cell therapies(Neelapu et al. 2018).

11.5.3. Management of IL-2 Toxicity

To reduce the intensity of fever and chills, pre-medication with acetaminophen/paracetamol 500-1000 mg PO and diphenhydramine 25-50 mg PO/IV before and 4 hours after each dose of IL-2 is recommended.

- Grade 3 toxicity: if the toxicity resolves to grade 2 or better within 48 hours, the IL-2 can be resumed at a reduced dose (4 million units or 2 million units/m^2 if < 45 kg). If the same toxicity persists, worsens or recurs, the IL-2 must be permanently discontinued
- Grade 4 toxicity: permanently discontinue IL-2

12. STATISTICAL CONSIDERATIONS

A formal Statistical Analysis Plan (SAP) will be prepared and finalized before the database lock for the clinical study report. The SAP will provide further technical details regarding the definition of analysis populations, analysis variables, and analysis methodology to meet all study objectives.

12.1. Design and Sample Size Considerations

The Phase I portion of the study is a conventional 3 + 3 design with four sequential dose cohorts. The starting dose will be 2.5 x 10^7 cells/kg. If all cohorts are completed, 24 patients will have been treated with a maximum of 6 patients per cohort. The goal is to determine the recommended phase II dose (RP2D) during the escalation phase. Phase I patients who are not evaluable for DLT may be replaced.

At the discretion of the study sponsor, after the dose escalation phase across the four doses is complete, up to an additional 12 patients enrolled in backfilled cohorts may be treated to further characterize the DLT and safety profiles by histology (follicular lymphoma or DLBCL/HGBCL) at one or two dose levels prior to the phase II expansion. This will be designated as "backfilling" a cohort in order to ensure that the cohort enrolls a minimum of 3 patients per histology. With the addition of these backfill patients, the MTD and/or RP2D may be determined. The RP2D may be different by histology (follicular lymphoma or DLBCL/HGBCL).
For each cohort in the Phase II portion of the study, a Simon's optimal 2-stage design will be employed based on the ORR (CR or PR) endpoint.

- In the FL cohort, 11 patients will be enrolled in the first stage. If ≥3 patients achieve ORR, it will continue to enroll an additional 21 patients in the second stage for a total of 32 patients in the cohort. At the end of stage 2, if ≥10 out of the 32 patients achieve ORR, it is considered promising for further evaluation. This design has 80% power to test the null hypothesis of 20% response rate against the alternative hypothesis of 40% with a 1-sided type 1 error rate not exceeding 0.075
- In the DLBCL/HGBCL cohort, 14 patients will be enrolled in the first stage. If ≥3 patients achieve ORR, it will continue to enroll an additional 17 patients in the second stage for a total of 31 patients in the cohort. At the end of stage 2, if ≥8 out of the 31 patients achieve ORR, it is considered promising for further evaluation. This design has 80% power to test the null hypothesis of 15% response rate against the alternative hypothesis of 33% with a 1-sided type 1 error rate not exceeding 0.075

Phase II patients who are not evaluable for response may be replaced. Patients who have at least one efficacy evaluation following GDA-201 infusion will be considered evaluable for response.

12.2. Study Endpoints

12.2.1. Primary Endpoints

- Phase I: DLT and safety

- Phase II: Overall response rate (ORR) based on investigator assessments

12.2.2. Secondary Endpoints

Phase I: ORR based on investigator assessments

Phase II:

- ORR based on Independent Radiological Review Committee (IRRC)
- Duration of response (DOR)
- Progression free survival (PFS)
- Overall survival (OS)
- Safety and tolerability

12.2.3. Exploratory Endpoints

- [redacted]

[redacted]

12.3. Analysis Population

DLT evaluable population: All patients who receive any amount of GDA-201 and are enrolled in the dose escalation part of the study. Patients without experiencing DLT who discontinue study prior to Day 28 for reasons other than toxicity may be replaced and excluded from the DLT evaluable population.

Safety analysis population: All patients who receive any amount of GDA-201. All safety analyses other than the DLTs will be based on the safety analysis population.

Efficacy evaluable population: All patients in the safety population who have at least one efficacy assessment after GDA-201 treatment. The efficacy evaluable population will be used for efficacy analyses.

12.4. Patient Disposition

The number of patients screened, enrolled and who received investigational product, will be summarized overall and by cohort assignment for all patients. For each analysis population, the number of patients included in the population will be presented. Disposition data will be presented based on all patients entered.

Patient discontinuations will be listed including the date of treatment discontinuation, reason for treatment discontinuation, exposure to investigational product, study discontinuation, and reason for study discontinuation.

Protocol deviations will be summarized and listed by patient.

12.5. Baseline Characteristics

Descriptive summary statistics will be provided for demographic variables (age, sex, race, ethnicity) and baseline disease characteristics (e.g., performance status). Relevant medical history and prior anti-cancer therapies/medications will also be summarized.

