A RANDOMIZED, OPEN-LABEL, PHASE 2 STUDY EVALUATING LYMPHODEPLETION WITH FLUDARABINE, CYCLOPHOSPHAMIDE, AND ALLO-647, VS. FLUDARABINE AND CYCLOPHOSPHAMIDE ALONE, IN SUBJECTS WITH RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA (LBCL) RECEIVING ALLO-501A ALLOGENEIC CAR T CELL THERAPY

Investigational Product Number:	ALLO-647 / ALLO-501A
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OVERVIEW OF CHANGES

An overall summary of the changes reflected in Amendment 1, dated 13 October 2022, along with the rationale for the changes, are provided in the following table.

Section	Summary of Changes	Rationale for Change
Synopsis; Figure 1 Schema; Figure 2 Lymphodepletion and Cell Dose; 1.2.4.3.2 ALLO-647 Dose and Lymphodepletion Regimen; 1.2.6.4 RP2D for Lymphodepletion Regimen; 3.1 Study Overview	Modified the dosing in the Fludarabine, Cyclophosphamide, and ALLO-647 arm to be FCA-90 (ALLO-647 90 mg total dose; 30 mg/day x 3 days), and deleted the FCA-60 dose and ALC-based dosing requirements.	Sponsor has determined the FCA-90 regimen to be optimal based on clinical response rates and safety tables, supported by the PK/PD data.
Synopsis; 3.1 Study Overview; 5.1 Allocation to Treatment; 9.3.5 Randomization;	Changed the randomization stratification factor to be based on the risk factors LDH and tumor lesion size: Stratum 1: ULN < LDH ≤ 2 x ULN **and** presence of lesion ≥5 cm Stratum 2: LDH ≤ ULN **or** all lesions <5 cm	The stratification factor is intended to balance randomized subjects across the 2 arms with less favorable disease characteristics of higher baseline LDH and bulky tumors.
Synopsis; 2.2 Objectives and Endpoints	Modified Secondary Objectives and Endpoints by moving ALLO-647 PK/PD and host T cells, and ALLO-501A cellular kinetics, and immunogenicity of ALLO-647 and ALLO-501A from Exploratory to Secondary.	To reflect the additional components of investigating ALLO-647's role in enhancing effectiveness of CAR T therapy.
Synopsis; 8.5 Data Safety Monitoring Board; 9.2 Sample Size Determination	Added the DSMB's review of SAEs for enrollment pausing criteria will occur after [redacted] have been randomized and had the opportunity to be followed after the first dose of lymphodepletion.	Providing additional information regarding the DSMBs activities in monitoring safety in an ongoing manner throughout the study, including the potential to pause enrollment.

Section	Summary of Changes	Rationale for Change
4.2 Exclusion Criteria	The following Exclusion Criteria were modified or added: • Clarified that untreated latent tuberculosis is ineligible. • Unstable arrhythmia. • History of solid organ transplant (corneal transplant permitted). • History of hemophagocytic lymphohistiocytosis (HLH). • History of progressive multifocal leukoencephalopathy (PML). • Clinically significant liver disease, including viral or other hepatitis or cirrhosis. Clinically significant pulmonary disease, such as severe COPD; bronchospasm requiring intubation; interstitial lung disease, or pneumonitis (drug-related or autoimmune).	These additional exclusion criteria provide further clarification that subjects with unstable or medically severe conditions, or a history of adverse reactions, may be unsuitable for CAR T therapy and are excluded.
5.12.3 Anti-Infective Prophylaxis	CMV-seropositive subjects on the FC arm may receive letermovir at the investigator's discretion.	Although CMV-seropositive subjects receiving the anti-CD52 antibody ALLO-647 are at the greater risk of CMV reactivation and should receive prophylaxis with letermovir, subjects receiving FC-alone may also be at risk, and may receive letermovir at the investigator's discretion.
7.9 Patient Reported Outcomes; Schedule of Activities	PROs are not required to be completed before any other assessment during a clinic visit.	PRO completion is aligned with visits where disease assessment scans are conducted. However, the scan results would not typically be available at the time the subject completes the PRO. To facilitate efficient and effective clinic

Section	Summary of Changes	Rationale for Change
		visits, the PRO does not have to be completed before any other procedure or assessment.
Schedule of Activities and Footnotes	Removed Day 4 lymph node biopsy procedure	A lymph node biopsy at this timepoint is not standard of care for lymphoma, and is removed from the protocol.
Schedule of Activities and Footnotes	Removed Day -5 ALLO-501A transgene level sample, and added Focal Copy Number Score sample during screening (for baseline).	Day -5 transgene levels before CAR is not necessary.
Schedule of Activities and Footnotes	Removed footnote instruction to collect bone marrow biopy at each timepoint when tumor assessments are performed, as this is not standard of care.	Inconsistent with standard of care, and not supporting study endpoints.
9.2 Sample Size Determination; 9.3 Statistical Methods	Updates to statistical definitions or analysis plans as needed to support study conduct, including DSMB reviews.	As needed for effective study planning.
Throughout as applicable	Corrected typos, formatting, section numbering, etc. as necessary.	Minor corrections for consistency and accuracy

PROTOCOL SYNOPSIS

Study Title: A randomized, open-label, Phase 2 study evaluating lymphodepletion with fludarabine (F), cyclophosphamide (C), and ALLO-647 (A) vs FC alone, in subjects with R/R LBCL receiving ALLO-501A allogeneic CAR T cell therapy.

Number of Subjects: The target accrual is approximately 70 subjects, with subjects randomized in a 1:1 ratio to one of 2 treatment arms: lymphodepletion with FCA or FC, followed by ALLO-501A CAR T cell therapy. This study is designed with an adaptive sample size re-adjustment. If the criteria to adjust the sample size are met, up to 136 subjects may be randomized in the same 1:1 ratio.

Test Products:

Investigational Medicinal Products (IMPs):

IMP1: ALLO-501A, an allogeneic CAR T targeting CD19.

IMP2: ALLO-647 is a humanized [redacted] monoclonal antibody that recognizes the human CD52 antigen and will be used as a part of the lymphodepletion regimen.

Non-IMPs:

Fludarabine, cyclophosphamide, as part of the lymphodepletion regimen.

Study Hypotheses: ALLO-647 (A), administered with fludarabine (F) and cyclophosphamide (C) in a lymphodepletion regimen before ALLO-501A is efficacious in subjects with relapsed/refractory (R/R) large B-cell lymphoma (LBCL), as determined by prolongation in progression-free survival (PFS) relative to FC alone as assessed per Lugano Classification and Independent Review Committee (IRC).

Study Objectives:

Primary Objective: To assess clinical efficacy of ALLO-647 (in a lymphodepletion regimen before ALLO-501A) compared to FC alone as measured by PFS and assessed by IRC in subjects with R/R LBCL.

Secondary Objectives:

- To assess the clinical efficacy of ALLO-647 as measured by ORR and assessed by IRC between treatment arms.
- To assess clinical efficacy of ALLO-647 with FC (in a lymphodepletion regimen before ALLO-501A) compared to FC alone as measured by EFS and assessed by IRC in subjects with R/R LBCL.
- To characterize the efficacy of ALLO-647 as measured by DOR and assessed by IRC between treatment arms.
- To characterize other aspects of the efficacy of ALLO-647 including PFS, response rate per investigator review, DOR, and overall survival.

- To characterize the depth and duration of lymphodepletion with and without ALLO-647
- To characterize the PK of ALLO-647.
- To characterize cellular kinetics of ALLO-501A when administered with lymphodepletion with and without ALLO-647.
- To characterize the pharmacodynamics of ALLO-647 on host T cells.
- To evaluate the immunogenicity of ALLO-647 and ALLO-501A.
- To evaluate the overall safety profile of ALLO-647 by comparing FCA lymphodepletion with FC lymphodepletion.
- To evaluate the overall safety profile of ALLO-501A following lymphodepletion.

Study Population: Key Eligibility Criteria

Key Inclusion Criteria:

1. Histologically confirmed diagnosis of relapsed/refractory large B cell lymphoma at last relapse per WHO 2017 criteria:
    a. DLBCL not otherwise specified, DLBCL coexistent with follicular lymphoma of any grade, EBV+ DLBCL, T cell/histiocyte rich large B cell lymphoma, DLBCL with IRF4/MUM1 rearrangement,
    b. High-grade B cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements,
    c. Transformation of follicular lymphoma or marginal zone lymphoma to DLBCL
    d. Primary mediastinal B cell lymphoma
    e. Follicular lymphoma Grade 3B
2. Relapsed or refractory disease after at least 2 lines of chemotherapy including an anthracycline and an anti-CD20 monoclonal antibody.
3. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.
4. Absence of significant donor (product)-specific anti-HLA antibodies (DSA) at screening.
5. Adequate hematologic, renal, and liver function, including absolute lymphocyte count (ALC) $\geq$300/μL.
6. Lactic acid dehydrogenase (LDH): $\leq$2 x ULN

Key Exclusion Criteria:

1. Active central nervous system (CNS) involvement by malignancy. Note: subjects with a history of CNS disease that has been effectively treated will be eligible.
2. Autologous or allogeneic HSCT within last 6 months (24 weeks) prior to lymphodepletion.

3. Prior treatment with anti-CD19 targeted therapies (including CAR T cell therapy and bispecific antibodies, etc) will be excluded.
4. Hypocellular bone marrow for age by institutional standard as determined from a bone marrow biopsy performed at time of screening.

Study Design:

Subjects must have relapsed or refractory LBCL after at least 2 lines of chemotherapy, including an anthracycline and an anti-CD20 monoclonal antibody.

The target accrual is approximately 70 subjects, with subjects randomized in a 1:1 ratio to a lymphodepletion regimen of either FC or FCA.

Randomization will be stratified based on the following risk factors:

Stratum 1: ULN < LDH ≤ 2 x ULN **and** presence of lesion ≥5 cm (50 mm)

Stratum 2: LDH ≤ ULN **or** all lesions <5 cm

- FCA: Lymphodepletion with FCA (n=35 subjects)
    - F 30 mg/m^2 Days -5, −4, −3
    - C 300 mg/m^2 Days -5, −4, −3
    - ALLO-647 30 mg/day Days -5, -4, -3
- FC: Lymphodepletion with FC (n=35 subjects)
    - F 30 mg/m^2 Days -5, −4, −3
    - C 300 mg/m^2 Days -5, −4, −3

All subjects will be treated with ALLO-501A 120 x 10^6 CAR$^+$ cells following lymphodepletion.

Response assessment for study efficacy endpoints will be determined by an Independent Radiology Committee (IRC). Secondary endpoints will include efficacy endpoints as assessed by the investigator.

Statistical Considerations

Sample Size Considerations

A target of approximately 70 subjects may be randomized in the study. This study is designed with an adaptive sample size re-adjustment. If the criteria to adjust the sample size are met, up to 136 subjects may be randomized.

Interim Analyses

The DSMB will review SAE information and enrollment pausing criteri[redacted] have been randomized and have had the opportunity to be followed for [redacted] after the first dose of lymphodepletion . In addition, the DSMB will review data at 2 interim analyses [redacted] The first interim analysis will be for safety and feasibility and will occur after [redacted] and have had the opportunity to be followed for 2 months after randomization. The second interim analysis will occur [redacted] have been observed at which time the DSMB will evaluate safety, feasibility, early stopping for futility, and the adaptive sample size re-adjustment. The DSMB may review data at other timepoints as needed.

Analysis Methods

The primary analysis will occur when [redacted] events have been observed [redacted] The primary analysis of PFS will be conducted using a stratified (randomization factor) log rank test. The primary endpoint of PFS will be defined as the time from randomization to disease progression per Lugano Criteria as assessed by IRC, or death from any cause. If the primary test of PFS is statistically significant, the secondary endpoint of ORR as assessed by IRC will be tested hierarchically.

As a general approach, continuous variables will be summarized using mean, standard deviation, median, Q1, Q3, minimum value, maximum value. Categorical variables will be summarized using frequency counts and percentages. Time to event data will be summarized using the Kaplan-Meier method. Where appropriate, confidence intervals around point estimates will be presented, and estimates of the median and other quantiles, as well as individual time points (for time to event data) will be produced. Cox model adjusted by the randomization stratification factor will be used to estimate the hazard ratio between treatment arm and associated confidence intervals.

Descriptive statistics will be generated to summarize demographic, medical history, and safety data.

Study Schema:

Figure 1. Study Treatment

F=Fludarabine; C=Cyclophosphamide; A=ALLO-647

Figure 2. Lymphodepletion and Cell Dose

	FCA Arm	FC Arm
[redacted]	Flu 30 Cy 300 ALLO-647 30	Flu 30 Cy 300
[redacted]	Flu 30 Cy 300 ALLO-647 30	Flu 30 Cy 300
[redacted]	Flu 30 Cy 300 ALLO-647 30	Flu 30 Cy 300
[redacted]	-	-
[redacted]	-	-
[redacted]	ALLO-501A 120	ALLO-501A 120

Flu = Fludarabine (dose in mg/m^2); Cy = Cyclophosphamide (dose in mg/m^2); ALLO-647 dose in mg; ALLO-501A dose in $\times 10^6$ CAR$^+$ cells.

Fludarabine dose should be adjusted based on renal function. Subjects with creatinine clearance < 80 mL/min should receive 20 mg/m^2 dose with each daily fludarabine dose or as per institutional guidelines (Fludarabine Drug Summary).

Figure 3. Study Analysis Schema


[redacted]

1. INTRODUCTION

1.1 Mechanism of Action/Indication

ALLO-501A is an allogeneic TRAC/CD52-knockout chimeric antigen receptor (CAR) T cell therapy targeting CD19. ALLO-647 is a novel human [redacted] monoclonal antibody (mAb) that recognizes the human CD52 antigen. The amino acid sequence of ALLO-647 is [redacted] to that of [redacted]. ALLO-501A is being evaluated for the treatment of subjects with relapsed or refractory (R/R) large B-cell lymphoma (LBCL) and is administered after a lymphodepletion regimen comprising fludarabine (F), cyclophosphamide (C), and ALLO-647 (A).

1.2 Background and Rationale

CD19 is a promising target antigen for CAR T cell therapy against B cell malignancies due to its very restricted pattern of expression. CD19 is present on normal and malignant B cells and it lacks homology to other known proteins (Tedder 2009; Wang et al, 2012). Additionally, virtually all B cell malignancies (with the exception of some very immature acute lymphoid leukemias) express CD19 on their surface (Tedder 2009). Its function is thought to be in establishing the threshold for B cell receptor-dependent and receptor-independent signaling, playing a role in modulating the balance between antigen-induced response and tolerance induction (Carter and Fearon, 1992).

1.2.1 Non-Hodgkin Lymphoma

Non-Hodgkin lymphoma (NHL) is the most common hematological malignancy in the United States, with an estimated 125,850 new cases diagnosed each year (Teras et al, 2016). Over 60 NHL subtypes have been identified, and each subtype represents different neoplastic lymphoid cells (T, B, or NK cells) that have arrested at different stages of differentiation. The most common subtype is B cell NHL (B-NHL), which accounted for over 90% of all new NHL cases in 2016.

B-NHL represents a group of different neoplasms that not only differ in pathology, but also in response to therapy and prognosis. NHL can be rapidly growing (aggressive) with short survival, eg, diffuse large B cell lymphoma (DLBCL), or it can be slow growing (indolent). Despite recent therapeutic advances, more than 50% of patients with aggressive B-NHL are incurable.

1.2.2 Large B-cell Lymphoma

LBCL, which comprises 20% to 30% of B NHLs, includes a group of molecularly diverse aggressive lymphomas that not only differ in their morphology, chromosomal alterations, but also in their signaling pathway activation and clinical outcome. The disease itself may be de novo or may result from transformation of indolent B lymphomas such as from transformed follicular lymphoma. In the US, the annual incidence rate of LBCL is 5.6 per 100,000 (SEER 2021), and in the EU, the annual incidence rate is 3.8 per 100,000 (Tilly et al, 2015), and is the most common form of B-NHL. LBCL is fatal if not cured. Primary mediastinal LBCL and transformed follicular lymphoma are typically treated along a LBCL paradigm.

Approximately half of all patients with aggressive B-NHL have R/R disease, with an estimated 10% to 15% of patients with LBCL having primary refractory disease and an additional 20% to 30% relapsing after an initial objective response (Chaganti et al, 2016). High-grade B cell lymphomas with aberrations in MYC, BCL2, and/or BCL6, including "double hit" and "triple hit" lymphomas, are associated with an inferior prognosis, even in the newly diagnosed setting (Rosenthal and Younes, 2017). Patients with germinal center B-cell like DLBCL experienced worse overall survival and higher relapse versus non-germinal center B-cell DLBCL following an autologous hematopoietic stem cell transplant (HSCT) (Iqbal et al, 2020). Prognosis is poor for patients with R/R LBCL who are ineligible for HSCT because of age, comorbidity, or inadequate response to salvage therapy, with median overall survival (OS) of approximately 6 months (Crump et al, 2017).

A meta-analysis (SCHOLAR-1 study) underscores the poor prognosis of patients with aggressive lymphoma that is R/R early after HSCT. In this analysis of 636 patients, the overall response rate (ORR) to modern salvage therapy was only 26%, complete response (CR) rates were 7%, and the median OS was 6.3 months (Crump et al, 2017). Patients with the activated B cell subtype of DLBCL, not otherwise specified, are the least responsive and have the worst prognosis (Lenz et al, 2008). For patients with R/R DLBCL, salvage therapies will lead to long-term survival in only 10% of cases.

1.2.3 Chimeric Antigen Receptor T cells

Adoptive cellular immunotherapy with CAR T cells has changed the treatment landscape of relapsed or refractory B NHL, especially for aggressive B cell lymphomas. Clinical trials with anti-CD19 CAR T cell therapy have shown great activity and long-term remissions in high-risk, poor-prognosis DLBCL when no other effective treatment options are available (Chavez et al, 2019). Three autologous CAR T-cell products (lisocabtagene maraleucel [Breyanzi], tisagenlecleucel [Kymriah], and axicabtagene ciloleucel [Yescarta]) have received marketing approval (by both the US Food and Drug Administration and the European Medicines Agency) for the treatment of refractory DLBCL after 2 lines of therapy (Breyanzi USPI, Breyanzi EPAR, Kymriah USPI, Kymriah SmPC, Yescarta USPI, Yescarta SmPC). Others are currently being studied in the clinic. CAR T cell-related toxicity with cytokine release syndrome (CRS) and neurotoxicity remain important complications of this therapy.

While an autologous approach has been the main focus for adoptive transfer therapies to date, there are a number of drawbacks to this approach. For example, the number of cells available for isolation from the patient may be scarce, and it is also possible that prior therapies or advanced age of the subject could have an impact on the cell's functionality. The need to isolate, expand and transfect T cells on an individual basis will generate prolonged waiting periods; therefore, prevent rapid access to therapy.

1.2.4 Lymphodepletion Regimen Including ALLO-647

Due to its allogeneic nature and human leukocyte antigen (HLA) mismatch, ALLO-501A is expected to elicit a faster endogenous CD8+ T cell-mediated host-versus-graft response than autologous products. As a result, ALLO-647 may be needed to produce a sufficiently deep

and/or durable suppression of lymphocytes, for optimal ALLO-501A expansion and persistence.

Depletion of the immune cells with cytotoxic agents has been shown to enhance the antitumor activity of adoptive cell transfer both in mouse tumor models (Dummer et al, 2002) and in cancer patients (Dudley et al, 2002; Childs and Barret, 2004). The mechanisms by which lymphodepletion enhances the anti-tumor activity have been shown to involve depletion of immune suppressive regulatory elements, an increase in beneficial cytokines such as IL-7 and IL-15, and removal of lymphocytes, which can be a sink for such cytokines (Gattinoni et al, 2005). These 2 cytokines, along with monocyte chemoattractant protein-1 (MCP-1), have been shown to increase in the serum of patients following administration of lymphodepletion chemotherapy with fludarabine and cyclophosphamide. Patients who achieved remission of lymphoma developed higher serum peak levels of IL-15 and IL-10 (Kochenderfer et al, 2017), suggesting superior lymphodepletion was achieved. Recently, a multivariate analysis of the effect of lymphodepletion on the clinical outcome of autologous CAR T cell in a study of patients with aggressive NHL indicates that serum Day 0 MCP-1 and peak IL-7 concentration following lymphodepletion were associated with better progression-free survival (PFS; Hirayama et al, 2019), suggesting that strategies to augment the cytokine response to lymphodepletion are warranted.

To increase the potential of developing a favorable cytokine profile at the time of CAR infusion and delay the host immune rejection of allogeneic cells, an additional anti-lymphocyte agent (that will have minimal impact on the infused CAR T cells) is hypothesized to be beneficial. CD52 is a cell-surface glycoprotein present on cells that may lead to a host-vs-graft reaction, such as T cells, but is also present on distinct B cell populations, natural killer (NK) cells, monocytes, macrophages, and dendritic cells (Rao et al, 2012); CD52 is also dimly expressed on neutrophils (Zhao et al, 2017).

Alemtuzumab was the first IgG1 mAb against the CD52 antigen and is known to be one of the most potent lymphodepleting agents (Poire et al, 2011; Morris et al, 2003). Binding of alemtuzumab to CD52 leads to rapid and long-lasting lymphodepletion, believed to be achieved through apoptosis and lysis of $CD52^{+}$ immune cells via antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) (Lemtrada USPI). Thus, the addition of an anti-CD52 mAb to the cytotoxic agents, may deepen and prolong the host lymphodepletion. ALLO-647 is a novel human [redacted] mAb that recognizes the human CD52 antigen. The amino acid sequence of ALLO-647 is [redacted] to that of [redacted]. Allogene is developing ALLO-647 as a lymphodepleting agent for use in combination with cytotoxic FC in patients prior to receiving allogeneic CD52 knockout, CAR T cell therapy.

Knock-out of the CD52 gene renders ALLO-501A insensitive to anti-CD52 targeted therapy. As a result, ALLO-501A cells should persist in the presence of anti-CD52 mAb, while wild-type host immune cells would be delayed in their reconstitution, allowing more time for tumor killing.

No significant direct anti-tumor activity benefit is expected from the anti-CD52 mAb. CD52 expression is heterogeneous among aggressive B cell lymphomas with 25% of DLBCL demonstrating no detectable CD52 (Rodig et al, 2006). A clinical trial studying up to 12 weekly cycles of CAMPATH-1H with a median cumulative dose of 492 mg (range, 83 to 2,099 mg) demonstrated only a 14% partial response (PR) rate in 50 patients with low-grade NHL (Lundin et al, 1998).

This strategy of intensifying lymphodepletion in the allogeneic setting was first tested in the PALL and CALM studies of UCART19, a first-in-class anti-CD19 allogeneic CAR T cell therapy, which combined alemtuzumab with fludarabine and cyclophosphamide in pediatric and adult patients with R/R acute lymphocytic leukemia (ALL). Patients who received a lymphodepletion regimen of FC only (n=4) prior to UCART19 had no cell expansion and did not achieve complete molecular response (minimal residual disease negative [MRD^-] CR), whereas 15 out of 17 patients who received alemtuzumab with the cytotoxic agents fludarabine and cyclophosphamide demonstrated cell expansion and 82% (14 of 17) achieved CR or CRi, of which 71% (10 of 14) achieved MRD^- CR (Benjamin et al, 2020). These observations suggest that the addition of an anti-CD52 mAb improves the host lymphodepletion, allowing for CAR T expansion and subsequent clinical benefit.

Inadequate lymphodepletion has also been reported with UCART22, a CD22-directed allogeneic CAR T cell product for the treatment of relapsed/refractory ALL, that is being developed by Cellectis and utilizes the same TALEN gene editing technology for CD52 knockout as UCART19, ALLO-501 and ALLO-501A (Jain et al, 2020). Of note, Cellectis announced that alemtuzumab (an anti-CD52 mAb with same amino acid sequence as ALLO-647) is being used as part of the lymphodepletion regimen for UCART22 in the BALLI-01 and for UCART123 in the AMELI-01 clinical trial in R/R acute myeloid leukemia (Cellectis 2020). Subjects (n=3) receiving alemtuzumab (with flu/cy for lymphodepletion) had extended host lymphocyte suppression and CAR T expansion, and subjects (n=5) who did not receive alemtuzumab had no expansion or response (Jain et al, 2021).

1.2.4.1 Fludarabine and Cyclophosphamide

Lymphodepletion regimens containing FC form the backbone of conditioning treatment prior to most cell therapies including autologous CAR T therapies for hematologic malignancies with various doses. Fludarabine doses up to 125 mg/m^2 are routinely used and cyclophosphamide total doses up to 1500 mg/m^2 are commonly used. Fludarabine and cyclophosphamide are used for conditioning before autologous CD19 CAR T therapies approved in the US and EU (Yescarta USPI, Yescarta SmPC, Kymriah USPI, Kymriah SmPC, Breyanzi USPI, Breyanzi EPAR).

Additionally, one potential mechanism of allogeneic rejection is due to host T cells as well as suppressor cells resident in the lymphoma microenvironment. Alemtuzumab has been shown to be effective in the vascular compartment but with limited activity in bulky lymph nodes (Lundin, 1998). Allogene hypothesizes that ALLO-647 used in combination with cyclophosphamide would be a means to remove tissue-resident cells in the tumor microenvironment potentially capable of mediating rejection of allogeneic CAR T cells.

Therefore, to date Allogene has evaluated ALLO-647 at total doses of 39 to 90 mg administered with fludarabine (at a total dose of 90 mg/m^2) and cyclophosphamide (at total doses ranging from 900 to 1500 mg/m^2).

1.2.4.2 ALLO-647

ALLO-647 is a novel human [redacted] mAb that recognizes the human CD52 antigen. The amino acid sequence of ALLO-647 is [redacted] to that of [redacted], and ALLO-647 has shown similar ADCC and CDC activity in vitro and similar pharmacokinetics (PK) in a GLP cynomolgus monkey toxicology study. Allogene is developing ALLO-647 as a lymphodepleting agent for use in combination with FC in patients prior to receiving allogeneic CD52 knockout CAR T cell therapy. The approved dose of alemtuzumab for patients with multiple sclerosis is 12 mg/day for 5 days for a total of 60 mg in 1 week. The approved dose for patients with chronic lymphocytic leukemia is 30 mg/day three times per week for 12 weeks. However, in patients with chronic lymphocytic leukemia, an inverse relationship exists between disease burden and PK parameters, such as C_{max} and AUC (Campath BLA). Furthermore, the PK of alemtuzumab has been shown to be impacted by the starting absolute lymphocyte counts in pediatric patients undergoing allogeneic HSCT (Marsh et al, 2017), thus the subject-to-subject variability in host lymphocyte counts suggest higher doses of an anti-CD52 agent may be required. Emerging clinical trial results across the allogeneic CAR T landscape have shown that, for other products, enhanced lymphodepletion (higher doses of flu or cy) or higher doses of CAR T cells, are required to avoid rejection and enable CAR T efficacy comparable to autologous CAR T therapy (Shah et al, 2021; CRISPR Therapeutics, 2020).

1.2.4.2.1 Non-Clinical Safety Information for ALLO-647

Further details on ALLO-647 non-clinical safety may be found in the Investigator's Brochure for ALLO-647.

1.2.4.3 Non-Clinical Efficacy for ALLO-647

ALLO-647 was shown to bind cynomolgus monkey and human CD52 and Fc receptors and mediate depletion of CD52 expressing lymphocytes. The binding properties of ALLO-647 to neonatal Fc receptors (FcRn) and Fc-gamma receptors (FcγR) demonstrated that ALLO-647 binding affinities were similar to the binding affinities of an isotype control human [redacted]. ALLO-647 also demonstrated dose-dependent binding to human T cells. Cynomolgus monkey was identified as a relevant nonclinical species by binding assays conducted on mouse, rat, and cynomolgus monkey T and B cells that demonstrated binding of ALLO-647 in monkey cells only. The specificity of ALLO-647 on human cells was demonstrated in a study of in vitro binding and CDC activity on CD52-knockout human T cells versus wild type T cells where binding and CDC activity was only seen on wild type T cells. To further demonstrate in vitro pharmacology, studies have been conducted to evaluate the ADCC and CDC potential of ALLO-647 and alemtuzumab and both antibodies have demonstrated concentration-dependent effects on human lymphocytes. For in vivo pharmacology, a single 4-hour IV infusion of ALLO-647 in cynomolgus monkeys was administered and the expected tolerability, pharmacokinetics (PK), and lymphodepletion were demonstrated.

Taken together these studies validate ALLO-647 as an [redacted] monoclonal anti-CD52 antibody capable of inducing lymphodepletion.

Further details on ALLO-647 non-clinical efficacy may be found in the Investigator's Brochure.

1.2.4.3.1 ALLO-647 Safety

Similar to cytotoxic agents fludarabine and cyclophosphamide, the identified and potential risks for ALLO-647 consist of infusion related reactions, cytopenias, CMV infection/reactivation, prolonged cytopenias, infections, immunogenicity and immune mediated events (ALLO-647 Investigator's Brochure). The safety of ALLO-647 as a lymphodepletion agent administered with fludarabine and cyclophosphamide before ALLO-501A CAR+ cells in Phase 1 cohorts in the ALLO-501A ALPHA2 study is described in Section 1.2.6.1.

1.2.4.3.2 ALLO-647 Dose and Lymphodepletion Regimen Selection

In the Phase 1 portion of the ALLO-501A ALPHA2 study, before receiving ALLO-501A treatment, subjects were lymphodepleted with a regimen of FCA. The following lymphodepletion regimens, followed by ALLO-501A, were evaluated:

	FCA-90	FCA-60	Consolidation-1	Consolidation-2
[redacted]	Flu 30 Cy 300 ALLO-647 30	Flu 30 Cy 300	Flu 30 Cy 300	Flu 30 Cy 500
[redacted]	Flu 30 Cy 300 ALLO-647 30	Flu 30 Cy 300 ALLO-647 30	Flu 30 Cy 300 ALLO-647 30	Flu 30 Cy 500
[redacted]	Flu 30 Cy 300 ALLO-647 30	Flu 30 Cy 300 ALLO-647 30	Flu 30 Cy 300 ALLO-647 30	Flu 30 Cy 500
[redacted]	-	-	-	ALLO-647 20
[redacted]	-	-	-	ALLO-647 20
[redacted]	ALLO-501A 40 or 120	ALLO-501A 120	ALLO-501A 120	ALLO-501A 120 ALLO-647 20
[redacted]	-	-	ALLO-647 30	ALLO-647 30
[redacted]	-	-	ALLO-501A 120	ALLO-501A 120

Flu = Fludarabine (dose in mg/m^2); Cy = Cyclophosphamide (dose in mg/m^2); ALLO-647 dose in mg; ALLO-501 dose in $\times 10^6$ CAR$^+$ cells.

The lymphodepletion regimen FCA-90 was also evaluated in the ALLO-501 ALPHA study. Because ALLO-501 and ALLO-501A express an identical CD19 CAR protein, target similar eligible large B-cell lymphoma patients, and investigate the same cell dose and lymphodepletion regimen in clinical trials, the data from these 2 clinical trials can be

analyzed together. FCA-90 (Lymphodepletion-A) has optimal efficacy in terms of response (ORR and CR) and durability in LBCL CAR naïve population (Section 1.2.6.2), and exposure-response modeling (data on file, Allogene Inc.) supports the benefit of higher ALLO-647 exposure on lymphodepletion, CAR T expansion, and better clinical outcomes.

Based on an evaluation of patient characteristics associated with safety outcomes, FCA-90 also has an acceptable safety profile (Section 1.2.6.1) comparable to what is already anticipated with autologous therapy using standard doses of fludarabine and cyclophosphamide.

Cytopenias are frequent with autologous CAR T cell therapies and have increasingly been seen to be relatively prolonged, including patients with marrow aplasia/hypoplasia lasting several weeks up to months following CAR T cell infusion and requiring stem cell transplants (Jain et al, 2020; Strati et al, 2021; Nahas et al, 2020). Lymphodepletion (and more specifically T cell depletion) is essential for CAR T activity and clinical benefit. However, controlling and reducing the rate of prolonged cytopenias is important to prevent serious and life-threatening infections.

Medical review and individual case evaluations of subjects who developed prolonged cytopenias across dose cohorts in the ALLO-501A/ALLO-501 program suggests that there are inherent risk factors for developing prolonged cytopenias. These factors include prior autologous CAR T, recent autologous or allogenic HSCT (within 6 months), hypocellular bone marrow at screening, and lower ALC counts.

In the current study protocol, the risk factors for prior autologous CAR T, recent autologous HSCT, and hypocellular bone marrow at screening are addressed in the protocol eligibility criteria.

Based on the Phase 1 experience, in Phase 2 subjects will be treated with ALLO-501A 120 x 10^6 CAR^+ cells following lymphodepletion with FCA-90 for subjects randomized to the FCA arm:

- F 30 mg/m^2 Days -5, −4, −3
- C 300 mg/m^2 Days -5, −4, −3
- ALLO-647 30 mg/day Days -5, -4, -3

Subjects randomized to the FC arm (without ALLO-647) will receive:

- F 30 mg/m^2 Days -5, −4, −3
- C 300 mg/m^2 Days -5, −4, −3

1.2.5 ALLO-501A

ALLO-501A is engineered using a self-inactivating lentiviral vector (LVV), which drives expression of a second-generation CAR, thus redirecting T cells to target CD19. The CAR

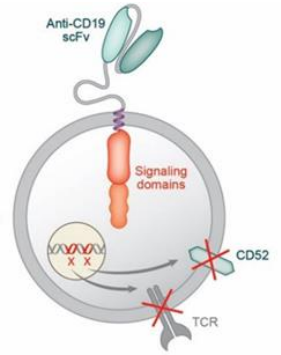
construct utilized in ALLO-501A combines a single-chain variable fragment (scFv) derived from a murine anti-human CD19 monoclonal antibody, with the human CD8 hinge and transmembrane domains, and a cytoplasmic tail composed of human 4-1BB co-stimulatory and human CD3ζ signaling domains.

ALLO-501A was additionally engineered using TALEN® gene editing technology. TALEN® are artificially engineered nucleases that are capable of generating site-specific double-strand DNA breaks at a desired target site leading to inactivation of the targeted gene. ALLO-501A is generated by transfection of two pairs of TALEN mRNA: one pair to inactivate TRAC and one pair to inactive CD52 (Figure 4).

The inactivation of CD52 leads to the loss of CD52 surface expression, allowing use of ALLO-501A in the presence of anti-CD52 depleting antibodies such as ALLO-647.

The inactivation of TRAC, which encodes the T cell receptor constant region, results in the elimination of a functional TCRα/β complex on the cell surface, thus circumventing the recognition of MHC disparities between donor and recipient through the donor cell's TCR and preventing the potential development of graft-versus-host disease (GvHD).

Figure 4. Schema of ALLO-501A and Attributes



ALLO-501A is a pre-manufactured, TCRαβ depleted T cell suspension designed to become active, proliferate, secrete cytokines and kill CD19+ B cells following administration to lymphodepleted subjects with relapsed/refractory LBCL.

Further details on ALLO-501A may be found in the Investigator's Brochure.

1.2.5.1 Non-Clinical Safety Information for ALLO-501A

A risk-based approach was followed to address the potential safety concerns connected with the use of ALLO-501A. The following risks have been identified.

1. Risk of off-target toxicity related to the CD19 CAR of ALLO-501:

   The specificity of the ALLO-501A scFv to its intended target antigen CD19 was demonstrated in a good laboratory practice (GLP) tissue cross-reactivity study. Specific

staining was observed in the normal B cell compartment whereas no unexpected off-target binding was observed in any other cell type of the 37 human tissues examined.

2. Risk of GvHD related to the allogeneic nature of ALLO-501A:

Residual TCRα^{+} T cells are depleted from ALLO-501A preparations after TALEN inactivation of *TRAC* and prior to cryopreservation, to minimize the number of TCRα^{+} T cells a subject may receive. Furthermore, an *in vivo* study demonstrated that TCRαβ^{-} _CD52$^{+/-}$_T cells did not induce GvHD in an immunocompromised mouse model (Poirot et al, 2015).

3. Risks of tumorigenicity related to:

The use of a lentiviral vector:

The risk of tumorigenicity is mitigated by the use of self-inactivating lentiviral vectors to prevent the transactivation of unwanted genes. As of today, no severe AEs have been observed in previous clinical experiences with such self-inactivating vectors (Cartier et al, 2009; Zhou et al, 2010; Biffi et al, 2011; Scaramuzza et al, 2013). Furthermore, the number of integrated lentiviral vectors per cell is controlled to minimize the risk of insertional mutagenesis.

The use of TALEN-mediated gene editing:

The risks of TALEN off-target editing and chromosomal translocations were assessed by high throughput sequencing of predicted off-target sites, whole genome sequencing (WGS), karyotype analysis, fluorescence *in situ* hybridization (FISH), and *in vitro* aberrant proliferation assays. To mitigate these potential risks the *TRAC* and *CD52* TALEN are introduced into the cells during the production process by electroporation of mRNA, thus resulting in only transient expression of the nucleases.

In vitro experiments showed that:

- No significant mutagenesis was identified at the top 15 predicted *TRAC* and *CD52* TALEN off-target sites in TALEN-transfected cells compared to control cells. Also, WGS revealed a similar number of variants in TALEN -edited and control samples, suggesting that the background is consistent (ie, detection of single-nucleotide polymorphisms [SNPs] and insertions/deletions [INDELs] was similar between all samples) and TALEN are not inducing mutations at a globally detectable rate in T cells;

- Karyotype, FISH, WGS, and PCR assays confirmed the presence of TRAC:CD52 translocations (ie, translocations involving the 2 chromosomes simultaneously targeted by the 2 TALEN). The TRAC:CD52 translocations, however, showed no significant increase following a 4,000-fold expansion in culture, suggesting TALEN gene-edited T cells do not acquire any proliferative advantage.

Risk of generating replication-competent lentivirus (RCL):

The lentiviral vector used to generate ALLO-501A is derived from HIV-1 and there is a theoretical risk that random recombination unintentionally reconstitutes a replication-competent and potentially pathogenic virus. The potential for generating RCL is mitigated through the use of a third-generation vector, in which all sequences that encode lentiviral proteins have been deleted from the transfer vector. Furthermore, the HIV-1 proteins tat and env, plus nef, vif, vpr, and vpu, all of which are essential for HIV-1 pathogenesis and replication in vivo, are not expressed during production of the lentiviral vector particles. RCL absence is part of the release criteria for all ALLO-501A Good Manufacturing Practice (GMP) batches.

1.2.5.2 ALLO-501A Potential Risks

The safety risks potentially associated with the administration of ALLO-501A are those expected from the lymphodepletion regimen, and those described for anti-CD19 autologous CAR T cell drug products (Breyanzi USPI and SmPC; Kymriah USPI and SmPC; Yescarta USPI and SmPC), and the allogenic CARs UCART19 and ALLO-501. They comprise CRS, neurotoxicity, infections, prolonged cytopenia, infusion-related reaction, hypogammaglobulinemia, acute and chronic GVHD, and genotoxicity/tumorigenicity. Tumor lysis syndrome (TLS) is a potential risk due to the underlying disease. Toxicity grading and management are provided in Section 8.

Refer to ALLO-501A IB for additional information on the potential risks.

CRS is common to anticancer immunotherapies (adoptive T-cell therapies and bispecific antibodies, eg, blinatumomab) and associated with elevated levels of inflammatory cytokines. The presentation of CRS can vary, and clinical signs and symptoms may include constitutional (fever, rigors, headaches, malaise, fatigue, arthralgia), vascular (hypotension), respiratory (hypoxia, dyspnea) cardiac (tachycardia), gastrointestinal (nausea, and vomiting), laboratory (coagulation, renal, and hepatic), skin (rash) and neurological (aphasia, altered level of consciousness). Treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids should be used as indicated at the first sign of CRS symptoms. The severity of CRS will be assessed according to the American Society for Transplantation and Cellular Therapy 2019 (Lee et al, 2019) grading criteria.

Neurological toxicities including severe or life-threatening reactions occurred in 60% and 81% of the subjects with R/R DLBCL following treatment with Kymriah and Yescarta, including Grade ≥3 in 19% and 26% of subjects, respectively (Kymriah USPI 06/2021; Yescarta USPI 04/2021). The onset of neurological toxicity can be concurrent with CRS, following resolution of CRS or in the absence of CRS. The most common neurological toxicities observed with Kymriah and Yescarta include headache (21% and 44%), encephalopathy (34% and 57%), delirium (6% and 17%), anxiety (9% and 9%), sleep disorders (9%), dizziness (11% and 21%), tremor (7% and 31%). Other manifestations included peripheral neuropathy, leukoencephalopathy, seizures, cerebral edema, mutism, and aphasia.

Due to the lymphodepletion prior to ALLO-501A infusion, all subjects are expected to experience a long-lasting lymphocyte count decrease and are at risk for prolonged cytopenias and infections. Study inclusion criteria are in place to reduce the risk for prolonged cytopenias; subjects will be screened and monitored for endemic infections and will be required to receive anti-infective prophylaxis as recommended by the US National Comprehensive Cancer Network for subjects receiving alemtuzumab (NCCN Guidelines, 2021; Section 5.12.3).

It is possible that B cell depletion and hypogammaglobulinemia will occur due to the effects of ALLO-501A on normal B cells. Gamma globulin may be administered for hypogammaglobulinemia according to institutional guidelines.