12.6. Safety Analysis

12.6.1. Safety Alert Criteria

The data emerging from this study will be reviewed periodically by the Study Steering Committee (SSC) and recommendations will be provided to the sponsor.
Ongoing safety assessment guidelines will be used to monitor the following events, and alert the SSC. A safety alert will be triggered if one of the following criteria is met:

1. Any death not related to disease progression
2. Grade 4 or above cardiac, CNS or pulmonary DLT in 2 subjects, that is at least possibly related to GDA-201
3. Any DLT occurring in Dose level 1
4. Grade 5 adverse event that is probably or directly related to GDA-201
5. Grade III-IV acute GvHD crossing the thresholds based on a Bayesian continuous monitoring model (Thall and Simon 1994)(Zhu 2016). The model assumes the background rate of the Grade III-IV acute GvHD is 5% with a prior beta distribution of beta (1,19). A prior distribution of beta (0.1,0.9) is assumed for the GDA-201 treated patients in the study. An alert will be triggered if there is a high posterior probability (greater than 80%) that the Grade III-IV acute GvHD rate is 3% higher than the background rate. For example, if 2 patients have experienced a Grade III-IV GvHD, and the number of patients treated are less or equal to 11, an alert is triggered.

Table 7: Alert threholds based on Grade III-IV acute GvHD

Number of patients with Grade III-IV acute GvHD observed	Alert triggerd if the number of patients treated is ≤ to the number indicated
1	≤ 3
2	≤ 11
3	≤ 19
4	≤ 28
5	≤ 36

If an alert occurs, accrual to the study will be temporarily halted. The SSC will consider the data in depth and make recommendations to the sponsor. It is understood that SSC recommendations to the sponsor are not binding and that the sponsor is the sole party responsible for final decisions regarding modification or continuation of the trial.

12.6.2. Analysis of AEs and Laboratory Values

All AEs will be coded to a system organ class (SOC) and a preferred term (PT) based on the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or later.

Patient incidence of all AEs, SAEs, AEs leading to discontinuation of treatment, and fatal AEs will be tabulated by SOC and PT.

The number and percent of patients reporting AEs will be evaluated overall and by dose level and will also be tabulated by severity and relationship to study treatment. The severity of each AE will be graded using The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 or later criteria.

For the Phase I portion of the study, DLTs (if any) will be summarized by dose and will be listed separately.

Changes in laboratory values and vital signs will be summarized with descriptive statistics. Use of concomitant medications, levels of GDA-201 cells in blood and incidence of anti-HLA antibodies will also be summarized.

12.7. Efficacy Analysis

The primary analysis for efficacy will be based on the cohort-specific efficacy evaluable analysis population. Sensitivity analyses may include pooling additional patients treated in phase I at the same dose level.

The ORR endpoint is defined as the incidence of either a complete response (CR) or a partial response (PR) by the Lugano response criteria as determined by the study investigators. All patients that do not meet the criteria for an objective response by the analysis cutoff date will be considered non-responders.

For the ORR endpoint, the Clopper-Pearson 85% and 95% confidence intervals (CIs) will be calculated. Confidence intervals adjusting for the 2-stage nature of the design may also be provided. Duration of response (DoR) will be calculated among responders (CR and PR). The Kaplan-Meier method will be used to estimate median DoR and the confidence intervals. Patients who continue to respond at the time of the analysis will be censored at the last assessment of response.

Progression-free survival (PFS) is measured from the date of first GDA-201 dose until the date when PD is first observed per the Lugano response criteria as determined by the study investigators, or death from any cause, whichever is earlier. Patients without PD or death will be censored at the last available tumor assessment. PFS will be summarized using the Kaplan-Meier method.

Overall survival (OS) is measured from the date of first GDA-201 dose until death. Patients who are alive will be censored at the last known alive date. OS will be summarized using the Kaplan-Meier method.

Sensitivity analyses of the ORR and PFS based on the assessments by the IRRC will also be provided.

12.8. Timing of analyses

For the phase I portion of the study, dose escalation recommendations will be made by the SSC for each dose cohort.

Periodic safety reviews will also be performed during the phase II portion of the study. For each cohort in the phase II portion, the ORR will be calculated and evaluated at the end of stage

1 following the Simon's 2-stage rule outlined in Section 12.1. The recommendation to proceed to stage 2 will be made by the SSC.

The primary safety and efficacy analyses of the study will be conducted after all patients have completed the main study follow-up, one year after the initial GDA-201 infusion. Additional follow-up data will be collected but are beyond the scope of the primary analyses.

A summary of those results shall be submitted to the appropriate regulatory agency(ies) according to local regulations.

12.9. Long Term Follow Up

For patients who received GDA-201, completed the one year study follow-up and enrolled in the observational long term follow-up sub-study, long-term outcomes will be collected at 2 years, 3 years, 4 years, 5 years and 6 years post GDA-201 infusion.

The overall research goals for this sub-study are:

- Describe survival, time to relapse and progression free survival

PFS and OS, will be assessed with a Kaplan-Meier curve with 2-sided 95% confidence intervals.

12.10. End of Study

End of the main study will be when all patients complete their participation in the study (Visit Day 365 or early Termination Visit).

End of Long Term Follow Up sub-study will be when all patients complete their last follow up visit (Year 6 or earlier).

13. TUMOR DEFINITIONS AND ASSESSMENT

Tumor measurements will be performed by PET-CT radiologic imaging techniques at baseline and at 28, 90, 180 and 365 days. The Lugano response criteria will be used to evaluate the response.

Response and progression will be also assessed by Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) scan, using the response criteria outlined in the Lugano Response Criteria.

For phase II an independent, central radiology review may be implemented.

Refer to (Cheson et al. 2014) the full disease response criteria according to the Lugano Classification (see Appendix C).