Acute GvHD cannot be completely excluded despite the depletion of TCRα/β expressing T cells in ALLO-501A manufacturing. Risk of chronic GvHD is mitigated by host immune recovery at a distance from lymphodepletion, and rejection of allogenic cells consequently. The risk of chronic GvHD will be monitored during the study and in long term follow-up (LTFU) studies. Institutional guidelines for the treatment of acute and chronic GvHD will apply.

Genotoxicity and tumorigenicity of ALLO-501A are inherent risks with gene editing through insertional mutagenesis with lentiviral transduction, and off-target gene deletion and/or chromosomal translocation after TALEN®. The risk of insertional mutagenesis is mitigated by the use of a nonreplicative self-inactivating LVV.

1.2.5.3 ALLO-501A Doses Evaluated in Phase 1 of ALPHA2

In Phase 1 of ALPHA2, the ALLO-501A cell doses that were evaluated were 40 x 10^6 (n=1 subject) and 120 x 10^6 CAR+ cells and Consolidation which entailed 2 dose doses of ALLO-501A dosed 28 days apart. The consolidation dose used 120 x 10^6 CAR+ cells per dose. The single cell dose of 120 x 10^6 CAR+ cells was selected as the RP2D to be used in Phase 2 (Section 1.2.6.3).

1.2.6 Summary of Clinical Results from the Phase 1 Portion of ALPHA2

In the Phase 1 portion of ALPHA2 as of 18 Oct 2021, 29 subjects have enrolled and 28 have been evaluated.

Lymphodepletion Regimen (with ALLO-501A on [redacted])	Enrolled	Treated
FCA-60: F 30 mg/m^2/day, C 300 mg/m^2/day, and A 30 mg/day on [redacted] and ALLO-501A 120 x 10^6 at [redacted]	2	2
FCA-90: F 30 mg/m^2/day, C 300 mg/m^2/day, and A 30 mg/day on [redacted]; one patient at ALLO-501A 40 x 10^6 and 4 at ALLO-501A 120 x 10^6 at [redacted]	5	5
Consolidation 1: F 30 mg/m^2/day, C 300 mg/m^2/day, and A 30 mg/day on [redacted], and ALLO-501A 120 x 10^6 at [redacted] plus ALLO-647 30 mg on [redacted] and ALLO-501A 120 x 10^6 on [redacted] (if eligible)	12	11
Consolidation 2: F 30 mg/m^2/day, C 500 mg/m^2/day, and A 20 mg/day on [redacted] and ALLO-501A 120 at [redacted] plus ALLO-647 30 mg on [redacted] and ALLO-501A 120 x 10^6 on [redacted] (if eligible)	10	10

One subject in FCA-90 was enrolled and completed lymphodepletion but experienced new onset CNS relapse and did not receive ALLO-501A. In Consolidation-1 one subject was withdrawn from the study due to COVID-19 infection prior to the start of lymphodepletion. No dose-limiting toxicities (DLTs) related to ALLO-647 or ALLO-501A were observed.

1.2.6.1 Safety Observed in the Phase 1 Portion of the Study

In a preliminary analysis of ALLO-501A-201 ALPHA2 Phase 1 data (Lekakis et al, 2021) among a total of 28 subjects evaluable for safety across the lymphodepletion regimen and dose levels of ALLO-501A, as of 18 Oct 2021 data cutoff, no DLTs attributed to ALLO-647 or ALLO-501A were observed. The reported safety events for ALLO-647 and ALLO-501A were manageable. Cytopenias were the most common AEs occurring in ≥30% of subjects regardless of relationship; neutropenia 57.1% (16/28), anemia, and thrombocytopenia 46.4% each (13/28) and white blood cell count decreased 35.7% (10/28). Similarly, the most common (≥25%) Grade ≥3 events were neutropenia 57.1% (16/28), thrombocytopenia 35.7% (10/28), anemia and white blood cell count decreased 32.1% each (9/28), and lymphopenia 28.6% (8/28). There were three subjects who experienced prolonged cytopenias, two of which were with the Consolidation-2 regimen where Cy 500 mg/m^2/day was explored as part of the lymphodepletion regimen. CRS of any grade was observed in 10.7% (3/28) of subjects, all ASTCT Grade 1 or 2, which resolved with standard treatment. Neurologic toxicity was reported in 21.4% (6/28) of subjects, including 1 Grade 2 ICANS. No events of GvHD (any grade) were observed. Infusion-related reactions, all Grade 1 or 2, were observed in 25% (7/28) of treated subjects, and no subject required dose reduction due to infusion-related reactions. Infection of any grade was observed in 35.7% (10/28), with the most common infections being viral infections (25.0%, 7/28). Two (7.1%) subjects had Grade 3 infections: 1 subject experienced Grade 3 CMV reactivation (FCA-60 regimen), and 1 subject experienced Grade 3 HHV-6 reactivation, bacterial sepsis, and fungaemia (Consolidation-2). Ten (35.7%) subjects experienced SAEs. Three (10.7%) subjects experienced SAEs related to ALLO-647: CMV reactivation, HHV-6 reactivation, and vomiting; and 4 (14.8%) subjects experienced SAEs related to ALLO-501A: aplastic anemia; bacterial sepsis; cytogenetic abnormality; fungaemia; ICANS Grade 2; CRS, pyrexia; and vomiting.

There was a finding of new chromosomal structural variant in donor derived T cells in a subject who was undergoing a bone marrow assessment as part of a workup for aplastic anemia (chromosome 14 inversion). Investigation concluded that the chromosomal abnormality was unrelated to transcription activator-like effector nucleases (TALEN)® gene editing or to Allogene's manufacturing process and was of no clinical significance. No other gross chromosomal abnormalities were noted, and the cell morphologic appearance, immunophenotype, clinical behavior of the cells, and localization were not suggestive of leukemia. Sequencing of the inversion junctions showed that the inversion sites were not associated with on-target or off-target TALEN activity but were sites of V(D)J recombination. Similar structural variants have been detected in post-thymic, mature T cells of normal individuals and are believed to be consequences of V(D)J recombination during normal T cell development (Callén et al 2009, Machado et al, 2021) and unrelated to TALEN gene editing.

The safety profile of the FCA-90 (n=5) lymphodepletion regimen in ALPHA2, although small numbers, was generally comparable with the other lymphodepletion regimens evaluated in Phase 1. There were no ALLO-647-related SAEs with FCA-90. There were no events of prolonged cytopenia, and although all 5 subjects experienced an infection, they were similar in type (CMV reactivation; HHV-6 reactivation) and of the same or lesser severity (Grade 1 or 2) as reported in other lymphodepletion regimen cohorts in the study.

1.2.6.2 Efficacy Observed in the Phase 1 Portion of the Study

In the ALPHA2 study, an ORR of 50% and a CR rate of 27.3% was observed in CAR T naïve subjects with R/R LBCL as of 18 Oct 2021. In the ALLO-501 ALPHA study (CD19 allogeneic CAR T), the same population had an ORR of 64%, with 43% CR rate (Neelapu et al, 2021).

In CAR-naïve LBCL subjects in FCA-90 lymphodepletion cohorts, in the ALPHA2 study there was 1 responder (CR) of 2 evaluable subjects, and in ALPHA, the ORR was 67%, with a CR rate of 67% (data cutoff 18 Oct 2021; data on file, Allogene).

1.2.6.3 ALLO-501A Phase 2 Dose

For the ALLO-647-201 study, to arrive at the ALLO-501A cell dose and the RP2D encompassing both the lymphodepletion regimen and the ALLO-501A dose, the totality of data from ALLO-501A, ALLO-501 and ALLO-647 were considered.

Across the ALPHA and ALPHA2 studies, allogeneic anti-CD19 CAR T cells were evaluated at cell doses of 40 x 10^6, 120 x 10^6, and 360 x 10^6. A manageable safety profile was observed across all cell doses evaluated with no DLT or GvHD observed (Neelapu et al, 2020). Anti-tumor activity was observed across all cell dose levels, and cell expansion was not markedly different between the 120 x 10^6 and 360 x 10^6 dose levels (Neelapu et al, 2020). Given this, and the manageable safety profile across all cell dose levels, the 120 x 10^6 cell dose level was selected as the RP2D for the ALPHA2 Phase 2 study.

1.2.6.4 RP2D for Lymphodepletion Regimen

Cohorts across the ALPHA and ALPHA2 studies were evaluated for selection of the RP2D encompassing both the cell dose and the lymphodepletion regimen. Among these cohorts, 8 subjects previously untreated with CD19 targeted CAR T cells were treated with the FCA-90 lymphodepletion regimen and a minimum cell dose of 120 x 10^6. This regimen demonstrated a response and CR rate of 62.5%, superior to other cohorts. Additionally, data indicate that 50% (4/8) of subjects in this group remain in ongoing complete remission, relative to ongoing complete remission rates of 0% to 30% in other dose cohorts. In addition, as durability data has matured, among subjects with the opportunity to be followed for 6 months, duration of response from this group is clinically meaningful (follow-up range from 17 to 24 months). Finally, Allogene's exposure-response analysis have shown that higher ALLO-647 exposure is associated with increased depth and duration of host T cell depletion, increased CAR T expansion, and higher rates of clinical response. Therefore, based on comparison of response rates and exposure-response modelling, Allogene considers the FCA-90 preferable to both FCA-60 regimen and the consolidation regimens previously tested.

1.2.7 Biomarker Rationale

1.2.7.1 ALLO-501A

The objectives of the biomarker assessments will be to understand the relationship between the cellular kinetics, phenotype, and pharmacodynamic activity of ALLO-501A, in relation to its anti-tumor activity and safety profile. This understanding may identify a phenotypic profile that optimizes anti-tumor activity while minimizing the risk of toxicity. In support of these efforts, various cellular, molecular and protein-based assays may be deployed such as multiparametric flow cytometry, qPCR, single cell RNA-seq, ELISA, IHC etc.

The cellular kinetics of ALLO-501A may be measured using multiparametric flow cytometry, and/or PCR-based molecular assays, to elucidate transgene levels, allowing for both the precise quantitation of CAR+ T cells, as well as immunoprofiling of the CAR T drug product at baseline and over the course of the study. The relative proportion of naïve, memory, activated and exhausted CAR+ T cells may be monitored and correlated with both the quantity and duration of the CAR T cells and any observed anti-tumor and/or safety response. The absence of risk of replication competent lentivirus (RCL) may be monitored, eg, PCR-based assay, for any relationship to safety and/or efficacy endpoints.

A second imperative of the biomarker plan will be to understand how ALLO-501A CAR T cell drug product behaves in the context of the lymphodepletion regimen comprising of fludarabine, cyclophosphamide, and ALLO-647 and how it interacts with the recipient's immune cells as they re-populate. The re-population of endogenous immune cells may be monitored by TBNK assays and multiparametric flow cytometry. Subjects' samples may be submitted to high resolution HLA typing (locally or centrally) to understand the influence of differing degrees of HLA mismatch between the recipient and the donor cell populations. Immunogenicity to the CAR T cell population may be monitored by measurement of anti-CAR (scFv), anti-TALEN antibodies and anti-donor HLA antibodies. Finally, the

proportion of CAR T cells that express TCR may be measured to monitor for TCR driven clonal expansion and the risk of GvHD.

[redacted]

1.2.7.2 ALLO-647

The goal of the lymphodepletion strategy is to deplete endogenous lymphocytes to a sufficient depth and duration to permit maximal expansion of allogeneic CAR T cells, leading to clinical response. The efficacy of ALLO-647 as a lymphodepletion agent will be assessed through measures of the depth and duration of host lymphocyte depletion. The depth and duration of lymphodepletion in peripheral blood will be quantitatively measured using local ALC assays for the baseline assessment and a central lab-based flow cytometric assay to detect T, B, and NK cell populations at specified timepoints, noted in the Schedule of Activities. Additionally, exposure of ALLO-647 in serum will be monitored using an immunoassay specific for ALLO-647. Finally, protein expression of CD52, the target of ALLO-647, may be monitored in peripheral blood samples, eg, using flow cytometric analysis, and/or in lymph node biopsies, eg, using immunohistochemical analysis. The collection of biomarker samples is described in the Schedule of Activities and the study laboratory manual.

2. STUDY HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

2.1 Study Hypothesis:

ALLO-647 (A), administered with fludarabine (F) and cyclophosphamide (C) in a lymphodepletion regimen before ALLO-501A is efficacious in subjects with relapsed/refractory (R/R) LBCL, as determined by prolongation in progression-free survival (PFS) relative to FC alone as assessed per Lugano Classification and Independent Review Committee (IRC).

2.2 Objectives and Endpoints

Primary Objectives:	**Primary Endpoints:**
Efficacy • To assess clinical efficacy of ALLO-647 (in a lymphodepletion regimen before ALLO-501A) compared to FC alone as measured by PFS and assessed by IRC in subjects with R/R LBCL.	*Efficacy* • PFS in FCA vs FC alone, defined as the time from randomization to disease progression, or relapse per the Lugano classification criteria (Cheson et al, 2014) as assessed by IRC or death

Secondary Objectives:	**Secondary Endpoints:**
Efficacy • To assess the clinical efficacy of ALLO-647 as measured by ORR and assessed by IRC. • To assess clinical efficacy of ALLO-647 with FC (in a lymphodepletion regimen before ALLO-501A) compared to FC alone as measured by EFS and assessed by IRC in subjects with R/R LBCL. • To characterize the efficacy of ALLO-647 as measured by DOR and assessed by IRC • To characterize other aspects of the efficacy of ALLO-647, including PFS, response rate per investigator review, DOR, and overall survival • To characterize the depth and duration of lymphodepletion with and without ALLO-647	*Efficacy* • ORR in FCA vs FC alone, defined as assessment of CR or PR, assessed using the Lugano classification criteria 2014; Cheson , et al, 2014) by IRC at any time up through commencement of new anti-cancer therapy or withdrawal of consent. • EFS in FCA vs FC alone, defined as the time from randomization to disease progression or relapse per the Lugano classification criteria 2014 as assessed by IRC and per investigator assessment, new anti-cancer therapy, or death • DOR, defined as time from the first observed response to disease progression or relapse (per IRC and per investigator assessment) or death • ORR in FCA vs FC alone per investigator assessment at any time up through commencement of new anti-cancer therapy or withdrawal of consent • Best overall response (CR, PR, SD, PD) (per IRC and per investigator assessment) at any time up through commencement of new anti-cancer therapy or withdrawal of consent • PFS in FCA vs FC alone, defined as time from the randomization to progression or relapse per investigator assessment per the Lugano classification criteria as assessed by investigator, or death • TTR, defined as the time from randomization to the first observed response (per IRC and per investigator assessment) • OS in FCA vs FC alone, defined as the time from randomization to death • Depth and duration of lymphodepletion, as assessed by lymphocyte count
• To characterize the PK of ALLO-647	• PK concentrations will be used in a population PK model
• To characterize cellular kinetics of ALLO-501A when administered with and without ALLO-647	• ALLO-501A expansion and persistence, eg, C_{max} and AUC.
• To characterize the pharmacodynamics of ALLO-647	• Pharmacodynamics will be evaluated on host T cell counts
• To evaluate immunogenicity of ALLO-501A and of ALLO-647	• The incidence of ADA against ALLO-501A scFv and/or TALEN® • The incidence of ADA against ALLO-647

Safety
• To evaluate the overall safety profile of ALLO-647 by comparing FCA lymphodepletion with FC lymphodepletion
• To evaluate the overall safety profile of ALLO-501A following lymphodepletion
	Safety
	• AEs as characterized by preferred term, frequency, severity, timing, seriousness, and relationship to ALLO-647, and by FCA vs FC
	  • The incidence of infusion-related reactions, cytopenias, and infections
	• AEs as characterized by preferred term, frequency, severity timing, seriousness, and relationship to ALLO-501A and by FCA vs FC
	  • The incidence and severity of CRS, neurotoxicity, infections, hematologic toxicities, prolonged cytopenias, and GVHD
	• The incidence and severity of clinically significant laboratory toxicities.

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

ADA = anti-drug antibody; AE = adverse event; CR = complete response; CRS = cytokine release syndrome; DOR = duration of response; EFS = event-free survival; [redacted] FC = fludarabine and cyclophosphamide; FCA = fludarabine, cyclophosphamide, and ALLO-647; GVHD = acute graft-vs-host disease; IRC = independent review committee; LBCL = large B-cell lymphoma; MRD = minimal residual disease; ORR = overall response rate; OS = overall survival; PK = pharmacokinetic(s); PD = progressive disease; PR = partial response; [redacted]; PFS = progression-free survival; [redacted]; R/R = relapsed/refractory; SD = stable disease; [redacted]; TTR = time-to-response

3. STUDY DESIGN

3.1 Study Overview

This is a randomized, open-label, multicenter Phase 2 study evaluating the safety, and efficacy of lymphodepletion with fludarabine (F), cyclophosphamide (C), and ALLO-647 (A) vs FC alone, in subjects with R/R LBCL receiving ALLO-501A allogeneic CAR T cell therapy.

The study treatment schema is shown in Figure 1, the lymphodepletion and cell dose is in Figure 2 and the study evaluation plan is shown in Figure 3. For an individual subject, the study will be divided into different periods including pre-screening (optional), screening, lymphodepletion, treatment, and follow up (Figure 1).

Subjects must have relapsed or refractory disease after at least 2 lines of chemotherapy, including an anthracycline and an anti-CD20 monoclonal antibody.

The target accrual is approximately 70 subjects, with subjects to randomized in a 1:1 ratio to one of 2 treatment arms:

- FCA: Lymphodepletion with FCA (n=35 subjects).
    - F 30 mg/m^2 Days -5, −4, −3
    - C 300 mg/m^2 Days -5, −4, −3
    - ALLO-647 30 mg/day Days -5, -4, -3
- FC: Lymphodepletion with FC (n=35 subjects)
    - F 30 mg/m^2 Days -5, −4, −3
    - C 300 mg/m^2 Days -5, −4, −3

All subjects will be treated with ALLO-501A 120 x 10^6 CAR$^+$ cells following lymphodepletion.

Treatment randomization will occur centrally. Subjects will be assigned randomly in a 1:1 ratio to a lymphodepletion regimen of either FC or FCA.

Randomization will be stratified based on the following risk factors:

Stratum 1: ULN < LDH ≤ 2 x ULN **and** presence of lesion ≥5 cm (50 mm)

Stratum 2: LDH ≤ ULN **or** all lesions <5 cm

Response assessment for study efficacy endpoints will be determined by an Independent Radiology Committee (IRC).

This study is designed with an adaptive sample size re-adjustment. If the criteria to adjust the sample size are met, up to 136 subjects may be randomized in the same 1:1 ratio.

3.2 Test Products

Investigational Medicinal Products (IMPs):

IMP1: ALLO-501A, an allogeneic CAR T targeting CD19.

IMP2: ALLO-647 is a humanized [redacted] monoclonal antibody that recognizes the human CD52 antigen and will be used as a part of the lymphodepletion regimen.

Non-IMPs:

Fludarabine; cyclophosphamide. as part of the lymphodepletion regimen.

3.3 Study Termination

The study will end when all subjects treated with ALLO-501A have been followed for at least [redacted] from randomization, have withdrawn consent for any further contact, been lost to follow-up, or died, unless the study is terminated by the sponsor earlier.

3.4 Duration of Study

The estimated accrual for the study is approximately 24 months. These patients will be followed for [redacted] from randomization. The overall duration of the study is expected to be approximately 84 months from first subject randomized to last subject last visit.

Subjects will participate in the study for approximately[redacted] and will subsequently roll-over to a long-term follow up study for an extended safety monitoring period.

4. SUBJECT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate subjects are enrolled/randomized. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol. Sponsor may request the review of selected screening assessments prior to randomization.

4.1 Inclusion Criteria

Subjects must meet all the following inclusion criteria to be eligible for randomization in the study. Eligibility based on disease characteristics will be determined locally (by investigator/site personnel).

1. Histologically confirmed diagnosis of relapsed/refractory large B-cell lymphoma at last relapse per WHO 2017:
    a. DLBCL not otherwise specified, DLBCL coexistent with follicular lymphoma of any grade, EBV+ DLBCL, T cell/histiocyte rich large B cell lymphoma, DLBCL with IRF4/MUM1 rearrangement,
    b. High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements,
    c. Transformation of follicular lymphoma or marginal zone lymphoma to DLBCL
    d. Primary mediastinal B cell lymphoma
    e. Follicular lymphoma Grade 3B
2. At least 1 measurable lesion at time of randomization according to the revised IWG Response Criteria for Malignant Lymphoma (Cheson et al, 2014)
    a. A measurable node must have a longest transverse diameter greater than 1.5 cm
    b. A measurable extranodal lesion must have a longest diameter greater than 1.0 cm
3. Relapsed or refractory disease after at least 2 lines of chemotherapy including an anthracycline and an anti-CD20 monoclonal antibody.
4. Male or female subjects ≥18 years of age.

5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.
6. Absence of donor (product)-specific anti-HLA antibodies (DSA) at screening.
7. Adequate hematological function, including:
   a. Absolute neutrophil count (ANC) ≥1,000/µL (without growth factor support in the previous 7 days with filgrastim or 14 days with pegfilgrastim prior to screening).
   b. Platelet count ≥50,000/µL (without transfusion support during the previous 7 days prior to screening)
   c. Hemoglobin ≥8 g/dL (≥5 mmol/L)
   d. Absolute lymphocyte count (ALC) ≥300/µL
8. Adequate Renal Function: estimated creatinine clearance ≥50 mL/min (Cockcroft-Gault) or directly measured with 24-hour urine collection.
9. Adequate Liver Function, including:
   a. Total bilirubin ≤1.5 × ULN, except in subjects with Gilbert's Syndrome who must have a total bilirubin ≤3 × ULN;
   b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 × ULN; ≤5.0 × ULN if there is liver involvement by the tumor;
   c. Alkaline phosphatase ≤2.5 × ULN (≤5 × ULN in case of bone metastasis).
10. Lactic acid dehydrogenase (LDH): ≤2 x ULN
11. Normal blood oxygen saturation level (SpO_2) >92% on room air.
12. Left ventricular ejection fraction (LVEF) ≥40% and no clinically significant cardiac-related pericardial or pleural effusion at screening.
13. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1 except for adverse events (AEs) not constituting a safety risk by investigator judgement.
14. Negative for hepatitis B antigen. (Subjects who are HBs Ag and/or Anti-HBc positive are not eligible. If indeterminate results are obtained, viral DNA levels should be measured to confirm negative viral status).
15. Seronegative for hepatitis C antibody. If hepatitis C antibody test is positive, then subjects must be tested for the presence of antigen by RT-PCR and subject must be HCV RNA negative.
16. Serum pregnancy test (for females of childbearing potential) negative at screening.
17. Female subjects of non-childbearing potential must meet at least 1 of the following criteria:
   a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed with a serum follicle stimulating hormone level confirming the postmenopausal state;
   b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

c. Have a medically confirmed ovarian failure.

All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential.

Fertile male subjects and female subjects of childbearing potential must be willing to use a highly effective method of contraception as outlined in Section 4.4 for at least 12 months (6 months for males) after the last documented use of cyclophosphamide.

18. Evidence of a signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
19. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other procedures.

4.2 Exclusion Criteria

1. Active central nervous system (CNS) involvement by malignancy. Note: subjects with a history of CNS disease that has been effectively treated will be eligible.
2. Clinically significant CNS dysfunction, eg, seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, cerebral edema, posterior reversible encephalopathy syndrome, or any autoimmune disease with CNS involvement.
3. Current thyroid disorder (including hyperthyroidism), except for subjects with hypothyroidism controlled on a stable dose of hormone replacement therapy.
4. Any other active malignancies that required systemic treatment within 3 years prior to randomization (Note: cancers that can be adequately treated with local measures like surgical resection or local radiation with limited chance of recurrence or spread such as basal cell or squamous cell skin cancer, carcinoma in situ, or low Gleason score prostate cancers are acceptable).
5. Radiation therapy within 2 weeks prior to lymphodepletion.
6. Prior irradiation to >25% of the bone marrow.
7. Hypocellular bone marrow for age by institutional standard as determined from a bone marrow biopsy performed at time of screening.
8. Donor lymphocyte infusion within 30 days prior to lymphodepletion.
9. Autologous or allogeneic HSCT within last 6 months (24 weeks) prior to lymphodepletion.
10. Prior treatment with anti-CD19 targeted therapies (including CAR T cell therapy and bispecific antibodies, etc).
11. Systemic anti-cancer therapy within 2 weeks prior to receiving lymphodepletion. If the last immediate anti-cancer treatment contained an antibody-based agent(s) (approved or investigational), then an interval of 28 days or 5 half-lives (whichever is shorter) of the agent(s) prior to receiving ALLO-647. No bridging therapy (including corticosteroids for

disease management) is permitted during the screening period before initiating lymphodepletion.

12. Participation in other studies involving investigational drug(s) within 28 days prior to lymphodepletion (with the exception of small molecule drugs for which only 14 days is required).
13. Ongoing treatment with immunosuppressive agents; for example:
    a. Corticosteroid use within 1 week prior to first dose of lymphodepletion, with the exception of inhaled steroid for asthma, topical steroid use, or another local corticosteroid administration. Subjects requiring systemic steroids at daily doses >10 mg prednisone (or corticosteroid equivalent), or those who are administered steroids for lymphoma control or WBC-count-lowering are not eligible for the study;
    b. Infliximab must be stopped at least 45 days prior to administration of ALLO-501A.
14. Active and clinically significant autoimmune disease requiring systemic therapy within the last 2 years including, but not limited to, Guillain-Barre syndrome, amyotrophic lateral sclerosis, rheumatoid arthritis, systemic lupus erythematosus, other connective tissue disorders, vasculitis, inflammatory bowel disease, immune cytopenias, severe psoriasis, autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura.
15. Subject known to be refractory to platelet or red blood cell transfusions.
16. Active acute or chronic graft-versus-host disease (GvHD), or GvHD requiring immunosuppressive treatment within 4 weeks of randomization.
17. Subjects with active systemic bacterial, fungal, or viral infection requiring systemic treatment (including positive blood cultures within 7 days before starting lymphodepletion).
    a. Subjects must not be receiving systemic anti-infectious agent for the treatment of an active infection within 48 hours before ALLO-501A administration (prophylactic use is allowed).
    b. Subjects who are CMV seropositive at screening must demonstrate CMV clearance (with a qPCR result of not detected) prior to start of lymphodepletion.
    c. Subjects with untreated latent tuberculosis (by interferon gamma release assay [IGRA]) are not eligible.
18. Any form of primary and acquired immunodeficiency (eg, severe combined immunodeficiency disease).
19. Myocardial infarction or unstable angina within 6 months prior to screening, or unstable arrhythmia.
20. Cardiac lymphoma involvement
21. History of hypertension crisis or hypertensive encephalopathy within 6 months prior to screening.
22. History of solid organ transplant (corneal transplant permitted).

23. History of hemophagocytic lymphohistiocytosis (HLH).
24. History of progressive multifocal leukoencephalopathy (PML).
25. Clinically significant liver disease, including viral or other hepatitis or cirrhosis
26. Clinically significant pulmonary disease, such as severe COPD (Gold3, FEV1<50%), history of bronchospasm requiring intubation, interstitial lung disease, or pneumonitis (drug-related or autoimmune).
27. Known or suspected hypersensitivity to murine and bovine products.
28. Other acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation in the judgment of the investigator
29. Subjects unwilling to undergo an extended safety monitoring period (long-term follow up).
30. Pregnant or breastfeeding or planning to become pregnant or breastfeed during the study or within 12 months (6 months for males) of last dose of cyclophosphamide.

4.3 Criteria for ALLO-501A Administration [redacted]

Following lymphodepletion, subjects will be assessed for eligibility for ALLO-501A infusion on [redacted]

1. Adequate organ functions including renal and hepatic function based on the last assessment performed within the lymphodepletion period, defined as:
    a. Estimated creatinine clearance ≥50 mL/min (Cockcroft-Gault) or directly measured with 24-hour urine collection.
    b. AST and ALT ≤3 × ULN; ≤5.0 × ULN if there is liver involvement by the tumor.
    c. Alkaline phosphatase ≤2.5 × ULN (≤5 × ULN in case of bone metastasis).
    d. Total bilirubin ≤1.5 × ULN, except in subjects with Gilbert's Syndrome who must have a total bilirubin ≤3 × ULN.
2. No clinical signs of cardiac failure.
3. No active systemic bacterial, fungal, protozoal, or viral infection not controlled by adequate treatment, and absence of positive blood cultures within 7 days before ALLO-501A administration. Subjects must be either:
    - fever free for ≥48 hours without anti-pyretic drug prior to ALLO-501A infusion, and must not be receiving systemic anti-infectious agent for the treatment of an active infection within 48 hours before ALLO-501A administration (prophylactic use is allowed), or
    - fever free on the day of ALLO-501 infusion in the case of fever due only to ALLO-647 related infusion-related reaction

4. Normal SpO_2 >92% on room air.
5. Non-hematological toxicity must be resolved to baseline or Grade 1 prior to ALLO-501A infusion.
6. Absence of viral reactivation (asymptomatic viremia not clinically significant are allowed).
7. No other medical condition(s) nor laboratory findings that, in the opinion of the investigator, might jeopardize subject's safety.

Two doses of tocilizumab must be available for each subject prior to infusion of ALLO-501A and ready for administration within 2 hours. In the event of a pandemic-related shortage, one dose of tocilizumab must be available on-site for immediate administration (within 2 hours), with access to an additional dose of tocilizumab within 8 hours after each previous dose of tocilizumab administered, if needed. In addition, a second line CRS agent must be available which, while not formally studied or FDA approved for use in CRS, have been used in CRS management (Riegler et al, 2019). This may include the anti IL6 agent siltuximab and IL-1R inhibitor anakinra, depending on the institution's CRS guidelines.

If a subject does not meet the eligibility criteria for ALLO-501A administration, the ALLO-501A infusion must be delayed until the event resolves or returns to baseline, up to a maximum delay of 3 days. If the event is not resolved or does not return to baseline during the allowed delay time, ALLO-501A must not be administered unless otherwise agreed between the investigator and the sponsor.

4.4 Contraception Requirements

All male subjects and female subjects who are of childbearing potential and who are sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 12 months (6 months for males) after the last dose of cyclophosphamide. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his or her partner(s) from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

a. Established use of estrogen and progesterone-containing hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the subject or male subject's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

b. Correctly placed copper containing intrauterine device.

c. Intrauterine hormone-releasing system.

d. Male sterilization with absence of sperm in the 90-day post-vasectomy ejaculate.

e. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

   NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

4.5 Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study numbers, contact information for the investigator site to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational products are ALLO-501A and ALLO-647.

5.1 Allocation to Treatment: Randomized Treatment Assignment:

The medical monitor may review to confirm subject eligibility and approval for enrollment/randomization. Subject enrollment will be approved by the Sponsor.

Treatment randomization will occur centrally. Subjects will be assigned randomly in a 1:1 ratio to a lymphodepletion regimen of either FC or FCA.

Randomization will be stratified based on the following risk factors:

Stratum 1: ULN < LDH ≤ 2 x ULN **and** presence of lesion ≥5 cm (50 mm)

Stratum 2: LDH ≤ ULN **or** all lesions <5 cm

5.2 Investigational Product Compliance

All doses of investigational products will be administered by the appropriately designated study staff at the investigational site.

The site will complete required dosage Administration Record; template forms will be located in the IP manual. The use of the Administration Record is preferred but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent /required information on the preparation and administration of the dose. This may be used in place of the Administration Record after approval from the sponsor and/or designee.

5.3 Investigational Medicinal Product Supplies

5.3.1 ALLO-501A

ALLO-501A is the investigational medicinal product 1 (IMP1).

5.4 Dosage Form(s) and Packaging of ALLO-501A

The ALLO-501A dosage form is composed of CAR^+_$TCR\alpha\beta^-$_$CD52^{+/-}$ CAR T cells formulated at 20×10^6 viable CAR^+ T cells/mL in a commercially available cryopreservation media. ALLO-501A injection is presented as a sterile solution for IV administration. Each vial is sealed with a coated stopper and an overseal.

The product is labeled according to local regulatory requirements.

5.4.1.1 Preparation and Dispensing of ALLO-501A

See the IP manual for instructions on how to prepare the ALLO-501A for administration. ALLO-501A should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician’s assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. ALLO-501A vials are for single use only.

Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of ALLO-501A per the study IP manual.

5.4.2 ALLO-647

ALLO-647 is the investigational medicinal product 2 (IMP2).

5.4.2.1 Dosage Form(s) and Packaging of ALLO-647

ALLO-647 drug product is provided as a [redacted] for intravenous administration in a glass vial at a concentration of 10 mg/mL. It is sealed with a coated stopper and an overseal, and labelled according to local regulatory requirements. The vial is designed for single use.

5.4.2.2 Preparation and Dispensing of ALLO-647

See the IP manual for instructions on how to prepare the ALLO-647 for administration. ALLO-647 should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of ALLO-647.

5.5 Non-Investigational Medicinal Product Supplies

Central supply or locally obtained commercial supplies of these drugs will be used in accordance with local regulations and the package insert. Fludarabine and cyclophosphamide are approved/authorized chemotherapy agents, and are used for conditioning before autologous CD-19 CAR T therapy which has been approved at a minimum in the US and EU (Yescarta USPI, Yescarta SmPC, Kymriah USPI, Kymriah SmPC, Breyanzi USPI, Breyanzi EPAR).

5.5.1 Fludarabine

Fludarabine phosphate is a synthetic purine nucleoside that differs from physiologic nucleosides in that the sugar moiety is arabinose instead of ribose or deoxyribose. Fludarabine is a purine antagonist antimetabolite.

5.5.2 Cyclophosphamide

Cyclophosphamide is a nitrogen mustard-derivative alkylating agent. Following conversion to active metabolites in the liver, cyclophosphamide functions as an alkylating agent; the drug also possesses potent immunosuppressive activity.

5.6 Administration

For specific details regarding administration of the non-IMPs, refer to the most recent version of the relevant prescribing information (Fludarabine USPI, Fludarabine SmPC; Cyclophosphamide USPI; Cyclophosphamide SmPC).

5.6.1 Fludarabine and Cyclophosphamide

Subjects must be prepared for ALLO-501A administration with lymphodepletion. Lymphodepleting chemotherapy will be fludarabine and cyclophosphamide with or without ALLO-647.

Fludarabine 30 mg/m^2 will be administered intravenously over approximately 15 to 30 minutes for [redacted], from [redacted].

Fludarabine dose should be reduced based on renal function. Subjects with creatinine clearance 50 to 80 mL/min should have a 20% dose reduction of each daily fludarabine dose (ie, 20 mg/m^2), or per institutional standard.

Cyclophosphamide 300 mg/m^2 will be administered intravenously over approximately 1 hr for [redacted], from [redacted].

Chemotherapy, including anti-emetics and hydration, should be administered according to institutional guidelines. Dexamethasone and other steroids are not to be administered as pre-medications.

Refer to the most recent version of the package insert for specific details surrounding the administration of non-IMPs.

5.6.2 ALLO-647

For subjects randomized to the FCA arm, ALLO-647 will be administered IV over approximately 4 hours. ALLO-647 must be administered after the completion of FC. ALLO-647 must not be infused concomitantly with other drug products.

Subjects should be closely monitored up to 2 hours after the completion of the infusion or per institutional guidelines.

Details for ALLO-647 infusion preparation are provided in the current IP manual.

5.6.2.1 Premedication Prior to ALLO-647 Infusion

During treatment, subjects receiving ALLO-647 must receive premedication with 10 mg/kg hydrocortisone IV (or equivalent) or per institutional standard maximum daily dose prior to ALLO-647 infusion on [redacted] (as applicable according to the ALLO-647 dose).

Subjects will also receive a standardized non-steroid premedication for infusion-related reaction on each day of ALLO-647 infusion, or per institutional standard practices. Subjects on the FC arm may receive premedications before fludarabine and/or cyclophosphamide per institutional standard practices:

Medication	Premedication
Fludarabine; Cyclophosphamide	Premedications if per institutional standard practices
ALLO-647	Steroid: Hydrocortisone 10 mg/kg IV (or equivalent) (or maximum daily dose)
	Antihistamine (eg, diphenhydramine)
	H2 blocker (eg, famotidine)
	Acetaminophen (paracetamol)
	Optional: long-acting non-sedating antihistamine
ALLO-501A	Premedications if per institutional standard practices

5.6.2.2 ALLO-647 Dose Interruption

Subjects experiencing toxicity despite supportive care may have the infusion interrupted or stopped. Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the investigator.

In the event of an infusion-related reaction, the infusion rate of ALLO-647 may be decreased by up to 50% of original rate of infusion or interrupted until resolution of the event and re-initiated until completion of the infusion (Appendix 6). If the infusion is not resumed and the patient received only a partial dose, the actual dose administered will be entered into the eCRF.

Lymphodepletion may be delayed as needed until toxicity resolution, for up to 3 days.

Resuming ALLO-647 following treatment interruption for treatment related toxicity may not occur until all of the following parameters have been met:

- Non-hematologic toxicities have returned to baseline or Grade ≤1 severity (or, at the investigator's discretion, Grade ≤2 if not considered a safety risk for the subject).

If a dose interruption results from worsening of hematologic or biochemical parameters, the frequency of relevant blood tests should be increased as clinically indicated.

5.6.3 ALLO-501A

Eligibility criteria for ALLO-501A administration will be assessed prior to infusion of ALLO-501A to ensure subjects' safety (Section 4.3).

Subjects will receive the intended dose of ALLO-501A treatment administered intravenously over approximately 5 minutes on [redacted].

Details for ALLO-501A infusion preparation are provided in the IP Manual.

Pre-treatment with antihistamine and acetaminophen (paracetamol) is permitted if per local institutional practices.

If a subject does not meet the eligibility criteria allowing ALLO-501A administration due to an AE or other reason (in consultation with the medical monitor) (Section 4.3), ALLO-501A infusion must be delayed until the event resolves or returns to baseline, up to a maximum delay of 3 days (Section 4.3). If the event is not resolved or does not return to baseline during the allowed delay time, ALLO-501A must not be administered unless otherwise agreed between the investigator and the sponsor.

For ALLO-501A, there will be no dose decrease.

5.7 Study Stopping Criteria

5.7.1 Stopping Criteria for ALLO-647

Accrual pausing criteria will be described in the Data Safety Monitoring Board charter.

5.7.2 Stopping Criteria for ALLO-501A

If a Grade ≥2 steroid resistant/refractory acute GVHD event occurs, and the subject received >7 × 10^4/kg TCR positive cells, then accrual to the study will be paused for further safety review.

5.8 Medication Errors

Safety Event	Recorded on the eCRF	Reported on the SAE Report Form to the Sponsor or Designee Within 24 Hours of Awareness
Medication error	All (regardless of whether associated with an AE)	Only if associated with a SAE.

Medication errors may result from the administration of the investigational product to the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Such medication errors occurring to a study participant are to be captured as a protocol deviation, on the appropriate product log page of the eCRF, and on the AE page if the medication error is related to an adverse event. Refer to the study eCRF completion guidelines for further instructions.

In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors should be reported to the sponsor or designee within 24 hours on the SAE report form only when associated with a serious adverse event.

5.9 Investigational Product Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational and non-investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements. Investigational products should be stored in their original containers and in accordance with the labels. It is preferred that ALLO-501A be stored in the liquid nitrogen shipper until product preparation.

See the IP manual for further details on storage and handling of ALLO-647 and ALLO-501A once diluted and package inserts for Flu/Cy for handling of those products once reconstituted and/or diluted.

Site systems must be capable of measuring and documenting (eg, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study.

Any excursions from the investigational product label storage conditions should be reported to Allogene immediately upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Allogene.

Once an excursion is identified, the investigational product must be quarantined and not used until Allogene provides permission to use the investigational product. It will not be considered a protocol deviation if Allogene approves the use of the investigational product after the temperature excursion. Use of the investigational product with a known temperature excursion or other product complaint prior to Allogene approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site by sponsor or its designee.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

5.10 Investigational Product Accountability

The appropriate, trained site staff will be required to maintain a record of the study treatment shipment documentation, study treatment inventory and study treatment accountability. Inventory and accountability records must be readily available to the study monitor, the sponsor, and any regulatory authority. Any study treatment destruction at the institution or by

institutional vendor must be performed ensuring compliance with 21 CFR 312.59 and ICH E6 8.4.2.

5.10.1 Return or Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the return or destruction of both used and unused investigational product (eg, at the site). If destruction is authorized by the sponsor to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Allogene, and all destruction must be adequately documented.

Any study treatment destruction at the institution or by an institutional vendor must be performed ensuring compliance with 21 CFR 312.59 and ICH GCP E6 4.6.

Refer to the ALLO-501A and ALLO-647 IP manual for specific instructions on return or destruction of investigational products.

5.11 Concomitant Treatments

Concomitant treatment considered necessary for the subject's well-being may be given at the discretion of the treating physician, unless specified as a prohibited medication.

All concomitant treatments, blood products, as well as nondrug interventions received by subjects will be recorded on the eCRF from screening through 3 months (90 days) after the ALLO-501A infusion, or initiation of a new anti-cancer therapy. After 3 months of follow-up, or initiation a new anti-cancer therapy, only targeted concomitant medication will be collected through 12 months including gammaglobulin, immunosuppressive drugs, anti-infective drugs, vaccinations, and any therapy for the treatment of the subject's disease (anti-lymphoma therapies).

New anti-cancer therapy administered must be entered in the eCRF.

Administration of hematopoietic growth factors (filgrastim, pegfilgrastim) are permitted after randomization as needed for ANC <500/μL in accordance with local or institutional guidelines.