13.1. Metabolic Criteria

13.1.1. Complete Response (CR)

Complete metabolic response requires all of the following:

- A score of 1, 2, or 3 with or without a residual mass on a PET 5 point scale; and
- Disappearance of any previously non-measured lesions; and
- No new lesions; and
- No evidence of FDG-avid disease in the marrow.

13.1.2. Partial Response (PR)

Partial metabolic response requires all of the following:

- A score of 4 or 5 on a PET 5 point scale with reduced uptake compared with baseline; and
- No new lesions.

13.1.3. Stable Disease

Does not meet metabolic criteria for complete response, partial response, or progressive disease.

13.1.4. Progressive Disease (after Partial Response, Stable Disease), Relapsed Disease (after Complete Response)

Metabolic progression or relapse requires at least one of the following:

- A score of 4 or 5 on a PET 5 point scale with increased uptake compared with baseline; or
- Any new FDG-avid foci consistent with lymphoma; or
- New or recurrent FDG avid foci in the bone marrow.

13.2. Radiographic Response Criteria

The following acronyms are used in the radiographic response criteria provided below:

LDi: longest transverse diameter of a lesion

SDi: shortest axis perpendicular to the LDi

SPD: sum of the product of the perpendicular diameters for multiple lesions

PPD: cross product of the LDi and perpendicular diameter

13.2.1. Complete Response

Complete radiographic response requires all of the following:

- All target nodes / nodal masses must have regressed as measured by CT to ≤ 1.5 cm in longest diameter; and
- Disappearance of any previously non-measured lesions; and
- No extralymphatic sites of disease; and
- No organomegally.

Normal morphology of bone marrow is also required for a complete radiological response if the marrow was an involved site. Immunohistochemical stains must be negative if morphology is indeterminate.

13.2.2. Partial Response

Partial radiographic remission requires all of the following:

- ≥ 50% decrease in the SPD of up to 6 target measurable nodes and extranodal sites (For lesions too small to measure on CT, assign 5mm x 5mm as the default value and then 0 mm x 0 mm when the lesion is no longer visible. For a node >5 mm x 5 mm, but smaller than normal, use the actual measurement of the node for calculations); and
- No increase in the size of previously non-measurable lesions; and
- No new lesions.

If splenomegaly is present, a > 50% decrease in spleen length is also required to report a partial radiological response

13.2.3. Stable Disease

Does not meet radiographic criteria for complete response, partial response, or progressive disease.

13.2.4. Progressive Disease (after Partial Response, Stable Disease), Relapsed Disease (after Complete Response)

Radiographic progression or relapse requires at least one of the following:

- An individual node must be abnormal with:
  - LDi >1.5 cm; and
  - ≥ 50% increase from nadir in the PPD; or
- An increase in LDi or SDi from nadir

- ≥ 0.5 cm increase in LDi or SDi from nadir for any lesion ≤ 2cm; or
- ≥ 1.0 cm increase in LDi or SDi from nadir for any lesion > 2 cm; or

- A 50% increase in spleen length compared to its prior increase beyond baseline; or
- New or recurrent splenomegally; or
- Clear progression of pre-existing non-measured lesions; or
- Regrowth of any previously resolved lesions; or
- A new node > 1.5 cm in any axis; or
- A new extranodal site > 1.0 cm in any axis or if < 1.0 cm in any axis, its presence must be unequivocally attributable to lymphoma; or
- Assessable disease of any size unequivocally attributable to lymphoma; or
- New or recurrent involvement of the bone marrow.

13.3. Definitions

1. Measurable disease:

FDG-avid lesions characterized by a Deauville score of 4-5 and which coincide with previously documented disease foci, or foci which are highly suspicious for lymphoma involvement, or

- Bidimensionally measurable lesions with clearly defined margins by:
  a. medical photograph (skin or oral lesion), or plain X-ray with at least one diameter 0.5 cm or greater (bone lesions are not included) or
  b. computed tomography (CT), magnetic resonance imaging (MRI) or other imaging scan with both diameters greater than the distance between cuts of the imaging study, or
  c. palpation with both diameters 2 cm or greater

2. Evaluable disease: unidimensionally measurable lesions, masses with margins not clearly defined, lesions with both diameters less than 0.5 cm, lesions on scan with either diameter smaller than the distance between cuts, palpable lesions with either diameter less than 2 cm, bone disease.
3. Non-evaluable diseases: pleural effusions, ascites, disease documented by indirect evidence only.
4. Objective status: to be recorded at each evaluation. If an organ has too many measurable lesions to measure at each evaluation, choose three to be followed before the patient is entered on study. The remaining measurable lesions in that organ will be considered evaluable for the purpose of objective status determination. Unless progression is observed, objective status can only be determined when all measurable and evaluable sites and lesions are assessed.

14. TREATMENT COMPLIANCE

The Investigator will document the time and dose of all administrations in the patient's medical notes and also record this information in the electronic case report form (eCRF). Any reasons for non-compliance will also be documented including:

- Missed visits
- Interruptions in the schedule of administration
- Non-permitted medications

15. ASSESSMENT OF SAFETY

All patients will be assessed for safety by monitoring AEs, clinical laboratory tests, vital signs, physical examinations and anti-drug antibody (anti-donor HLA) testing.

15.1. Relationship to Study Drug

15.1.1. Adverse Event (AE)

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of study drug (treatment-emergent).