IVIG administration in accordance with local and institutional guidelines is also permitted during screening and after randomization as needed to maintain an IgG serum concentration above 400 mg/dL.

5.12 Toxicity Mitigation and Management

5.12.1 Cytokine Release Syndrome

Cytokine release syndrome (CRS) is a symptom complex associated with the use of monoclonal antibodies and adoptive cell therapies that activate lymphocytes. The condition results from the release of cytokines from cells targeted by antibodies, immune effector cells recruited to the tumor area and subject's immune cells activated during this process. When

cytokines are released, a variety of clinical signs and symptoms associated with CRS present themselves including cardiac, gastrointestinal, laboratory (coagulation, renal and hepatic), neurological, respiratory, skin, vascular (hypotension), and constitutional (fever, rigors, headaches malaise, fatigue arthralgia, nausea and vomiting). CRS can range from mild, flu-like symptoms to a severe life-threatening syndrome including progression to hemophagocytic lymphohistiocytosis.

The severity of CRS will be assessed according to the American Society for Transplantation and Cellular Therapy (ASTCT; formerly American Society for Blood and Marrow Transplantation, ASBMT) grading criteria described by Lee et al (2019) (Table 1). A suggested treatment algorithm for the management of CRS is provided in Appendix 5.

Table 1. ASTCT CRS Consensus Grading

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

ASTCT (Lee et al 2019)

Abbreviations: ASBMT = American Society for Blood and Marrow Transplantation; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

a Fever is defined as temperature ≥38°C not attributable to any other cause. In subjects who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

b CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a subject with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

c Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Subjects shall be closely monitored for signs and symptoms of CRS, ie, fever, hypoxia, and hypotension. Subjects should be advised to seek immediate medical attention should signs or symptoms of CRS occur at any time. At the first sign of CRS, institute treatment with supportive care, tocilizumab, or tocilizumab, and corticosteroids as indicated.

Subjects who experience Grade 2 or higher CRS (eg, hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For subjects experiencing Grade ≥3 CRS, an echocardiogram should be performed to assess cardiac function and subjects should be promptly considered for intensive care supportive therapy.

5.12.1.1 Hypotension and Renal Insufficiency in the Setting of CRS

Hypotension and renal insufficiency should be treated as described here or according to medical judgment and institutional practice guidelines. Vigorous intravenous fluid hydration may be needed to manage hypotension and vascular leak in the setting of CRS. Subjects should be closely monitored to prevent fluid overload, and in some cases continuous veno-venous hemodialysis may be required. Invasive hemodynamic monitoring, for example, with a pulmonary artery catheter, may be helpful to optimize fluid management in settings of concurrent severe capillary leak, aggressive IVF administration, and/or pulmonary edema. Anti-hypertensives should be withheld whenever blood pressure begins to decrease below baseline values.

The baseline blood pressure is defined for this guideline as the average of all blood pressure readings obtained during the 24 hours prior to ALLO-501A infusion. The first treatment for hypotension is administration of IV normal saline boluses.

- Subjects with a systolic blood pressure, diastolic blood pressure, or mean arterial pressure that is 80% or less of their baseline or less than the lower limit of normal should receive 1-liter normal saline bolus.
- If the hypotension does not respond adequately within 1 hour, a second bolus at a volume per investigator discretion should be given.
- If hypotension persists despite 2 fluid boluses, consideration should be given for monitoring in the intensive care unit and administering vasopressor support.

These guidelines may be modified based on institutional guidelines and the clinical characteristics of individual subjects, such as pulmonary status, cardiac function, and other factors.

5.12.1.2 Cardiac Toxicity in the Setting of CRS

Cardiac manifestations of CRS may include arrhythmias, decreased ejection fraction/heart failure, myocardial ischemia, and cardiac arrest. Tachycardia is common in the setting of CRS and medications to slow sinus tachycardia should be avoided. Hypotension should be managed as in Section 5.12.1.1.

Subjects with persistent hypotension not responsive to fluids should be evaluated for decreased ejection fraction/heart failure by echocardiogram. These toxicities should be emergently managed per medical judgment and institutional practice guidelines.

Subjects with ≥Grade 2 cardiac toxicity should be monitored with continuous cardiac telemetry and pulse oximetry. Tocilizumab and corticosteroids should be administered per

Appendix 5. Follow-up ECGs and echocardiograms are recommended to monitor the course of toxicity to potential resolution.

5.12.2 Neurologic Toxicity

Neurologic toxicities that were fatal or life-threatening occurred following treatment with autologous CAR T cell therapies. The most common neurologic toxicities included encephalopathy, headache, tremor, dizziness, aphasia, delirium, insomnia, and anxiety.

Subjects who experience Grade 2 or higher neurologic toxicities should be monitored with continuous cardiac telemetry and pulse oximetry. Intensive care supportive therapy should be provided for Grade ≥3 neurologic toxicities. Non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis should be considered for any Grade 2 or higher neurologic toxicities. In the event of Grade ≥3 neurological toxicity suspected related to ALLO-501A, a lumbar puncture should be performed, if safe to do so, and CSF collected, for infectious workup (including HHV6 and HHV7). If neurologic toxicity is suspected, the recommendations presented in Appendix 10 should be closely followed. For AEs of neurological toxicity, a neurotoxicity (ICANS) eCRF should be completed in the EDC, including the Immune Effector Cell-Associated Encephalopathy (ICE) score. When relevant an assessment for new or reoccurrence of CNS disease should be considered including MRI.

In general, neurological toxicities will graded according to CTCAE version 5.0. The ASTCT recently developed the immune effector cell-associated neurotoxicity syndrome (ICANS) consensus grading guidelines (Lee et al, 2019), which are provided in Appendix 8. The ICE assessment tool is incorporated into the grading of ICANS and is also provided in Appendix 9. In the event of ICANS or Grade ≥3 neurotoxicity data specific to the ASTCT ICANS consensus definition, including the ICE assessment will be collected on the SAE/AESI/eCRF form as outlined in the safety reporting guidance. Events of Grade ≥3 neurological toxicity are considered an AESI and require reporting to the sponsor within 24 hours of awareness.

5.12.3 Anti-Infective Prophylaxis

Similar to alemtuzumab, ALLO-647 may be associated with prolonged and severe lymphopenia. and the effects of ALLO-501A on normal B cells may lead to B cell depletion and hypogammaglobulinemia, therefore, patients will be at increased risk for infection.

Subjects should follow institutional guidelines for food hygiene, mask wearing in high-risk situations and maintain hand hygiene. Subjects should receive inactivated or recombinant influenza vaccine annually and follow local guidelines regarding vaccination for COVID-19 (see Section 5.13.3).

Protocol inclusion and exclusions regarding infections are outlined in Section 4.1 and Section 4.2.

For subjects living in or travelling to endemic areas screening should be considered for West Nile Virus, *Strongyloides, Cocciomycosis, and Histoplamosis. Serum Aspergillus*

galactomannan antigen should be performed in subjects with a past history of invasive aspergillosis and other high-risk patients.

Subjects in FC and FCA arms shall receive anti-infective prophylaxis as recommended by the US National Comprehensive Cancer Network for subjects receiving fludarabine, alemtuzumab (NCCN Guidelines, 2020), or per institutional guidelines. Any anti-infective prophylaxis administered will be recorded in the eCRF. Refer to the full prescribing information for a complete description of the individual product.

From Day −5 until the ANC is >500 cells/µL, all subjects are recommended to receive the following anti-infective prophylaxis (or per institutional guidelines):

- Bacterial – fluoroquinolone prophylaxis during neutropenia. If intolerant to fluoroquinolone, consider TMP/SMX or an oral their-generation cephalosporin.

- Fungal – posaconazole or voriconazole. Both posaconazole and voriconazole are potent inhibitors of hepatic cytochrome P450 3A4 (CYP3A4) isoenzymes and may significantly decrease the clearance of agents which are sensitive substrates of CYP3A4. Examples of CYP3A4 substrates can be found in Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers (Drug Interactions, 2020).

- Pneumocystis jirovecii prophylaxis (PCP) – TMP/SMX. The following agents can also be considered: atovaquone, dapsone, pentamidine (aerosolized or IV).

From Day −5 for a minimum of 2 months after FC or FCA and until the CD4 count is >200 cells/µL:

- Prophylaxis for herpes viruses – acyclovir, famciclovir, valacyclovir

CMV Prophylaxis and Surveillance:

- FCA subjects who are CMV-seropositive at screening receive antiviral therapy for CMV prophylaxis (recommend letermovir [480 mg administered orally once daily for 100 days, or longer if clinically indicated beginning during lymphodepletion; intravenous prophylaxis should only be used if clinically necessary]). CMV-seropositive subjects on the FC arm may receive letermovir at the investigator's discretion.

- All subjects who are CMV seronegative at baseline should consider condom use to prevent primary infection via sexual intercourse.

- Consists of weekly monitoring by PCR for a minimum of 2 months after FC or FCA.

- In case of CMV reactivation, administer therapy per institutional standards (valganciclovir, ganciclovir, other recommended agents) or per guidance of local Infectious Disease specialists.

- If CMV remains detectable or in case of viral infection, further ID evaluation is recommended.

Subjects should receive inactivated or recombinant influenza vaccine annually.

5.12.4 B Cell Depletion

It is possible that B cell depletion and hypogammaglobulinemia will occur due to the effects of ALLO-501A on normal B cells. Gamma globulin will be administered for hypogammaglobulinemia according to institutional guidelines. At a minimum, trough IgG levels should be kept above 400 mg/dL including at baseline, and as indicated, especially in the setting of infection (ie, American Society for Blood and Marrow Transplantation, Center for International Bone Marrow Transplant Research; Hill et al, 2019).

5.12.5 Graft Versus Host Disease

Cutaneous Grade 1 acute GvHD will be managed with topical corticosteroids. In case of Grade ≥2 acute GvHD, institutional guidelines for the treatment of GvHD will be applied and could include the use of systemic corticosteroids. Investigators are advised to activate the rituximab-induced ablation of ALLO-501A in case of steroid resistant/refractory acute GvHD; up to 4 weekly doses of 375 mg/m^2 is recommended.

A system to grade the severity of acute GVHD is provided in Appendix 3.

The monitoring of chronic GvHD will be pursued for at least 2 years after the last ALLO-501A infusion. The National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease has issued the staging classification, provided in Appendix 4. Institutional guidelines for the treatment of chronic GVHD should be applied.

5.12.6 Infusion-Related Reactions

Following the first infusion of some therapeutic mAbs, subjects may experience infusion-related reactions characterized by fever and chills, and less commonly, hypotension, headache, nausea, or vomiting. These adverse events are generally ascribed to lysis of the cellular targets, cytokine release, or complement activation.

In the event of infusion related reactions, the investigator should institute treatment measures according to best medical and nursing practice. A suggested treatment algorithm for the management of infusion-related reactions is provided in Appendix 6; however, if local standard of care is a different regimen, it should be utilized.

Details on pre-medications to be administered prior to ALLO-647 are provided in Section 5.6.2.1. The pretreatment medications will not be supplied by Allogene.

Detailed guidance on treatment and dose interruption is provided in Appendix 6.

5.12.7 Blood Product Support for Anemia and Thrombocytopenia

All blood products should be irradiated and leukocyte reduced. Using CBCs as a guide, the subject should receive platelets and packed red blood cells as needed per institutional guidelines. Cross-match-compatible blood products for transfusion should be used where feasible. Leukocyte filters should be utilized for all blood and platelet transfusions to decrease sensitization to transfused WBCs and decrease the risk of cytomegalovirus infection.

5.12.8 Fever and Neutropenia

Evaluation for a source of infection should be performed per institutional guidelines. Fevers should be treated with acetaminophen and comfort measures. NSAIDs and corticosteroids should be avoided. Subjects who are neutropenic and febrile should receive broad-spectrum antibiotics. Maintenance IV fluids (normal saline) should be started on most subjects with high fevers, especially if oral intake is poor or if the subject has tachycardia. G-CSF (eg, filgrastim, or biosimilars) should be used according to published guidelines (eg, Infectious Disease Society of America). Subjects who develop prolonged neutropenia should be managed according to the institutional guidance. Alternate reasons for the prolonged neutropenia e.g. viral (CMV, EBV, Parvovirus 19, ADV, HHV-6), drug related, and metabolic causes should be ruled out. A thorough evaluation for acquired bone marrow failure syndromes should be performed where clinically indicated. This may include performing bone marrow biopsy, and testing for TCR-beta clonality on the bone marrow sample when clinically indicated. Myelosuppressive medications should also be avoided.

5.12.9 Hematopoietic Growth Factors

Primary prophylactic use of granulocyte colony stimulating factors is permitted to treat expected treatment emergent neutropenia as indicated by the current American Society of Clinical Oncology guidelines. Administration of filgrastim or pegfilgrastim (or biosimilars of either) is permitted per protocol and recommended for ANC <500 cells/µL following lymphodepletion and CAR^+ T cell infusion in accordance with local or institutional guidelines.

Erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia.

5.12.10 Anti-Diarrheal, Anti-Emetic Therapy

Primary prophylaxis of diarrhea, nausea and vomiting is permitted at the investigator's discretion. The choice of the prophylactic drug as well as the duration of treatment is up to the investigator assuming there is no known or expected drug-drug interaction and assuming the drug is not included in the Prohibited Treatment(s) section (Section 5.13).

5.13 Prohibited Treatments

5.13.1 Anti-Inflammatory Therapy

Systemic steroids must not be administered within 2 days prior to ALLO-501A (except to treat or prevent ALLO-647 infusion reactions). Other steroid use should be checked with the sponsor before starting lymphodepletion.

Corticosteroids and other immunosuppressive drugs should also be avoided for 3 months after ALLO-501A infusion, unless used to manage ALLO-501A or ALLO-647 related toxicities. Acute emergency administration, topical applications, inhaled sprays, eye drops, or local injections of corticosteroids are allowed.

Other medications that might interfere with the evaluation of the investigational product, such as non-steroidal anti-inflammatory agents, should also be avoided for the same time period unless medically necessary.

5.13.2 Other Antitumor/Anticancer or Experimental Drugs

No additional radiation or systemic anti-tumor treatment will be permitted until documented progressive disease, unless otherwise specified in this protocol.

There is no information on potential interactions with the concurrent use of select vitamins or herbal supplements, therefore their use should be avoided.

5.13.3 Viral vaccines

The safety of immunization with live viral vaccines during or following ALLO-501A treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting regimen, during ALLO-501A treatment, and until immune recovery following treatment with ALLO-501A.

The administration of COVID-19 vaccines which have been authorized by Health Authorities under an Emergency Use Authorization (EUA) or equivalent is permitted on study, as per institutional guidelines.

6. STUDY PROCEDURES

For an individual subject, the study will be divided in different periods including pre-screening (optional), screening, lymphodepletion, treatment, and follow-up.

6.1 Prescreening

Prescreening period is optional and may be used for the assessment of the absence of donor-specific anti-human leukocyte antigen (HLA) antibodies prior to a subject entering the screening period. The results may be used to determine a subject's eligibility for study participation.

All subjects being considered for the study and eligible for optional pre-screening must sign a pre-screening informed consent form before completing any study-specific pre-screening

procedures. The investigator (or appropriate delegate at the site) will obtain informed consent from each subject in accordance with the procedures described in the Schedule of Activities and on the informed consent form. A subject identification number will be assigned after the form has been signed and upon entering the subject into pre-screening in the eCRF.

Donor-specific anti-HLA antibody assessment completed during pre-screening must be repeated at screening if subject receives a transfusion (ie, red blood cells, platelets, plasma) between time of pre-screening and screening.

6.2 Screening

All subjects being considered for the study and eligible for screening must sign an informed consent form before completing any study-specific procedures. The investigator (or appropriate delegate at the site) will obtain informed consent from each subject in accordance with the procedures described in the Schedule of Activities and on the informed consent form. A subject identification number will be assigned after the form has been signed and upon entering the subject into screening in the eCRF.

For screening procedures see the Schedule of Activities.

Screening will start after the informed consent form is signed. Subject's eligibility criteria will be checked. The Screening period [redacted]. Sponsor may request the review of selected screening assessments prior to randomization. Subjects who meet all eligibility criteria at the end of the Screening period will then enter the Lymphodepletion Period. Screening assessments may be repeated to meet eligibility.

Screen failures are defined as participants who consent to participate in the clinical trial, who do not meet one or more criteria required for participation in the trial during the screening period and are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE. This information will be captured in the eCRF and in site source documents (patient medical record).

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened. Refer to the eCRF completion guidelines for assignment of subject identification numbers for rescreened participants.

6.3 Lymphodepletion

Lymphodepletion begins on [redacted].

For procedures performed during the lymphodepletion period, see Section 6 and the Schedule of Activities.

6.4 Treatment

Treatment will be on [redacted] with the administration of ALLO-501A.

For procedures performed during the treatment period, see Section 6 and the Schedule of Activities.

6.5 Follow-up

6.5.1 Follow-up for Subjects Completing Treatment

For subjects treated with ALLO-501A, follow-up in this study will last through [redacted]. For follow up procedures see the Schedule of Activities and Study Assessments (Section 6), and Appendix 11 for a summary of follow-up after disease progression.

During follow-up, subjects who completed treatment and subsequently have documented radiographic disease progression may be treated with anti-cancer therapy including investigational trials, while remaining in follow-up for safety and survival follow-up in this study. Scans documenting disease progression, including additional scans if available, must be sent to the IRC for central review.

If a subject starts a new anti-cancer therapy, no further disease assessments, local blood analyses, and central research samples (except described below) are necessary, however, the subject should continue to be followed to the extent possible for:

- Related serious adverse events as well as events relevant for long-term follow-up: new incidence of infection (potentially product-related), malignancy(ies), and/or hematologic disorder, as well as new incidence or exacerbation of a pre-existing neurologic, prior rheumatologic, or other autoimmune disorder (Section 8.1.3).
- Targeted concomitant medications (Section 5.11) including gamma globulin, immunosuppressive drugs, anti-infective drugs, vaccinations, and any therapy for the treatment of the subject's disease (anti-lymphoma therapies).
- Blood sample for RCL, genomic safety biospecimen, and PBMCs (Schedule of Activities).
- Survival status (Section 6.6)

Subjects who experience progressive disease but do not start a new anti-cancer therapy do not need to complete additional disease assessments. They should continue to be followed per the above bullet points with the following adjustment:

- Subjects experiencing progression before three months (from Day 0) should continue to report AEs through 3 months and then transition to reporting only related serious adverse events (Section 8.1.3)

At the EOS visit, or at the time of withdrawal from the study, subjects will be asked to participate in a noninterventional safety-monitoring long term follow-up (LTFU) study. In that study, subjects treated with ALLO-501A will be followed for a total of 15 years per requirement of the regulatory authorities for the follow-up of any subject having received a gene therapy treatment.

6.5.2 Follow-up after Randomization when subject did not receive study treatment

For all randomized subjects who do not receive study treatment, provide tumor assessment data (imaging or similar) until disease progression or death is observed, or study completion at [redacted], whichever is earlier. Safety assessments do not need to be completed.

After disease progression, they should be followed for subsequent anti-cancer therapies, and survival only, until the study is completed. No other clinic visits or assessments are required. Subjects who received no study treatment may be treated with anti-cancer therapy including investigational trials, while remaining in follow-up for safety and survival in this study.

Reasons for not receiving any study treatment include:

- Infection or adverse event (which precludes dosing)
- Disease progression (clinical)
- Full consent withdrawal

6.5.3 Follow-up after Randomization and Lymphodepletion when subject did not receive ALLO-501A

If a subject is randomized and receives lymphodepletion including at least 1 dose of FC or ALLO-647, but does not receive ALLO-501A, provide tumor assessment data (imaging or similar) until disease progression or death is observed, or study completion at Month 60, whichever is earlier. Also complete study safety visits including laboratory assessments relative to FC or FCA.

After disease progression, they should be followed as described in Section 6.5.1 including subsequent anti-cancer therapies, safety, and survival, until the study is completed. Blood samples for RCL and participation in the 15-year follow-up are not required if the subjects did not receive ALLO-501A CAR T cells. Subjects who received partial treatment (and not ALLO-501A) may be treated with anti-cancer therapy including investigational trials, while remaining in follow-up for safety and survival in this study.

Reasons for withdrawal from ALLO-501A treatment include:

- Infection or adverse event (which precludes dosing)
- Disease progression (clinical)

- Full consent withdrawal

6.6 Survival Follow-up

For subjects who decline further protocol-required procedures or assessments after starting a new anti-cancer therapy, subjects can be contacted to assess survival status by clinic visit or telephone to assess survival until death, withdrawal by subject, lost to follow-up, or study terminated by Sponsor, whichever comes first.

6.7 Subject Withdrawal

6.7.1 Reasons for Withdrawal from Study (End of Study)

Reasons for withdrawal from the study include:

1 Full withdrawal of consent (see Section 6.7.2)
2 Lost to follow-up (see Section 6.7.3)
3 Death
4 Completed study

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return for the EOS visit and follow up with the subject regarding any unresolved AEs

6.7.2 Withdrawal of consent:

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

Subjects can decline to continue to receive study required treatment and/or other protocol required procedures at any time during the study but continue to participate in the study.

If the subject declines continuing protocol required procedures, the investigator must discuss with the subject the appropriate process for discontinuation from investigational product, study treatment or other protocol required therapies and must discuss options for continued participation, completion of procedures and the associated data collection as outlined in the Schedule of Activities. The level of follow-up and method of communication should also be discussed between the research staff and the subject and documented in the source documents.

Withdraw of consent for a study means that the subject does not wish to receive further protocol required therapy or undergo procedures and the subject does not wish to continue further study follow-up. Subject data collected up to withdraw of consent will be retained and included in the analysis of the study, and where permitted by local regulations, publicly available data (death records) can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

As part of the study, sites may be asked to conduct searches of public records, such as those establishing survival status, if available, to obtain survival data for any subject for whom the survival status is not known. Sites may be also asked to also retrieve autopsy reports to confirm status of disease at the time of death.

The investigator and/or sponsor can also decide to withdraw a subject from the investigational product and/or other protocol-required therapies, or protocol procedures, at any time prior to study completion.

6.7.3 Lost to follow-up:

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's study source records. The site staff will consult publicly available sources, such as public health registries and databases, to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's study source records and in the eCRF. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study.

Subjects may withdraw from treatment at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given investigator site.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol -required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, this will be recorded as a protocol deviation (see Section 11.3). The study team will be informed of these incidents in a timely manner.

For samples being collected and shipped to central laboratories, detailed collection, processing, storage, shipment instructions and contact information will be provided in the study central laboratory manual.

7.1 Safety Assessment

Safety assessments will include collection of AEs, SAEs, vital signs and physical examination, electrocardiogram (ECG [12-lead]), laboratory assessments, including pregnancy tests and verification of concomitant treatments.

7.1.1 Adverse Events

Assessment of adverse events will include the type, incidence, severity (graded by the NCI CTCAE version 5.0, unless otherwise specified) timing, seriousness, and relatedness (see Section 8). The severity of CRS and neurotoxicity will be assessed according to the grading described in Table 1 and Appendix 9, respectively. The severity of acute graft versus host disease will be assessed according to the grading described in Appendix 3.

7.1.2 Laboratory Safety Assessment

Hematology and blood chemistry will be drawn at the time points described in the Schedule of Activities and analyzed at local laboratories unless otherwise stated in Table 2.

Table 2. Safety Laboratory Tests

<table>
<tr><th>Hematology</th><th>Chemistry</th><th>Infection</th><th>Coagulation</th><th>Urinalysis</th><th>Pregnancy Test</th></tr>
<tr><td>Hemoglobin and hematocrit</td><td>ALT</td><td rowspan="3">Serologies for HBV and HCV</td><td>PT or INR</td><td rowspan="6">Urine dipstick for protein, glucose, creatinine, and blood: If positive collect 24-hr and/or microscopic cell count (Reflex Testing)</td><td rowspan="2">For female subjects of childbearing potential, serum</td></tr>
<tr><td>Platelets</td><td>AST</td><td>PTT</td></tr>
<tr><td>WBC</td><td>Alk Phos</td><td>Fibrinogen</td></tr>
<tr><td>Absolute/% Neutrophils</td><td>Sodium</td><td>RCL (Central laboratory)</td><td>D-Dimers</td><td rowspan="14"></td></tr>
<tr><td>Absolute/% Lymphocytes</td><td>Potassium</td><td rowspan="3">Aerobic and anaerobic blood cultures</td><td rowspan="13"></td></tr>
<tr><td>Absolute/% Monocytes</td><td>Magnesium</td><td rowspan="12"></td></tr>
<tr><td>Absolute/% Eosinophils</td><td>Chloride</td></tr>
<tr><td>Absolute/% Basophils</td><td>Serum calcium</td><td rowspan="12">Interferon gamma release assay (IGRA) for latent TB

Screening for endemic infections as needed

Screening and Monitoring for CMV and EBV and adenovirus if indicated</td></tr>
<tr><td rowspan="3">Reticulocyte count</td><td>Total bilirubin[a]</td><td rowspan="11"></td></tr>
<tr><td>BUN or Urea</td></tr>
<tr><td>Creatinine
Creatinine clearance</td></tr>
<tr><td rowspan="10"></td><td>Uric Acid</td></tr>
<tr><td>Glucose</td></tr>
<tr><td>LDH</td></tr>
<tr><td>Albumin</td></tr>
<tr><td>Phosphorus or Phosphate</td></tr>
<tr><td>Bicarbonate</td></tr>
<tr><td>Total Protein</td></tr>
<tr><td>TSH</td></tr>
<tr><td>Ferritin</td></tr>
<tr><td>CRP</td></tr>
</table>

Abbreviations: Alk Phos = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CMV = cytomegalovirus, CRP = C-reactive protein, EBV = Epstein-Barr virus, HBC = hepatitis B core, HCV = hepatitis C virus,
INR = international normalized ratio, LDH = lactate dehydrogenase, PT = prothrombin time, PTT = partial thromboplastin time, RCL = replication competent lentivirus, TB = tuberculosis, TSH = thyroid stimulating hormone, WBC = white blood cell

[a] For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, alkaline phosphatase, total bile acids and acetaminophen drug and/or protein adduct levels.

7.1.3 Vital Signs and Physical Examination

Subjects will have a physical examination to include weight, vital signs, Immune Effector Cell-Associated Encephalopathy (ICE) score (baseline and as clinically indicated), neurological exam, assessment of ECOG performance status (Appendix 2), and height; height will be measured at baseline only.

7.1.4 Electrocardiogram (12-Lead)

At each time point (see Schedule of Activities), a single ECG should be performed to for cardiac safety and to determine the QTcF (Fridericia's) interval. If the QTcF is prolonged (>500 msec, ie, CTCAE Grade ≥3) (except with underlying bundle branch block), then the ECG should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading verifies a QTcF of > 500 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTcF interval) should be performed. In addition, repeat ECGs should be performed hourly for at least 3 hours until the QTcF interval falls below 500 msec. If QTcF interval reverts to less than 480 msec, and in the judgment of the investigator(s) and sponsor is determined to be due to cause(s) other than investigational product, treatment may be continued with regular ECG monitoring. If in that timeframe the QTcF intervals rise above 500 msec the investigational products will be held until the QTcF interval decreases to 480 msec. If the QTcF interval has still not decreased to ≤480 msec after 2 weeks, or if at any time a subject has a QTcF interval >515 msec or becomes symptomatic, the investigational product will be stopped. An additional ECG may be performed as clinically indicated.

Prior to concluding that an episode of prolongation of the QTcF interval is due to investigational product, thorough consideration should be given to potential precipitating factors (eg, change in subject clinical condition, effect of concurrent medication, electrolyte disturbance) and evaluation by specialist should be considered.

If a subject experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke), an ECG (triplicate) should be obtained at the time of the event.

7.1.5 Echocardiogram or Multigated Acquisition Scan

LVEF will be assessed by echocardiography (ECHO) or multi-gated acquisition scan (MUGA) at Screening.

The same technique that was used during Screening should be used for a given subject throughout the study. The Simpson's method is the most commonly used method and the one recommended for LVEF measurement.

7.1.6 Pregnancy Testing

For female subjects of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at screening and following timepoints defined in the Schedule of Activities.

A negative pregnancy test result is required before the subject may receive the investigational products. Pregnancy tests will also be done whenever 1 menstrual cycle is missed (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

7.2 Tumor Response Assessment

Subjects will be evaluated for disease response by the site investigator at times indicated in the Schedule of Activities. Disease assessments will be evaluated per the Lugano classification criteria 2014 (Cheson et al, 2014). Flow cytometric, molecular or cytogenetic studies will not be used to determine response.

Tumor assessments will include all known or suspected disease sites. Disease-specific imaging as clinically appropriate will be performed. Anti-cancer activity will be assessed at baseline, during treatment as specified in the Schedule of Activities, and whenever disease progression is suspected (eg, symptomatic deterioration).

Disease assessments after ALLO-501A will be used to determine the time when PD occurs. Subjects 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 Schedule of Activities.

A bone marrow aspirate and biopsy will be performed in subjects who are being assessed for CR. Per the revised IWG Response Criteria for Malignant Lymphoma (Cheson et al, 2014), a bone marrow aspirate and biopsy should be performed only when the subject had bone marrow involvement with lymphoma prior to randomization or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after randomization. For treatment response confirmation, the bone marrow aspirate and 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.

All subjects' files and radiologic images must be available for source verification by the sponsor.

7.2.1 Imaging Assessments for Independent Review Committee

In addition to the investigator's assessment, disease-specific imaging as clinically appropriated, and additional clinical data will be submitted to and reviewed by the central radiology vendor (IRC) per the instructions in the imaging manual. For subjects who discontinue the study due to an assessment of PD, any additional imaging data, current and subsequent to the image in question, will be submitted to the central reviewer to confirm disease response.

Imaging requirements, specifications, and transmittal requirements are outlined in the study imaging manual.

7.3 Cell Kinetics and Pharmacokinetics Assessments

Biospecimens will be collected at various time points and examined using cellular, molecular and protein-based assays such as an ELISA-based monitoring of ALLO-647, fludarabine, and cyclophosphamide PK, vector copy number (VCN) analysis by qPCR, and cellular kinetics analysis by flow cytometry. Samples for ALLO-501A and ALLO-647, fludarabine, and cyclophosphamide monitoring will be collected into appropriately labeled tubes as

outlined in the Schedule of Activities and central laboratory manual. The cellular kinetics and PK sampling schedule may be modified based on emerging cellular kinetics and PK data.

In addition to samples collected at the scheduled times, an additional blood sample should be collected from subjects experiencing unexpected and/or serious AEs and the date and time of blood sample collection will be documented in the eCRF and source records. Such samples may be used to explore levels of ALLO-501A cells in subjects experiencing unexpected and/or SAEs.

Where noted in the Schedule of Activities, blood samples for ALLO-647, fludarabine, and cyclophosphamide concentrations and ALLO-501A cellular kinetics assessment will be collected at approximately the same time as other assessments such as pharmacodynamics, wherever possible.

All efforts will be made to obtain the cellular kinetics and PK samples at the scheduled nominal time relative to dosing. The time of the sample collection will be noted on the eCRF, sample labels, and requisition forms. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of the clinical investigator, subject, and sponsor.

Cellular kinetics samples for ALLO-501A and PK samples for ALLO-647, fludarabine, and cyclophosphamide will be assayed using a validated analytical method in compliance with the selected vendor's standard operating procedures (SOPs).

The cellular kinetics and PK samples must be processed and shipped as indicated in the central laboratory manual provided to the investigative site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may decide whether sample integrity has been compromised.

As part of understanding the PK of the investigational product, samples may be used for evaluation of the bioanalytical method, as well as for other internal exploratory purposes. These data will not be included in the clinical study report (CSR).

Additional instructions for sample collection, processing, storage, and shipping will be provided in the study laboratory manual.

7.4 Biomarker and Pharmacodynamic Assessments

Biospecimens collected for pharmacodynamic and other biomarker assessments may include peripheral blood, body fluids, tumor tissues, and bone marrow aspirate, and may be used to analyze DNA, RNA, proteins, or metabolic biomarkers, for achieving planned biomarker objectives. Refer to the Schedule of Activities for sample collection time points and to the study laboratory manual for sample processing and shipping.

The following biospecimen types are planned to be collected in support of study objectives. Additional biospecimens collected over the course of subject disease management may be submitted for biomarker analyses.

7.4.1 Archival/De Novo Tumor Biopsies

Lymph node tumor biospecimens from archival and de novo biopsies may be used to analyze candidate nucleic acid and protein biomarkers for their ability to identify those subjects who are most likely to benefit from treatment with the study drugs. Biomarkers may include, but are not limited to target expression, nucleic acid analyses, as well as cell types and constituents of the tumor microenvironment. *De novo* tumor biopsies obtained upon disease progression may be used to investigate acquired mechanisms of resistance and detection of ALLO-501A cells. Additional information on tissue collection procedures can be found in the Schedule of Activities and the study laboratory manual.

7.4.2 Peripheral Blood and Derivatives

Peripheral blood and derivatives may be used to characterize cell phenotypes, measure soluble proteins, and analyze nucleic acids to support study objectives. Examples may include cytokines and immunophenotyping, with additional analyses may be warranted based on emerging data.

Subjects may be evaluated for disease response by the site investigator at times indicated in the Schedule of Activities. Disease assessments will be evaluated per the revised IWG Response Criteria for Malignant Lymphoma (Cheson et al, 2014). Flow cytometric or cytogenetic studies will not be used to determine response. MRD may be assessed by molecular assay as exploratory measurement to define response and duration of response.

7.5 Immunogenicity

Blood samples may be analyzed for the detection of anti-drug antibody (ADA) and neutralizing antibody (Nab) against ALLO-647, TALEN and ALLO-501A scFv. ADA and Nab samples will be analyzed using validated analytical methods in compliance with the vendor's standard operating procedures and FDA/EMA guidelines, eg, ADA sample assay and analysis may follow a ECL approach of screening, confirmation, and titration. Only those samples tested to be positive for ADA may be further analyzed for Nab.

Additional instructions for sample collection, processing, storage, and shipping are provided in the study laboratory manual.

As part of understanding the immunogenicity of the investigational products, samples may be used for evaluation of the bioanalytical methods. These data may be used for internal exploratory purposes and may not be included in the CSR. The samples will be retained in accordance with local regulations and if not used within this timeframe, will be destroyed.

7.6 Gene Expression

In order to identify changes in expression signatures potentially associated with ALLO-501A expansion, efficacy and/or persistence, a whole transcriptome analysis including, but not

limited to, the study subject's baseline state, as well as expanding versus declining populations of CAR+ T-cells in peripheral blood and in tumor tissue may be performed and compared to a) the infusion product's expression, b) between subjects who respond vs non-responders, and/or c) in reference to the subject's baseline.

7.7 Genomic Analyses

During the manufacturing process, ALLO-501A undergoes both lentiviral integration of a foreign gene and TALEN®-mediated gene disruption. Although existing experience suggests that risks of T-cell transformation following a lentiviral insertion or gene disruption are low, there is still a theoretical potential that the modifications introduced in ALLO-501A could lead to cell transformation. If a secondary T-cell transformation occurs, genomic assays may be performed to assess the mechanism of the transformation.

Blood and/ or tissue samples may be collected at the time specified in the Schedule of Activities, and when a safety signal is detected and archived until assay. For example, in case a secondary T-cell malignancy occurs, an attempt should be made to collect bone marrow (BM) samples, as well as blood. The initial BM sample should be collected as close as possible to the diagnosis of said secondary malignancy. Further BM samples should be collected at the next scheduled visits.

Samples may be drawn and processed under the conditions described in the procedure manual, and subsequently cryopreserved at ≤–70°C until shipment to a third-party laboratory, where they may be processed and/or archived until a suitable assay is performed or until shipment to a central biorepository at the end of the study.

7.8 Banked Biospecimens

Banked biospecimens, including serum/plasma, whole blood, bone marrow, and PBMC may be collected from subjects for other activities relating to the treatment response and disease under study, including assay bridging, sample stability, equivalency, etc. These specimens are not, by definition, pre-planned assessments described in the protocol. They would be handled in a manner that protects each subject's privacy and confidentiality. Biospecimens will be assigned the subject's study identification code, as generated in the eCRF. The data generated from assaying these biospecimens will also be indexed by this ID, and so not returned to the study subject. Biospecimens will be kept until destruction in facilities with access limited to authorized personnel, and biospecimen derived data will be stored on password protected computer systems. The key between the subject's ID and the subject's direct personally identifying information (eg, name, address) will only be held at the study site, and NOT by the Sponsor. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored for many years (no time limit) to allow for research in the future, including research conducted during the lengthy drug development process and also post marketing research. Subjects may withdraw their consent for the use of their banked biospecimens at any time prior to the assay, by making a request to the investigator; in this case, any remaining biospecimens will be destroyed, but data already generated from the biospecimens will continue to be available to protect the integrity of existing analyses.

Unless prohibited by local regulations or ethics committee decision, a blood biospecimen (dipotassium edetic acid [ethylenediaminetetraacetic acid] [K_2EDTA] whole blood collection optimized for a variety of assays) will be collected at the time specified in the Schedule of Activities for potential biomarker assays, e.g. known, novel, and complex fusion events, as well as other common alterations (substitutions, indels, and CNVs), etc, related to treatment and disease under study. Similarly, the specimen may be used to assay for pathogens, either pre-existing and latent, or pathogens which appear following lymphodepletion. Such pathogens (eg, HHV6, HHV7, HTLV-1, etc.) may not be routinely clinically tested, depending on the standard of care at the site.

Detailed collection, processing, storage, and shipment instructions are provided in the study laboratory manual.

It is possible, though highly unlikely, that these biospecimens may result in commercially viable products, eg, an assay developed to detect a nucleic acid sequence identified in a study subject. Subjects will be advised in the informed consent document/subject information sheet that they will not be compensated in this event.

7.9 Patient Reported Outcomes

Reducing mortality and morbidity is still the most important factor in clinical research. Nevertheless, issues such as reducing side effects, symptom relief and improving patients' satisfaction have also become relevant parameters in the evaluation of medical strategies. Cancer treatments may produce adverse effects and diminish the quality of life (QoL) even when survival is extended. Progress in the acceptance of new cancer therapies is sometimes critically dependent on their QoL consequences. Health related QoL is a multidimensional concept, which represents the physiological, psychological and social influences of the disease and the therapeutic process from the patients' perspective. It comprises 4 principal components: physical, psychological, social well-being, and daily-life functioning.

The EQ-5D-5L is a generic patient questionnaire for assessing the overall health status of a patient. The EQ-5D-5L consists of a 5-dimension descriptive system including questions on mobility, selfcare, usual activities, pain/comfort, and anxiety/depression and a visual analogue scale (EQ VAS) which allows the respondent to record health on a vertical scale (eg, best health to worst health) thus allowing a quantitative measure of health outcome.

Quality of life will also be assessed with the EORTC Quality of Life Questionnaire (QLQ-C30) version 3. This is composed of multi-item and single scales. These include 5 functional scales (physical, role, emotional, social, and cognitive), 3 symptoms (fatigue, nausea and vomiting, and pain), and a global health status/QoL scale and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). All scales and single items meet the standards for reliability. The reliability and validity of the questionnaire is highly consistent across different language-cultural groups.

EQ-5D-5L (PRO) and the QLQ-C30 (PRO) will be completed as outlined in the Schedule of Activities where possible. The study staff; however, cannot interpret any of the questions for

the subject. A subject may be exempt from completing the questionnaire if he or she is unable to read the questionnaire in one of the country languages available.

8. ADVERSE EVENT REPORTING

8.1 Requirements

Table 3 summarizes the requirements for recording safety events on the CRF and for reporting safety events to sponsor or designee per the study guidelines. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events; and (3) exposure to the investigational product under study during pregnancy or breastfeeding.

Table 3. Adverse Event Reporting

Safety Event	Recorded on the eCRF	Reported on separate Form to Sponsor or Designee Within 24 Hours of Awareness*
SAE	All	All, use SAE/AESI report form
Non-serious AE	All	None
Adverse Event of Special Interest	All	All, use SAE/AESI report form
Exposure to the investigational products under study during pregnancy or breastfeeding	All (regardless of whether associated with an AE)	Exposure during pregnancy, exposure via breastfeeding, (regardless of whether associated with an AE)

* As per the reporting time period.

All observed or volunteered events or suspected causal relationship to the investigational products will be reported as described in the following paragraphs.

Events listed in Table 3 that require reporting to the sponsor or designee on the SAE/AESI Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to the sponsor or designee must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event. Refer to the study safety reporting guidelines for more details on using the safety report forms to report SAEs, AESIs, or exposure to the investigational products under study during pregnancy or breastfeeding.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see Section 8.2.4). In addition, the investigator may be requested by the sponsor or designee

to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the eCRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the sponsor or designee. Any pertinent additional information must be reported on the SAE/AESI Report Form; additional source documents (eg, medical records, eCRF, laboratory data) are to be sent to the sponsor or designee **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1 Additional Details on Recording Adverse Events on the eCRF

All events detailed in Table 3 will be recorded on the AE page(s) of the eCRF. It should be noted that the paper report form for reporting of SAE information to sponsor pharmacovigilance is not the same as the AE page of the eCRF. When reporting SAEs, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same SAE term should be used on both the eCRF and the paper report form for reporting of SAE information.