15.1.2. Serious Adverse Event (SAE)

A serious adverse event (SAE) is any AE, occurring at any dose level and regardless of causality that:

1. Results in death
2. Is life-threatening: Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, (i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form)
3. Requires inpatient hospitalization or prolongation of existing hospitalization
4. Results in persistent or significant disability/incapacity
5. Is a congenital anomaly/birth defect
6. Is an important medical event: an important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

Note: A hospitalization for an elective procedure will not be considered a SAE

For the purpose of this study, Progressive Disease and/ or Relapse and / or any events that are unequivocally related to PD and / or Relapse are expected outcomes of the subject's disease and therefore are not considered SAEs and do not require SAE reporting, unless life-threatening or fatal.

15.1.3. Unexpected Adverse Event (AE)

An unexpected AE is an AE that is not reported in the Investigator's Brochure (IB).

15.1.4. Relationship of Adverse Events (AEs) to Study Drug

The following classifications should be used when evaluating the relationship of AEs and SAEs to the investigational drug.

1. None: No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or patient's clinical state
2. Unlikely: The current state of knowledge indicates that a relationship is unlikely
3. Possibly: A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction might have been produced by the patient's clinical state or other modes of therapy administered to the patient
4. Probably: A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction cannot be reasonably explained by the known characteristics of the patient's clinical state or other modes of therapy administered to the patient
5. Definitely: A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug and can be confirmed with a positive re-challenge test or supporting laboratory data

15.1.5. AE Severity

15.2. Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on general guideline described in CTCAE version 5.0.Procedures for Adverse Event (AE) Recording and Reporting

Patients will be evaluated and questioned generally for AE/SAE during the course of the study. The Medical History eCRF should be comprehensive of patient's medical history up to Day -10 when study treatment starts.

Any event after written informed consent has been obtained and prior to study treatment initiation should be recorded as medical history unless the event is directly related to a screening procedure, in such case it would be considered an AE/SAE and documented on the AE/SAE eCRF.

All AEs/SAEs occurring from initiation of study treatment (first dose of Rituximab) until the End of Study visit are to be documented on the AE/SAE eCRF.

When new significant information is obtained as well as when the outcome of an event is known, the Investigator should record the information on a new SAE form. If the patient was hospitalized, a copy of the discharge summary must be included as part of the patient medical file. In all instances, the Investigator should follow up with patients until the outcome of the SAE is known.

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded on the AE eCRF. Any clinically relevant change in laboratory

assessments or other clinical findings is considered an AE and must be recorded on the AE eCRF. All AEs are to be followed until the event resolves or the clinical course is stabilized.

For SAEs, a SAE form must be completed with as much information as possible and submitted in the time frame described below.

On discovery, all SAEs should be immediately reported (latest within 24 hours of knowledge of the event) to Parexel Safety Services by:

- Entering the AE in the appropriate section (AE page and/or SAE page) of the eCRF, indicating that the event is considered serious, and providing all the details per the eCRF completion guidelines.
- Completing the SAE Report Form and transmitting the documents to Parexel MSS, using direct transmission, the appropriate regional Parexel SAE fax number or email address below:
- For non-US sites - France (Paris) Fax: +33 1 44 90 32 75 or +33 1 44 90 35 34
- For US sites - North America (Billerica) fax: +1 781 434 5957
- Global: Medical_Paris@parexel.com
- - In the event that the site is unable to complete the SAE form to report the event within 24 hours of their knowledge of the event, the investigators may report the SAE over the telephone via the SAE answering service, and then transmit the completed SAE form via direct transmission, fax or email, If questions arise regarding the reporting procedures or the specifics of the reporting of an event, sites may call utilizing the following number:
- For non-US sites - France (Paris) Phone: +33 1 44 90 32 90

For US sites - North America (Billerica) phone: +1 781 434 5010 If there are serious, unexpected AEs associated with the use of the study drug, Parexel will notify the appropriate regulatory agency(ies) including reporting to the Eudravigilance database and all appropriate parties on an expedited basis. It is the responsibility of the Investigator to promptly notify the Institutional Review Board (IRB)/Ethics Committee (EC) of all unexpected SAEs involving risk to human patients.

15.3. Other Required Safety Assessments

A clinically significant worsening from Baseline of any abnormal study assessment, such as laboratory test, physical examination, or vital signs, should be considered an AE and recorded accordingly. If possible, a diagnosis for the clinically significant study assessment should be provided by the Investigator (e.g., urinary tract infection or anemia). In the absence of a diagnosis, the abnormal study assessment itself should be listed as the AE (e.g., bacteria in urine or decreased hemoglobin).

An abnormal study assessment is considered clinically significant if the patient has one or more of the following related to the abnormal study assessment:

1. Concomitant clinical signs or symptoms
2. Further diagnostic testing or medical/surgical intervention
3. A change in the dose of study drug or patient discontinued from the study

Repeat testing to determine whether the result is abnormal, in the absence of any of the above criteria, does not necessarily meet clinically significant criteria. The determination of whether

the study assessment results are clinically significant will be at the discretion of the Investigator.

15.4. Pregnancy

15.4.1. Pregnancy Reporting

Details of all pregnancies occurring in female participants or female partners of male participants will be collected after the start of study intervention and until delivery if pregnancy consent has been obtained.