8.1.2 Eliciting Adverse Event Information

The investigator is to record on the eCRF all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3 Time Period for Collecting AE/AESI/SAE Information

The time period for actively eliciting and collecting AEs, AESIs and SAEs for each subject begins from the time the subject provides informed consent (does not include prescreening consent) which is obtained before the subject's participation in the study (ie, before receiving investigational products), through 60-month follow-up visit scheduled [redacted] after the initial dose of ALLO-501A according to the guidance below.

All AEs will be collected through [redacted] months ([redacted] days) after the last dose of ALLO-501A or until a subject begins a new anti-cancer therapy, whichever happens first. After [redacted] AESIs and SAEs will be collected until [redacted], disease progression, or initiation of a new anti-cancer therapy, whichever happens first. SAEs that are assessed as related to the IMP by the investigator should be collected and reported regardless of the time of occurrence (including beyond disease progression and initiation of new anti-cancer therapy). Events relevant for long-term follow-up (ie, the long term AESIs (Section 8.2.2) malignancy, hematological disorders, autoimmune disorders, neurological disorders, infections potentially

related to product) will be followed for a total of 5 years in this protocol and in a separate long term follow up protocol for a total of 15 years.

For AEs that do not meet the definition of a SAE and which occur during the period from the time the screening informed consent is signed but prior to the subject receiving lymphodepletion, only those associated with protocol-related procedures should be reported.

For subjects who are screen failures, the data collection period ends when screen failure status is determined.

8.1.4 Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the eCRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational products caused or contributed to an AE (ie, is there a reasonable possibility that the AE is related to the study treatment - No [unrelated] or Yes [related]). Generally, the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and eCRF, and report such an assessment in the dedicated section of the SAE Report Form and in accordance with the SAE reporting requirements.

8.1.5 Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable ICH, EU, and country specific guidelines. In the US, the FDA will be notified according to guidelines for expedited safety reporting in accordance with 21 CFR 312.32 c(1) and *Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies Dec 2012*.

The reference safety information for ALLO-501A and ALLO-647 will be the Investigator Brochure for each respective investigational product.

8.2 Definitions

8.2.1 Adverse Events

An adverse event or experience is defined as any symptom, sign, illness, abnormal test finding, or untoward experience that develops or worsens during the course of the study, whether or not the event is considered related to the investigational product(s).

When a diagnosis is possible, it is preferable to record it, rather than a series of signs or symptoms relating to the diagnosis, on the case report form.

Examples of adverse events include:

- A worsening, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition;
- Development of an intercurrent illness during the study;
- Development of symptoms which may or may not be related to the use of a concomitant medication or study drug;
- Injury or accidents: if a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as 2 separate medical events (eg, for a fall secondary to dizziness, both “dizziness” and “fall” should be recorded separately).

Adverse events are detected in 2 ways:

- Clinical: symptoms reported by the subject or signs detected on examination;
- Ancillary Tests: clinically significant abnormalities of vital signs, ECG, laboratory tests, and other diagnostic procedures.

An adverse event **does not** include:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is an adverse event;
- Pre-existing diseases or conditions present or detected prior to the start of study drug administration that do not worsen;
- Situations where an untoward medical event has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions);
- Overdose of either study drug or concomitant medication without any signs or symptoms.
- Hospitalizations for study treatment infusions or precautionary measures per institutional policy.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error.

8.2.2 Adverse Events of Special Interest

An AE of special interest (AESI) is a noteworthy event for the particular product or class of products that a sponsor may wish to monitor carefully. It could be serious or non-serious AE which may require further investigation to characterize and understand it.

The following events, regardless of causality to ALLO-501A and ALLO-647, are considered as AESIs (see Section 8.1.3):

- Grade ≥3 CRS
- Grade ≥3 Neurologic toxicity
- Grade ≥3 Infection
- GvHD
- Autoimmune disorders
- Secondary malignancies
- Suspected transmission of an infectious agents by a medicinal product (STIAMP)

The following events regardless of causality to ALLO-501A and ALLO-647 are considered as long-term AESI (see Section 8.1.3 and Appendix 11):

- Chronic GvHD
- New incidence or exacerbation of a pre-existing rheumatologic or Autoimmune disorders
- New incidence or exacerbation of a pre-existing neurologic disorder
- Secondary malignancies and/or haematological disorders
- New incidence of infection (potentially product-related)

All AESIs should be reported within 24 hours of staff becoming aware of them and handled the same as SAEs.

8.2.3 Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.4 Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.
- Is considered an important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Events that require an escalation of care when the subject is already hospitalized should be recorded as an SAE, eg, movement from routine care in the hospital to the ICU or if the event resulted in a prolongation of the existing planned hospitalization.

8.2.5 Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.2.6 Disease Progression as an Adverse Event

It is anticipated that a proportion of subjects will experience disease progression. Disease progression assessed by measurement of malignant lesions on radiographs or other methods but with no worsening of signs and symptoms should not be reported as AEs.

Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period (see Section 8.1.3). A death attributed to disease progression of the underlying lymphoma should be recorded with the preferred term of B-cell lymphoma, with NCI CTCAE Grade 5 (see Severity Assessment in Section 8.3) and must be reported immediately to the sponsor.

8.3 Severity Assessment

Severity will be graded by the NCI CTCAE version 5.0 or Table 4 below if not covered by CTCAE. CRS will be assessed per ASTCT 2019 (Table 1) and GvHD will be assessed as per Appendix 3 and Appendix 4.

Table 4. Adverse Event Severity Assessment

Grade	Clinical Description of Severity
1	Mild asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (such as preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (such as bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
4	Life-threatening consequences; urgent intervention indicated
5	Death related to AE

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs listed in Table 4.

8.4 Special Situations

8.4.1 Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

In the majority of DILI cases, elevations in AST and/or ALT precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject's individual baseline values and underlying conditions. Subjects who present with the

following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;
- For subjects with baseline AST OR ALT OR TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

  Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

  Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The subject should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time/international normalized ratio, total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a co-formulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.2 Exposure to the Investigational Product During Pregnancy or Breastfeeding

Exposure to the investigational product under study during pregnancy are reportable to the sponsor or designee within 24 hours of investigator awareness.

For both unapproved/unlicensed products and for marketed products, an EDP occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

- An example of environmental exposure would be a case involving direct contact with an Allogene product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must report this information to the sponsor and/or designee following the safety reporting guidelines provided to the investigational site.

In addition, the investigator must submit information regarding environmental exposure to an Allogene product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage). This must be done irrespective of whether an AE has occurred and Allogene will be notified within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify the sponsor or designee of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

Additional information about pregnancy outcomes that are reported to the sponsor or designee follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality. In addition, infant deaths after 1 month should be reported when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). The investigator will provide the subject or the subject's partner with the Pregnancy Informed Consent Form. The investigator must document the consent statement in the trial source documents for the subject or the subject's partner.

8.5 Data Monitoring Committee/Data Safety Monitoring Board

An independent data and safety monitoring board (DSMB) will be chartered to review accumulating safety and efficacy data throughout the study.

The DSMB will review SAE information and enrollment pausing criteria after [redacted] have been randomized and have had the opportunity to be followed for [redacted] after the first dose of lymphodepletion.

During these periodic reviews and formal interim analyses, DSMB will also review all available study conduct data (e.g. accrual), and trial progress data. The DSMB may request additional safety data or recommend modifications of the study conduct, including the accrual of additional subjects or termination of the trial.

At the time of second interim analysis the DSMB will also provide a recommendation such as stopping treatment for futility or to implement the adaptive sample size adjustment. The DSMB may request additional reviews as needed.

The sponsor may request additional reviews by the DSMB, or the DSMB may request additional reviews to the sponsor if safety or feasibility concerns are identified. The DSMB may make recommendations regarding study conduct of the study if safety or feasibility concerns are identified. Data submitted to the DSMB may be monitored or unmonitored to facilitate and ensure timely DSMB review. The scope and remit of the DSMB will be described in a DSMB Charter.

Sponsor access to the ongoing trial data will be controlled and described in the DSMB Charter and Trial Integrity Document.

9. STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study are outlined here and further detailed in statistical analysis plans (SAPs) separately.

The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, PK and biomarker measurements.

9.1 Analysis Sets

1. Intent-to-Treat Analysis Set (All Randomized): The intent-to-treat (ITT) analysis set will consist of all randomized subjects. Unless otherwise specified, the ITT analysis set will be used as the primary analysis set for all efficacy analyses. Subjects will be analysed based on randomized treatment assignment, regardless of treatment received.
2. Modified Intent-to-Treat Analysis Set: The modified intent-to-treat (mITT) analysis set includes all randomized subjects who received ALLO-501A. The mITT analysis set will be used for sensitivity analyses of efficacy endpoints. Subjects will be summarized according to the actual treatment received.
3. Safety Analysis Set: The safety analysis set includes all randomized subjects who receive at least one (partial or complete) dose of ALLO-647 or ALLO-501A. This analysis set will be used for analyses of safety. Subjects will be summarized according to the actual treatment received. Separate safety analysis sets will be defined for ALLO-647 and ALLO-501A with details in the SAP.
4. PK Analysis Sets: Separate PK analysis population will be defined for ALLO-647 and ALLO-501A.
    (a) The PK parameter analysis population is defined as all randomized subjects treated who do not have protocol deviations influencing PK assessment and have sufficient information to estimate at least 1 of the PK parameters of interest.
    (b) The PK concentration population is defined as all randomized subjects who are treated and have at least 1 analyte concentration at baseline and post baseline.
5. Pharmacodynamic/Biomarker Analysis Set: The pharmacodynamic/biomarker analysis population is defined as all randomized subjects with at least 1 of the pharmacodynamic/biomarkers evaluated at pre and/or post-dose.
6. Immunogenicity Analysis Set: The immunogenicity analysis set includes all randomized subjects who receive at least 1 dose of study treatment and have at least 1 valid result for the ADA testing.

9.2 Sample Size Determination

A target of approximately 70 subjects may be randomized 1:1 to FC and FCA arm in the study. This study is designed with an adaptive sample size re-adjustment. [redacted]

A PFS hazard ratio (FCA/FC) of 0.40 is hypothesized in the intent-to-treat (ITT; all randomized) analysis set. Assuming an exponential distribution for PFS and a median PFS of 2 months in the FC arm, this implies a 250% relative improvement in PFS and under the assumption of an exponentially distributed PFS time, corresponds to median PFS of 2 versus 5 months (CRISPR Therapeutics 2021; Precision Biosciences 2020; Neelapu et al, 2017, Jain et al, 2021, and Locke et al, 2019). The primary analysis is planned when 50 PFS have been

observed; the study has been sized to achieve 90% power at the 1-sided 2.5% significance level to detect a 250% improvement in median PFS time. [redacted]

The secondary endpoint ORR will be tested hierarchically using stepwise method after primary endpoint of PFS is statistically significant.

An independent DSMB will be chartered to conduct interim analyses and provide recommendations on study conduct. The DSMB will review SAE information and enrollment pausing criteria [redacted] have been randomized and have had the opportunity to be followed for 30 days after the first dose of lymphodepletion. Additionally, the DSMB chair will receive all expedited safety reports at the time of regulatory submission and may request additional safety data at any time. The DSMB will review data at 2 formal interim analyses. The first interim analysis will be for safety and feasibility and will occur after 15 subjects have been randomized and have had the opportunity to be followed for 2 months after randomization. The second interim analysis will occur when 25 PFS events have been observed, at which time the DSMB will evaluate safety, feasibility, early stopping for futility, and the adaptive sample size re-adjustment. Evaluation of early efficacy will not be assessed at the time of the 2nd interim analysis. The study will have an overall alpha level of 2.5% with 1-sided testing. The futility interim analysis will use an O'Brien-Fleming spending rule. Finally, if the event goal of 50 PFS events is unattainable within 1 year of the projected analysis timing, the DSMB may recommend conducting the primary analysis prior to the observation of 50 events at event target determined by the DSMB. Under the design assumptions, this will preserve 80% power and enable a conclusion from the study to be reached. A schematic of the study is provided in Figure 2. The DSMB may recommend stopping the study for futility if the futility criteria are met.

In the event the DSMB makes recommendations on changes to the trial conduct, Allogene, or the DSMB on behalf of Allogene, will discuss these recommendations with the agency prior to their implementation.

Adaptive Sample Size Re-adjustment

The adaptive sample size re-adjustment will be evaluated at the time of the 25-PFS event interim analysis. At this interim analysis time, the conditional power for the primary analysis will be calculated under the observed interim analysis hazard ratio. The conditional power will be considered in the 'promising zone' if the conditional power is ≥ 50% or < 90%. [redacted]

If the conditional power falls outside the promising zone, either < 50% or ≥ 90%, study will be terminated due to futility or no change to the sample size will be made. As shown in Chen , 2004, and Mehta , 2011, this adaptive strategy, defined by pre-specification of a promising zone with a lower limit of conditional power of at least 50% and the pre-specification of a maximum number of events for the adjustment can be analyzed with unadjusted testing methods while preserving the overall type I error at 2.5%. The independent statistician, in conjunction with the DSMB, will evaluate the interim analysis and implement any adaptive sample size re-estimation in accordance with this method pre-specified and further documented in DSMB charter.

Access to Individual Subject Treatment Assignments

In this randomized study, investigators will be aware of treatment received. Data handling procedures for the study will be devised to reduce potential sources of bias and maintain the validity and credibility of the study. These procedures will be outlined in the SAP, DSMB charter, and Trial Integrity Document.

9.3 Statistical Methods and Properties

9.3.1 Study Endpoints

All corresponding endpoints to study objectives are listed in Section 2.2.

9.3.1.1 Primary Endpoints

The primary efficacy endpoint for the evaluation of ALLO-647 efficacy will be PFS between treatment arms, defined as the time from randomization to disease progression, or relapse per the Lugano classification criteria (Cheson et al, 2014), as assessed by IRC, or death. Subjects not meeting the criteria for progression by the analysis data cutoff date will be censored at their last evaluable disease assessment date. Subjects who receive new anti-cancer therapy in the absence of documented disease progression will have PFS censored at the last evaluable disease assessment prior to the new anti-cancer therapy.

The primary analysis for the evaluation of ALLO-647 will be conducted when 50 PFS events have been observed. The details of the primary analysis plan will be provided in the study SAP.

9.3.1.2 Secondary Efficacy Endpoints

Objective response rate (ORR): defined as assessment of CR or PR, assessed using the Lugano classification criteria 2014; Cheson et al, 2014) by IRC at any time up through commencement of new anti-cancer therapy or withdrawal of consent. Secondary analyses will use disease assessments per the investigator.

EFS defined as the time from randomization to disease progression or relapse per the Lugano classification criteria 2014 as assessed by IRC, death, or commencement of a new anti-cancer therapy.

Duration of response (DOR): DOR for subjects who experience a CR or PR is defined as the date of their first response to the date of disease progression per Lugano classification criteria 2014 (Cheson et al, 2014) as assessed by the IRC or death regardless of cause, whichever happens earlier. For subjects who receive new anti-cancer therapy with no documented disease progression, duration of response will be censored at the last evaluable disease assessment prior to the new anti-cancer therapy. Secondary analyses will use disease assessments per the investigator.

Best overall response (BOR): BOR is defined as the best response (CR, PR, SD, PD) by IRC at any time up through commencement of new anti-cancer therapy or withdrawal of consent. Secondary analyses will use disease assessments per the investigator.

Time to response (TTR): TTR is defined as the time from randomization date to the date of first CR or PR as assessed by the IRC per the Lugano classification criteria 2014 (Cheson et al, 2014). Secondary analyses will use disease assessments per the investigator.

Overall survival: OS is defined as the time from randomization to the date of death. Subjects who have not died by the analysis data cutoff date will be censored at their last contact date or the data cut-off date, if confirmed to be alive after the data cut-off date.

9.3.2 Efficacy Analysis

9.3.2.1 Primary Efficacy Endpoint

The primary analysis of PFS between treatment arms will be conducted using a stratified (randomization stratification factors) log rank test. KM curves will be presented, and KM estimates and 2-sided 95% confidence intervals will be calculated for event time quartiles, event-free rate at 3-month intervals, and for the difference in event-free rates between treatment arms at those times. Additionally, stratified (randomization stratification factors) Cox regression model will be used to estimate the relative PFS hazard ratio (FCA/FC) along with 2-sided 95% confidence intervals. The primary analysis is based on ITT population.

Sensitivity analyses of the primary efficacy endpoint will be conducted in a similar fashion:

1. Based on mITT population
2. PFS based on investigator disease assessments

3. Unstratified COX regression analysis

Summaries of off-schedule disease assessments by treatment arm will be provided. Sensitivity analyses to address ascertainment time bias will be provided in the SAP.

9.3.2.2 Analysis of Secondary Efficacy Endpoint

After the primary endpoint showed statistical significance, the secondary efficacy endpoint ORR per IRC assessment will be tested hierarchically using stepwise method. The test will be performed with the Cochran Mantel Haenszel (CMH) test stratified by the randomization stratification factor.

Analysis of all secondary efficacy endpoints will be performed by treatment arms.

ORR: The ORR based on IRC assessment and on investigator assessment between treatment arms will be compared using exact binomial test. The Clopper Pearson exact interval 95% CI for rate in each treatment arm will be provided. The Wilson confidence interval will be provided as sensitivity analysis. CMH test stratified by randomization stratification factor will be used to compare the proportion difference of ORR between treatment arm along with 95% C.I.

DOR: DOR for subjects who experience a CR or PR will be summarized. For subjects who have a CR or PR as assessed by the IRC and assessed by investigator, Kaplan-Meier (KM) estimates and 2-sided 95% CIs will be generated for DOR.

BOR: The percentage of subjects with each response category (CR, PR, SD, PD) as their BOR will be summarized based on IRC assessment and on investigator assessment. Two-sided 95% confidence intervals for the proportion of subjects with BOR of CR and of PR will be provided. The Clopper Pearson exact interval 95% CI for rate in each treatment arm will be provided. The Wilson confidence interval will be provided as sensitivity analysis. CMH test stratified by randomization stratification factor will be used to compare the proportion difference of ORR between treatment arm along with 95% C.I.

EFS, and OS: The KM method will be used to estimate EFS, and OS proportions, 95% CIs, and summary statistics at landmark times after randomization. The stratified log rank test will compare EFS or OS rate at landmark times. The number of subjects who have progressed and/or have ongoing responses will be summarized along with KM plots. Analysis will be based on IRC assessment and investigator assessment. In addition, the stratified Cox regression model will be used to estimate the HR between treatment arm (FCA vs FC) along with 95%CI.

TTR will be summarized between treatment arm (FCA vs FC alone) for subjects who responded to treatment.

Sensitivity analyses of secondary endpoints will be performed in a similar fashion to the sensitivity analyses of primary endpoint and will be detailed in SAP.

Further details and all sensitivity analyses for secondary efficacy endpoints, including their detailed definitions and estimands will be provided in the SAP.

[redacted]

9.3.3 Safety Analysis

Summaries and analyses of safety parameters will include all subjects in the safety analysis set and will be conducted by treatment arms.

9.3.3.1 Adverse Events

AEs will be graded by the investigator according to the CTCAE version 5.0 and coded using MedDRA. CRS will be graded using ASTCT; however, as per ASTCT end-organ damage will be graded using CTCAE. Data will be collected to allow grading of Grade ≥3 events of neurotoxicity and ICANS using the ASTCT definition. AE data will be analyzed using the principle of treatment emergence. The treatment-emergent period will be defined as the period of time from the first dose date of lymphodepletion (fludarabine, cyclophosphamide, or ALLO-647 and/ or ALLO-501A) up to the end of study, death or the date of initiation of another anti-cancer investigational agent, whichever occurs first. Adverse event data will be reported in listings. Summaries of adverse event by mapped terms, appropriate thesaurus level, toxicity grade, and seriousness and relationship to study treatment will be presented, as well as summaries of adverse events leading to death and premature withdrawal from study. The number and percentage of subjects who experienced any AE, SAE, treatment related AE, and treatment related SAE will be summarized according to worst toxicity grades. Treatment emergent adverse events of special interest (as defined in Section 8.2.2) will be summarized accordingly. In addition, the grading of neurotoxicity AEs will be summarized based on CTCAE criteria. The summaries will present AEs on the entire study period. Adverse events will be summarized by treatment arm.

The severity of acute GvHD and CRS will be assessed according to the modified grading described in Appendix 3 and Appendix 5, respectively.

9.3.3.2 Laboratory Test Abnormalities

The number and percentage of subjects who experienced laboratory test abnormalities will be summarized according to worst toxicity grade (as graded by NCI CTCAE version 5.0) observed for each laboratory assay. The analyses will summarize laboratory tests as characterized by type, frequency, severity and timing. For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal, or not done. Laboratory test abnormality will be summarized by the treatment arm.

9.3.3.3 Electrocardiogram

The analysis of ECG results will be based on subjects in the safety analysis set with baseline and on-treatment ECG data.

ECG measurements will be used for statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal timepoints will not be averaged along with the preceding measurement. The percentage of subjects in each treatment group with new, abnormal, and clinically significant ECG findings will be summarized by study visit.