If a pregnancy is reported, the Investigator should record the information on the appropriate form and submit it to Parexel Safety Services within 30 days of learning of the pregnancy. The Investigator must follow-up and document the course and the outcome of all pregnancies even if the patient was discontinued from the study or if the study has finished.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. Abnormal pregnancy outcomes (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered to be SAEs. Any post-study pregnancy-related SAE considered reasonably related to study drug by the Investigator will be reported to the Sponsor. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any pregnancy related SAE that occurs during pregnancy (including SAEs occurring after last administration of study drug) must be recorded on the SAE report form (e.g., maternal serious complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.
The pregnancy will be followed to determine the outcome. The Investigator will collect any follow-up information on the participant/participant's partner and the neonate and the information will be forwarded to Parexel. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of the pregnancy will be reported, regardless of foetal state (presence or absence of anomalies) or indication for the procedure. All outcomes of pregnancy must be reported by the Investigator to Parexel on the appropriate form within 30 days after he or she has gained knowledge of the spontaneous or elective abortion or delivery of the baby.
Any female participant who becomes pregnant while participating in the study will discontinue study drug or will be withdrawn from the study.

15.4.2. Females of Childbearing Potential and Contraception

A woman is considered of childbearing potential (ie, fertile) after menarche and until becoming postmenopausal unless surgically sterilized. Surgical sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal ligation and bilateral oophorectomy.

Contraception methods should be used from the time of screening pregnancy test and for ≥ 4 months after the last dose of GDA-201.

Contraception methods include the following:

- Combined (estrogen- and progestogen containing) hormonal contraception associated with the inhibition of ovulation
  - Oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with the inhibition of ovulation
  - Oral, injectable, implantable
- An intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner (provided that the vasectomized partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse)

  Total sexual abstinence should only be used as a contraceptive method if it is in line with the patients' usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of exposure to investigational medicinal product, and withdrawal are not acceptable methods of contraception.

Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception, and, if used, this method must be used in combination with another acceptable method listed above.

If a woman of childbearing potential is using hormonal contraceptives such as birth control pills or devices, a second barrier method of contraception (eg, condoms) must also be used.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient.

16. SPECIAL REQUIREMENTS AND PROCEDURES

16.1. Study Monitoring

The Clinical Monitor will arrange to visit the Investigator sites at regular intervals during the study. The monitoring visits must be conducted according to the applicable International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities. During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be resolved. The Clinical Monitor will be given access to study relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality assurance officers named by Gamida Cell or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

16.1.1. Audits and Inspections

The Investigators and clinical sites will permit trial related monitoring, audits, IRB review, and regulatory inspections as requested by regulatory health authorities, Gamida Cell or designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed ICFs, etc.) in addition to eCRFs.

16.1.2. Data Quality Control and Quality Assurance

The Investigator is responsible for ensuring the study is conducted according to the protocol, Code of Federal Regulations (CFR), GCP, and applicable regulatory requirements. The responsibilities outlined in these documents along with the identification that a signed informed consent must be obtained prior to a patient participation in the study.

16.2. Confidentiality

To maintain patient privacy, all eCRFs, study drug accountability records, study reports and communications will identify the patient by the assigned patient identification number. The Investigator will grant monitor(s) and auditor(s) from Gamida Cell or designee and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

All information regarding the investigational product supplied by Gamida Cell to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from Gamida Cell. It is understood that there is an obligation to provide Gamida Cell with complete

data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.

16.2.1 Publication Policy

The sponsor will review the data periodically, and the results of this study may be presented at one or more medical congresses and/or published in scientific journals. After completion of the study, the sponsor will prepare a clinical study report based on data from all participating countries. This study and its results may be submitted for inclusion in appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

16.3. Protocol Amendments

Protocol amendments that impact patient safety, change the scope of the investigation, or affect the scientific quality of the study must be approved by the IRB/IEC and submitted to the appropriate regulatory authorities before implementation of such modifications to the study.

In the event that the protocol needs to be modified immediately to eliminate an apparent hazard to a patient, Gamida Cell will amend and implement the protocol change and subsequently notify the regulatory authorities and/or the IRB/IEC, as appropriate.

The Investigator should not modify the protocol without agreement from Gamida Cell and prior review or approval by the IRB/IEC. Any deviations from the protocol should be documented by the Investigator or designee.

16.4. Obligations of the Principal Investigator

16.4.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

The Investigator must obtain written IRB/IEC approval of the protocol, approval for relevant supporting information and all types of patient recruitment and advertisement and the ICF prior to starting the study. The IRB/IEC will meet all local regulatory requirements governing IRBs/IECs.

Gamida Cell or the designee must approve the ICF submitted to the investigational site's IRB/IEC. All patient recruitment and advertisements must be submitted to Gamida Cell or designee prior to submission to the IRB/IEC, for review.

16.4.2. Ethical Conduct of the Study

Gamida Cell and the Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines and must also conduct the study in accordance with local regulations.

16.4.3. Written Informed Consent

Written informed consent is required from each patient prior to any testing under this protocol, including screening tests and evaluations. The ICF, as specified by the investigational site's IRB/IEC, must follow the Protection of Human Subjects regulations.

The background of the proposed study and the benefits and risks of the procedures and study must be explained to the patients. It is the responsibility of the Investigator to obtain consent and to provide the patient with a copy of the signed and dated ICF. Confirmation of a patient's informed consent must also be documented in the patient's medical record prior to any testing under this protocol, including screening tests and evaluations.

All ICFs used in this study must be approved by the appropriate IRB/IEC and by Gamida Cell or designee. The ICF must not be altered without the prior agreement of the relevant IRB/IEC and Gamida Cell.

16.4.4. Patient Data Protection

The participants will be informed that their personal study-related data (including explanation on the level of disclosure) will be used by the sponsor in accordance with local data protection law. The participants will be required to give consent for their data to be used as described in the informed consent.
All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participants personal data. Such measures will include omitting participant names or other directly identifiable data on any blood collection tubes, sponsor forms, reports, publications, or in any other disclosures, except where required by applicable laws.
Personal data will be stored at the study site in encrypted electronic and/or paper form and will be stored in a secure location.
In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.
To protect the rights and freedoms of natural persons with regards to the processing of personal data, when study data are compiled for transfer to sponsor and other authorized parties, participant names will be removed and will be replaced by a single, specific participant code. All other identifiable data transferred to the sponsor or other authorized parties will be identified by this single, participant-specific code.
The investigator site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his actual identity. The participants will be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, [by appropriate IRB/IEC members,] and by inspectors from regulatory authorities.

17. DATA HANDLING AND RETENTION OF RECORDS

17.1. Electronic Case Report Form Completion

eCRFs will be completed for each enrolled patient. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the patient's eCRF. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status.

Investigators will maintain copies of the eCRFs at the clinical site. For patients who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuance or termination clearly and concisely specified on the appropriate eCRF.

17.2. Retention of Records

The Investigator will maintain all study records according to ICH GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. Gamida Cell must be notified in writing if a custodial change occurs.

18. REFERENCES

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APPENDIX A. PERFORMANCE STATUS SCALE AND NYHA CLASSIFICATION

ECOG PERFORMANCE STATUS SCALE

Grade	ECOG PERFORMANCE STATUS
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 house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

REFERENCE
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NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound patients.

REFERENCE
The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9t

APPENDIX B. INFECTIOUS DISEASES SOCIETY OF AMERICAS (IDSA) GUIDELINES ON CLEARANCE OF HEPATITIS B AND C INFECTION

Hepatitis B (HBV) – Lok et al. Chronic Hepatitis B: Updated 2009. *Hepatology*, September 2009.

Resolved hepatitis B— Previous HBV infection without further virologic, biochemical or histological evidence of active virus infection or disease.

1. Previous known history of acute or chronic hepatitis B or the presence of anti-HBc ± anti-HBs
2. Hepatitis B surface antigen (HBsAg) negative
3. Undetectable serum HBV DNA (very low levels may be detectable using sensitive PCR assays)
4. Normal ALT levels

HBsAg and anti-HBc testing should be performed in persons who have high risk of HBV infection prior to initiation of chemo- or immunosuppressive therapy. Pro-phylactic antiviral therapy should be administered to hepatitis B carriers (regardless of baseline serum HBV DNA level) at the onset of cancer chemotherapy or a finite course of immunosuppressive therapy, and maintained for 6 months afterwards.

While HBV reactivation can occur in persons who are HBsAg negative but anti-HBc and anti-HBs positive and in those with isolated anti-HBc, this is infrequent, and there is not enough information to recommend routine prophylaxis for these individuals. These patients should be monitored and antiviral therapy initiated when serum HBV DNA becomes detectable.

Hepatitis C (HCV) - https://www.hcvguidelines.org/evaluate/monitoring

It is essential to test for HCV RNA 12 weeks (or longer) after treatment completion. Undetectable or unquantifiable HCV RNA 12 weeks or longer after treatment completion is defined as a sustained virologic response (SVR), which is consistent with cure of HCV infection. Virologic relapse is rare 12 weeks or longer after treatment completion. Nevertheless, repeat quantitative HCV RNA testing can be considered at 24 or more weeks after completing treatment for patients in whom ALT increases to above the upper limit of normal (ULN).

APPENDIX C. DEFINITIONS OF TUMOR RESPONSE (LUGANO, 2014)

Response	Site	PET-CT Metabolic Response	CT Radiologic Response
Complete Response	LN and extralymphatic sites	Score 1, 2, or 3 with or without a residual mass on a 5-point scale	All of the following: Target LN regress to ≤ 1.5 cm in longest transverse diameter (LDi) No extralymphatic sites of disease
	Non-measured lesion	Not applicable	Absent
	Organ enlargement	Not applicable	Regress to normal
	New lesions	None	None
	Bone marrow	No evidence of FDG-avid disease in BM	Normal by morphology; if indeterminant, IHC negative
Partial Response	LN and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of measurable LN and extranodal sites
	Non-measured lesion	Not applicable	Absent/normal, regressed, no increase
	Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
	New lesions	None	None
	Bone marrow	Residual uptake higher than normal marrow but reduced compared with baseline	Not applicable
Response	**Site**	**PET-CT Metabolic Response**	**CT Radiologic Response**
No response or stable disease	LN and extralymphatic sites	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of LN or extranodal sites. No criteria for PD are met
	Non-measured lesion	Not applicable	No increase consistent with PD
	Organ enlargement	Not applicable	No increase consistent with PD
	New lesions	None	None
	Bone marrow	No change from baseline	Not applicable

Progressive Disease	LN and extralymphatic sites	Score 4 or 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma	Requires at least one of the following: LN/lesion with LDi > 1.5 cm and increase by ≥ 50% from PPD nadir and an increase in LDi or SDi from nadir of 0.5 cm for lesions ≤ 2 cm and 1.0 cm for lesions > 2 cm. Spleen increased length by 50%; new or recurrent splenomegaly, must increase by at least 2 cm from baseline.
	Non-measured lesion	None	New or clear progression of preexisting non-measured lesions
	New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology	Regrowth of previously resolved lesions New LN > 1.5 cm in any axis New extranodal site ≥ 1.0 cm in any axis Assessable disease of any size unequivocally due to lymphoma
	Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: LDi, longest transverse diameter of a lesion; LN, lymph nodes; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; SPD, sum of the products of the diameters; PD, progressive disease; PPD, perpendicular diameter.

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

APPENDIX D. GVHD ASSESSMENT

Acute GvHD Definition

Acute GvHD will be classified according to the Consensus Conference on Acute GvHD grading (Przepiorka et al. 1995).

Table 8: GvHD classification

Overall Grade	Skin	Liver	Gut
I	Stage 1-2	None	None
II	Stage 3 or	Stage 1 or	Stage 1
III		Stage 2-3 or	Stage 2-4
IV	Stage 4 or	Stage 4	

*See following table for individual organ staging. The overall grade of GvHD, however, reflects the actual extent of disease. For each overall grade, an assessment of skin disease plus liver and/or gut involvement is required.

Table 9: Clinical manifestations and staging of acute graft versus host disease

Organ	Clinical Manifestations	Staging[e]
Skin[a]	Erythematous, maculopapular rash involving palms and soles; may become confluent Severe disease: bullae	Stage 1: <25% rash Stage 2: 25-50% rash Stage 3: generalized erythroderma Stage 4: bullae
Liver[b]	Painless jaundice with conjugated hyperbilirubinemia and increased alkaline phosphatase	Stage 1: bilirubin 2-3 mg/dL Stage 2: bilirubin 3.1-6 mg/dL Stage 3: bilirubin 6.1-15 mg/dL Stage 4: bilirubin >15 mg/dL
Gastrointestinal tract[c]	Upper: nausea, vomiting, anorexia Lower: diarrhea, abdominal cramps, distention, ileus, bleeding	Stage 1: diarrhea >500 ml/day or persistent nausea, vomiting, or anorexia [d] Stage 2: diarrhea >1000 ml/day Stage 3: diarrhea >1500 ml/day Stage 4: large volume diarrhea and severe abdominal pain +/- ileus

[a] Use 'Rule of Nines' or burn chart to determine extent of rash

[b] Range given as TBili. Downgrade one stage if a cause of elevated bilirubin other than GvHD has been documented.

[c] Downgrade one stage if a cause of diarrhea other than GvHD has been documented.

[d] Downgrade upper GI one stage if biopsy result is negative, or if no biopsy done and GvHD is not an etiology, or if the biopsy is equivocal and GvHD is not an etiology.

[e] Although GvHD will be assessed at every protocol-specified visit, GvHD will only be analyzed if it occurs after primary neutrophil engraftment. If GvHD is not an etiology for any organ, then GvHD is downgraded to stage 0.

Chronic GvHD Definition

Chronic GvHD will be classified as mild, moderate, or severe, according to the National Institute of Health consensus grading criteria[i] summarized below:

Table 10: NIH Global Severity of chronic GvHD

Global Severity	Criteria
Mild	1-2 organs involved with a max organ severity score of 1 AND Lung score=0
Moderate	≥3 organs involved with a max organ severity score of 1 OR Any organ (except lung) with a severity score of 2 OR Lung score=1
Severe	Any organ with a severity score of 3 OR Lung score ≥2

Notes for global severity scoring:

Clinical centers must reference the 2014 consensus criteria for organ specific severity grading (Jagasia et al. 2015). A record of the organ specific scoring must be kept on file at the clinical center. See cGvHD scoring worksheet in the Data Management Handbook; either the provided worksheet or an equivalent EMR adaptation of the form (approved by the sponsor) must be used to document chronic GvHD.

In skin: higher of the 2 scores to be used for calculating global severity.

In lung: FEV1 is used instead of clinical score for calculating global severity.

If the entire abnormality in an organ is noted to be unequivocally explained by a non-GvHD documented cause, that organ is not included for calculation of the global severity.

If the abnormality in an organ is attributed to multifactorial causes (GvHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

APPENDIX E. EXPECTED TOXICITIES OF STUDY MEDICATION

Rituximab		
common	**less common**	**rare, but may be serious**
• mild allergic reaction with first infusion (may include fever, headache, chills, itching, hives, nausea, shortness of breath) • upper respiratory tract infection • nasopharyngitis • urinary tract infection • bronchitis	• allergic reaction with second and later infusions (same symptoms as under common) • low white blood cell (WBC) count with increased risk of infection • cough • rash, itching • nausea • vomiting • diarrhea • muscle aches • runny nose • sinus infection	• serious allergic reaction, with hives, trouble breathing, tightness in the chest or throat • heart attack, or shock • serious skin reaction • kidney damage • low platelet count with increased risk of bleeding • blockage or hole in the bowel, with abdominal (belly) pain • low red blood cell count (anemia) with tiredness and weakness • death due to allergic reaction, infection, lung damage, tumor lysis syndrome, serious skin rash, bowel obstruction, liver failure from reactivated hepatitis b, and other causes

Prescribing Information for Rituximab:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761088s018lbl.pdf

IL-2		
common	**less common**	**rare, but may be serious**
• fever • chills • skin rash • decreased platelet count • nausea • vomiting • diarrhea • low blood pressure • fast heart rate • confusion • shortness of breath	• fatigue • tiredness • fluid retention • weight gain • abnormal liver function tests • infection • mouth sores • poor appetite • dizziness • dry or peeling skin	• capillary leak syndrome • hypothyroidism • abnormal renal function tests

• low urine output		

Prescribing Information for Proleukin (IL-2):
https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103293s5130lbl.pdf

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Lymphodepleting Preparative Regimen (All patients)

Cyclophosphamide		
Common	**Less Common**	**Rare, but may be serious**
• low white blood cell (WBC) count with increased risk of infection • hair loss or thinning, including face and body hair (usually grows back after treatment) • nausea • vomiting • loss of appetite • sores in mouth or on lips • bleeding from bladder, with blood in urine • diarrhea • long-term or short-term infertility (inability to have children) in women and men	• low platelet count (mild) with increased risk of bleeding • darkening of nail beds • acne • tiredness • infection • fetal changes if you become pregnant while taking cyclophosphamide	• heart problems with high doses, with chest pain, shortness of breath, swollen feet or rapid weight gain • severe allergic reactions • skin rash • scarring of bladder • kidney damage (renal tubular necrosis) which can lead to kidney failure • scarring of lung tissue, with cough and shortness of breath • second cancer, which can happen years after taking this drug • death from infection, bleeding, heart failure, allergic reaction, or other causes
Fludarabine		
Common	**Less Common**	**Rare, but may be serious**
• low white blood cell (WBC) count with increased risk of infection • low platelet count with increased risk of bleeding • low red blood cell count (anemia) with tiredness and weakness • tiredness (fatigue) • nausea • vomiting • fever and chills • infection	• pneumonia • diarrhea • loss of appetite • weakness • pain	• numbness and tingling in hands and/or feet related to irritation of nerves • changes in vision • agitation • confusion • clumsiness • seizures • coma • cough • trouble breathing • intestinal bleeding • weakness • death due to effects on the brain, infection, bleeding, severe anemia, skin blistering, or other causes

Prescribing Information for Cyclophosphamide:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212501s000lbl.pdf

Prescribing Information for Fludarabine:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020038s032lbl.pdf**Risks associated with pre-medications**

Acetaminophen

Risks associated with acetaminophen are rare but can include possible low WBC count, low RBC count, low PLT count and skin rash. Acetaminophen can also cause liver injury if more than the prescribed dose is taken. Subjects should not exceed the maximum total daily dose of 4 g/day and should avoid consuming alcohol when taking acetaminophen.

Prescribing Information for Acetaminophen:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/204767s000lbl.pdf**Acyclovir**
The most common side effects observed in individuals receiving acyclovir PO are low RBC count, low WBC count and malaise. There are reports of worsening in subjects with a history of renal disease, however, this has been reported for higher doses than the 400 mg of acyclovir received in this study.

Prescribing Information for Acyclovir:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/018828s030,020089s019,019909s020lbl.pdf**Allopurinol**
The most common risks associated with allopurinol are increased risk of gout and skin rash which may sometimes be severe. Other common risks include diarrhea, nausea, alkaline phosphatase increase, increase in liver enzymes, possible low WBC count, low RBC count, and low platelet count. Rarely patients experience renal dysfunction. The risks of developing gout and possible renal dysfunction can be reduced by ensuring sufficient fluid intake to maintain a balanced daily urine output (2 liters).

Prescribing Information for Allopurinol:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/016084s044lbl.pdf**Diphenhydramine**
The most common side effects observed in individuals receiving diphenhydramine are sedation, sleepiness, dizziness, disturbed coordination, pain in the middle of the upper abdomen and thick secretions from the respiratory tract.

Prescribing Information for Diphenhydramine:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/091526lbl.pdf

APPENDIX F. THE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) VERSION 5.0

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

APPENDIX G. INSTRUCTIONS FOR DILUTION AND ADMINISTRATION OF IL-2

For the purposes of this study, subcutaneous (SC) IL-2 6 million units will be given every other day for a total of 3 doses beginning after the NK cell infusion. Dose for patients weighing less than 45 kg: 3 million units/m^2

A vial containing 22 million International Units (mIU) of Proleukin should be reconstituted with 1.2 ml of sterile water as follows:
Using sterilised injection syringe and injection needle, inject 1.2 ml sterile water into the vial of Proleukin. Direct the diluent against the side of the vial to avoid excessive foaming. Swirl gently to facilitate complete dissolution of the powder. Do not shake.
Following reconstitution, the concentration of the obtained solution is 18mIU/ml. Withdraw 0.33 ml (containing 6 mIU of Proleukin) with a sterile injection syringe and inject subcutaneously.

Reconstituted or diluted Proleukin is stable for up to 48 hours at refrigerated and room temperatures, 2° to 25°C (36° to 77°F). However, since this product contains no preservative, the reconstituted and diluted solutions should be stored in the refrigerator (from the Product Label).