QT intervals will be corrected for heart rate (QTc) using standard correction factors (ie, Fridericia's [default correction], Bazett's). Data will be summarized and listed for QT, HR, QRS, QTcF, and by dose and the treatment arm. Individual QT intervals will be listed by time and dose.

9.3.4 Analysis of Pharmacokinetics and Pharmacodynamics

9.3.4.1 ALLO-501A

The ALLO-501A PK analysis set will be defined as subjects having received at least 1 dose of ALLO-501A and 1 measurable post-dose PK concentration. Descriptive statistics (count [N], arithmetic mean, geometric mean, standard deviation, minimum, median, maximum, and coefficient of variation [CV]) will be performed per dose group (Phase 1) and by treatment arms on ALLO-501A vector copy number (VCN) in blood at each measurement time. Graphical displays of mean values will also be presented for PK analysis set. Derived parameters (AUC, C_{max}, etc.) will also be computed.

A model-based PK analysis will also be performed using the PK analysis set and will be described in a separate analysis plan. The PK/pharmacodynamic relationship between circulating ALLO-501A and relevant activity or safety measurements may also be investigated.

9.3.4.2 ALLO-647

The ALLO-647 PK analysis set will be defined as the subjects having received at least 1 dose of ALLO-647 and 1 measurable post-dose PK concentration.

Descriptive statistics (N, arithmetic mean, geometric mean, standard deviation, min, median, max, CV) will be performed on ALLO-647 plasma concentrations at each timepoint. Graphical displays of mean values will also be presented. PK data collected will be used in a population PK modeling approach to estimate individual PK parameters such as clearance, half-life, etc. Population PK will be used to estimate individual exposure parameters such as C_{max} and AUC.

9.3.4.3 Analysis of Pharmacodynamics

9.3.4.3.1 Analysis to characterize depth and duration of lymphodepletion

Descriptive summary of minimum of ALC after [redacted] will be summarized by dose groups (Phase 1) and treatment arms (Phase 2). The time to recovery of TBNK cell burden analysis will be performed for subjects (in both the Phase 1 and Phase 2 portions of the study), comparing values before and after ALLO-647 administration (after

[redacted]). The study SAP will provide details of the definition of TNBK recovery and the analysis methodology.

9.3.4.3.2 Analysis of Biomarker Endpoints

A separate SAP may be created for the exploratory biomarker analyses. For samples (see Section 7.4), summary statistics (eg, mean, standard deviation, median, and minimum/maximum levels of continuous, and frequencies and percentages of categorical biomarker measures) are normally determined at baseline and post-treatment.

Clinically relevant and interpretable biomarker assessments generated in support of primary and secondary objectives may be summarized in the clinical study report. Other biomarker data might be summarized in a separate technical document.

9.3.4.3.3 Analysis of Immunogenicity Data

For the immunogenicity data, the percentage of subjects with positive ADA will be summarized. For subjects with positive ADA or neutralizing antibodies, the magnitude (titer), time of onset, and duration of ADA or neutralizing antibodies response may also be described, if data permit.

9.3.5 Randomization

Subjects will be randomized in a 1:1 ratio to a lymphodepletion regimen of either FC or FCA.

Randomization will be stratified based on the following risk factors:

Stratum 1: ULN < LDH ≤ 2 x ULN **and** presence of lesion ≥5 cm (50 mm)

Stratum 2: LDH ≤ ULN **or** all lesions <5 cm

Additional stratification factor(s) may be considered, and further details will be provided in the statistical analysis plan.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Allogene or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors will review source documents to confirm that the data recorded on eCRFs are accurate. The investigator and institution will allow Allogene monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also continue to occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Allogene, or companies working with or on behalf of Allogene, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Allogene or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Allogene or its agents to prepare the investigator site for the inspection and will allow Allogene or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Allogene or its agent. Before response submission to the regulatory authorities, the investigator will provide Allogene or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1 Case Report Forms/Electronic Data Record

The study will be using an electronic data capture system. All electronic case report forms will be designed and provided electronically to the site by Allogene (or designee) and electronic data capture system vendor. All case report forms are to be completely filled out and reviewed and signed by the investigator or sub-investigators listed on the Form FDA 1572 and/or other appropriate local health authority documents. Every effort should be made to have the case report forms completed and signed as soon as possible following a subject’s study visit.

IRC vendor is responsible for their own data handling as described in the independent review charter.

11.2 Data Management

Clinical data management will be performed according to procedures described in the study Data Management Plan which will be subject to review and approval by Allogene. The Data Management Plan will include procedures for all aspects of the processing of the data from this study and, where clinical data management is outsourced, the responsibilities of the sponsor or designee. Adverse events and medications will be coded using MedDRA and the World Health Organization Drug Dictionary, respectively. The Data Management Plan will include specific details of which version of these dictionaries has been used.

11.3 Protocol Deviation

A protocol deviation is any departure from the procedures and/or processes described in the study protocol as prepared by the sponsor, agreed to by the investigator and approved by the IRB/IEC.

Protocol deviations should be reported to the sponsor or designee as they occur or are discovered and most of the time these will be documented in the study source records. In addition, protocol deviations should be reported to the IRB/IEC per IRB/IEC guidelines. The study monitor will document deviations discovered throughout the course of monitoring

visits, or medical review of the clinical database. These deviations, and any corrective actions taken, will be reviewed and discussed with the sponsor and the investigators as applicable.

Study monitoring will be performed in accordance with ICH GCP, sponsor's and/or the designee's procedures, the protocol, and applicable local regulations.

11.4 Record Retention

The investigator must make study data accessible to the Study Monitor or other authorized representatives of Allogene (or designee) and Regulatory Agency (eg, FDA) inspectors upon request. A file for each subject must be maintained that includes the signed informed consent form as well as all source documentation related to that subject. The investigator must ensure the reliability and availability of source documents from which the information on the case report form was derived.

Subject identity information recorded will be maintained on the Subject Confidentiality Log for a duration in accordance with local requirements for an extended safety monitoring period.

Investigators must maintain all study documentation for at least a period of 2 years following the approval of the drug, or until 2 years after the investigational drug program is discontinued; or in accordance with local requirements (if longer). Study documentation includes all Essential Documents as defined in ICH E6 Guidelines for Good Clinical Practice. Allogene or designee will notify the investigator when any records may be discarded.

12. ETHICS

12.1 Institutional Review Board/Ethics Committee

The IRB/EC must prospectively approve the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, as applicable. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to the sponsor or its designee.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Allogene in writing immediately after the implementation.

12.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, the European Union Clinical Trial Regulation (EU-CTR) 536/2014, and the Declaration of Helsinki

12.3 Subject Information and Consent

Study Sites are required to comply with the data collection and processing requirements of the Study protocol, and the parties involved in the execution of this study (eg, the Sponsor, Contract Research Organization ("CRO"), Investigator, site staff and designees, employees, and agents) involved with the Study are obligated to comply with applicable local, state, federal, and regional laws, relating to the protection of personal data. CROs, laboratories, and contractors engaged by the Sponsor to support the execution of the clinical Study are subject to an assessment of implemented privacy and security controls and contractually obligated to implement appropriate safeguards to protect the personal data, including coded data, processed in the execution of the Study.

The Investigator will obtain a signed Informed Consent Form from each Study Subject participating in the clinical Study. Thereafter, the Investigator and authorized Site personnel will obtain personal data of Study Subjects and review Study Subject information, including medical records, to complete and provide all necessary documents, information, and reports required by the Protocol. To ensure that personal data of Study Subjects are kept confidential, the Subject's name, contact information, and any other directly identifying information that allows the Subject to be directly identified will not be included in any records or samples that the Investigator or Study Site provides to the Sponsor or the Sponsor's representatives. Instead, Study Subjects will be assigned a unique code ("Study ID") that is not derived from information related to the Study Subject and may only be traced back to a particular individual by referencing a key, which will be securely maintained by the Study Site. Investigator and Study Site will only identify the Subject with Sponsor and its representatives by such Study ID. Investigator and Study Site will store the Study ID in a secure area at all times. The study data entry and study management systems used by Study Sites, CROs, and the Sponsor will be secured, and password protected.

At the end of the Study, Study Site shall ensure that all records containing personal data will continue to be kept in a secure location for as long a period as dictated by local Ethics Committees / IRB and Study Site regulations, and applicable law. Results of the Study may be presented in reports, published in scientific journals, or presented at medical meetings; however, no directly identifying personal data of Study Subjects will be used. To ensure patient safety and in adherence with regulatory guidelines, Study Subject information may be reviewed by authorized Sponsor representatives, the IRB/IEC, and/or government regulatory authorities.

Security incidents impacting personal data are managed pursuant to the Sponsor's Privacy Event Management procedures, and all Sponsor personnel, third-party service providers, vendors and processors are required to report Privacy Events to the Sponsor Data Protection Officer or other appropriate management. Sponsor shall determine the extent of the Event and potential impact to Study Subjects, mitigate risks as possible, and comply with applicable reporting obligations. Study Site will employ reasonable efforts to adopt all of the technological and organizational measures required by applicable regulations to protect the data gathered to conduct the Study and protect against any accidental or illegitimate destruction or accidental loss or damage, alteration, disclosure, or unauthorized access to such data.

The informed consent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws. The informed consent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Allogene, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Allogene should be informed immediately.

In addition, the investigator will inform Allogene immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF STUDY

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related visit or assessment, discontinues from the trial or is lost to follow-up (ie, the subject is unable to be contacted by the investigator).

After participating in this study, subjects will be followed in a separate, noninterventional, long-term, safety-monitoring study (LTFU) for a combined total of 15 years.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Allogene. In addition, Allogene retains the right to discontinue development of ALLO-501A and/or ALLO-647 at any time.

If the study is prematurely terminated, Allogene will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 5 business days. As directed by Allogene, all study materials must be collected and all eCRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1 Communication of Results by Allogene

Allogene fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov) and the European Clinical Trials Database (EudraCT), and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Allogene in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Allogene posts clinical trial results as required by applicable law on www.clinicaltrials.gov for Allogene-sponsored interventional studies (conducted in subjects) that evaluate the safety and/or efficacy of an Allogene product. Results are submitted for posting within 1 year of the primary completion date.

Primary completion date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Allogene posts clinical trial results, as required by applicable laws, including European Union requirements, on EudraCT for all Allogene-sponsored interventional studies. Results are submitted for posting within 1 year of the end of the clinical trial for studies in adult populations or within 6 months of the end for studies in pediatric populations.

15.2 Publications by Investigators

Allogene supports the exercise of academic freedom and has no objection to publication by the principal investigator of the results of the study based on information collected or generated by the principal investigator, whether or not the results are favorable to the Allogene product, in a publication. Publication means any disclosure of the study results in a journal article, abstract, presentation, or any other type of public disclosure that reports any study results. To ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Allogene an opportunity to review any proposed publication before it is submitted or otherwise disclosed.

The investigator will provide any publication to Allogene at least 60 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights or other proprietary rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any confidential information belonging to Allogene before disclosure. For the purpose of publication, the study results are not considered the confidential information of Allogene.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 18 months of completion or termination of the study at all participating sites, the principal investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution and principal investigator will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Trial Agreement (CTA) between Allogene and the institution. In this section entitled Publications by investigators, the defined terms shall have the meanings given to them in the CTA.

If there is any conflict between the CTA and any attachments to it, the terms of the CTA control. If there is any conflict between this protocol and the CTA, this protocol will control as to any issue regarding treatment of study subjects, and the CTA will control as to all other issues.

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APPENDIX 1 ABBREVIATIONS

Abbreviation	Definition
A	ALLO-647
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
ALC	absolute lymphocyte count
Alk Phos	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASBMT	American Society for Bone and Marrow Transplantation
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
B-NHL	B-cell non-Hodgkin lymphoma
BM	bone marrow
BP	blood pressure
BOR	best overall response
BUN	blood urea nitrogen
C	cyclophosphamide
CAR	chimeric antigen receptor
CAR T	chimeric antigen receptor T cells
CBC	complete blood cell count
CD	cluster of differentiation
CDC	complement-dependent cytotoxicity
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CRP	C-reactive protein
CRS	cytokine release syndrome
CTA	clinical trial agreement
CTCAE	Common Terminology Criteria for Adverse Events
C or Cy	cyclophosphamide
DILI	drug-induced liver injury
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DMC	data monitoring committee
DOR	duration of response
DSA	donor specific antibody
DSMB	data and safety monitoring board
EBV	Epstein-Barr virus
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDP	exposure during pregnancy
ELISA	enzyme-linked immunosorbent assay
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C-30
EOS	end of study
EQ-5D	EuroQol standardized instrument
EudraCT	European Union Drug Regulating Authorities Clinical Trials
F or Flu	fludarabine
Fc	fragment, crystallizable

Abbreviation	Definition
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVHD	graft-vs-host disease
HBC	hepatitis B core
HCV	hepatitis C virus
HLA	human leukocyte antigen
HSCT	hematopoietic stem cell transplant
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	Immune Effector Cell-Associated Encephalopathy
IFNγ	interferon gamma
Ig	immunoglobulin
IMP	investigational medicinal products
IND	Investigational New Drug
INR	International normalized ratio
IP	investigational product
IRB	Institutional Review Board
IRC	Independent Radiology Committee
IV	intravenous
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
LVV	lentiviral vector
LTFU	long-term follow up
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility
mITT	modified intent-to-treat
mRNA	messenger ribonucleic acid
MRD	minimal residual disease
MRI	magnetic resonance imaging
MUGA	multi-gated acquisition scan
NAb	neutralizing antibody
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
NK	natural killer
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PRO	patient-reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
QLQ	Quality of Life Questionnaire
QoL	quality of life
qPCR	quantitative polymerase chain reaction
RCL	replication competent lentivirus

Abbreviation	Definition
R/R	relapsed or refractory
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
scFv	single-chain variable fragment
SD	stable disease
TALEN	transcription activator-like effector nucleases
TBili	total bilirubin
TCR	T cell receptor
TRAC	T cell receptor alpha constant
TSH	thyroid stimulating hormone
TTR	time to response
UCART19	universal engineered chimeric antigen receptor T cells targeting CD19
ULN	upper limit of normal
VAS	visual analog scale
VCN	vector copy number
WBC	white blood cell

APPENDIX 2 SUBJECT PERFORMANCE STATUS ECOG

STATUS	*GRADE*	*STATUS*
KARNOFSKY		ECOG - ZUBROD / WHO
Normal, no complaints; no evidence of disease.	100	
		0 Fully active, able to carry on all pre-disease performance without restriction.
Able to carry on normal activity; minor signs or symptoms of disease.	90	
Normal activity with effort, some signs or symptoms of disease.	80	
		1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.
Cares for self but unable to carry on normal activity or to do work.	70	
Requires occasional assistance but is able to care for most of personal needs.	60	
		2 Ambulatory and capable of self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
Requires frequent assistance and medical care,	50	
Disabled; requires special care and assistance.	40	
		3 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
Severely disabled; hospitalization is indicated although death not imminent.	30	
Very ill; hospitalization and active supportive care necessary.	20	Completely disabled.
		4 Cannot carry on any self-care.
Moribund, fatal processes progressing rapidly.	10	Totally confined to bed or chair.
Unresponsive. Dead.	0	5 Dead.

* As published in (Oken et al, 1982)

APPENDIX 3 ACUTE GVHD GRADING

GvHD Target Organ Staging (Harris et al, 2016)

Stage	Skin (Active Erythema Only)	Liver (Bilirubin)	Upper GI	Lower GI (stool output/day)
0	No active (erythematous) GVHD rash	<2 mg/dL	No or intermittent nausea, vomiting, or anorexia	Adult: <500 mL/day or <3 episodes/day Child: <10 mL/kg/day or <4 episodes/day
1	Maculopapular rash <25% BSA	2-3 mg/dL	Persistent nausea, vomiting or anorexia	Adult: 500-999 mL/day or 3-4 episodes/day Child: 10-19.9 mL/kg/day or 4-6 episodes/day
2	Maculopapular rash 25-50% BSA	3.1-6 mg/dL		Adult: 1000-1500 mL/day or 5-7 episodes/day Child: 20-30 mL/kg/day or 7-10 episodes/day
3	Maculopapular rash >50% BSA	6.1-15 mg/dL		Adult: >1500 mL/day or >7 episodes/day Child: >30 mL/kg/day or >10 episodes/day
4	Generalized erythroderma (>50% BSA) plus bullous formation and desquamation >5% BSA	>15 mg/dL		Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume).

Overall clinical grade (based on most severe target organ involvement):

- Grade I: Stage 1-2 skin without liver, upper GI, or lower GI involvement.
- Grade II: Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI.
- Grade III: Stage 2-3 liver and/or stage 2-3 lower GI, with stage 0-3 skin and/or stage 0-1 upper GI. Grade IV: Stage 4 skin, liver, or lower GI involvement, with stage 0-1 upper GI.

APPENDIX 4 CHRONIC GVHD GRADING

National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report.

	Score 0	Score 1	Score 2	Score 3
Performance Score: **KPS ECOG LPS**	• Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	□ Symptomatic fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	□ Symptomatic fully ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	□ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN **SCORE % BSA** *GvHD features to be scored by BSA:* **Check all that apply:** □ Maculopapular rash/erythema □ Lichen planus-like features □ Sclerotic features □ Papulosquamous lesions or ichthyosis □ Keratosis pilaris-like GvHD	□ No BSA involved	□ 1-8% BSA	□ 19-50% BSA	□ >50% BSA
SKIN FEATURES **SCORE:**	□ No sclerotic features		□ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** □ Deep sclerotic features □ "Hidebound" (unable to pinch) □ Impaired mobility □ Ulceration

Other skin GvHD features (NOT scored by BSA)

Check all that apply:

□ Hyperpigmentation
□ Hypopigmentation
□ Poikiloderma
□ Severe or generalized pruritus
□ Hair involvement
□ Nail involvement
□ *Abnormality present but explained entirely by non-GvHD document cause (specify):*

MOUTH

Lichen planus-like features present: □ Yes □ No	□ No symptoms	□ Mild symptoms **with** disease signs but not limiting oral intake significantly	□ Moderate symptoms with disease signs **with** partial limitation of oral intake	□ Severe symptoms with disease signs on examination **with** major limitation of oral intake
□ *Abnormality present but explained entirely by non-GvHD documented cause (specify):*				

Figure 1. Organ scoring of chronic GvHD. ECOG indicates Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status; LPS, Lansky performance status; BSA, body surface area; ADL, activities of daily living: LFTs, liver function tests; AP alkaline phosphatase; ALT, alanine aminotransferase; ULN, normal upper limit. *Weight loss within 3 months. †Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility of ulceration (Score 3), the higher level should be used for the final skin scoring. ‡To be completed by specialist or trained medical providers. **Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.

	SCORE 0	**SCORE 1**	**SCORE 2**	**SCORE 3**
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* □ **Yes** □ **No** □ **Not examined**	□ No symptoms	□ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 × per day)	□ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 × per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	□ Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
□ *Abnormality present but explained entirely by non-GvHD documented cause (specify):*				
GI Tract ***Check all that apply:*** □ Esophageal web/proximal stricture or ring □ Dysphagia □ Anorexia □ Nausea □ Vomiting □ Diarrhea □ Weight loss ≥5%* □ Failure to thrive	□ No symptoms	□ Symptoms without significant weight loss* (<5%)	□ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	□ Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most caloric needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
□ *Abnormality present but explained entirely by non-GvHD documented cause (specify):*				
LIVER	□ Normal total bilirubin and ALT or AP < 3 × ULN	□ Normal total bilirubin with ALT ≥3 to 5 × ULN or AP ≥ 3 × ULN	□ Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULM	□ Elevated total bilirubin > 3 mg/dL
□ *Abnormality present but explained entirely by non-GvHD documented cause (specify):*				

LUNGS**				
Symptom score:	□ No symptoms	□ Mild symptoms (shortness of breath after climbing one flight of steps)	□ Moderate symptoms (shortness of breath after walking on flat ground)	□ Severe symptoms (shortness of breath at rest, requiring 0_2)
Lung score:	□ FEV1≥ 80%	□ FEV1 60-79%	□ FEV1 40-59%	□ FEV1 ≤39%

%FEV1 ☐

Pulmonary function tests

□ Not performed

□ *Abnormality present but explained entirely by non-GvHD documented cause (specify):*

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7): Elbow (1-7): Wrist/finger (1-7): Ankle (1-4):	□ No symptoms	□ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	□ Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	□ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self, etc.)

□ *Abnormality present but explained entirely by non-GvHD documented cause (specify):*

Genital Tract *(See Supplemental Figure)*	□ No signs	□ Mild signs and females with or without discomfort on exam	□ Moderate signs and may have symptoms with discomfort on exam	□ Severe signs with or without symptoms

□ Not examined

Currently sexually active

□ Yes

□ No

□ *Abnormality present but explained entirely by non-GvHD documented cause (specify):*

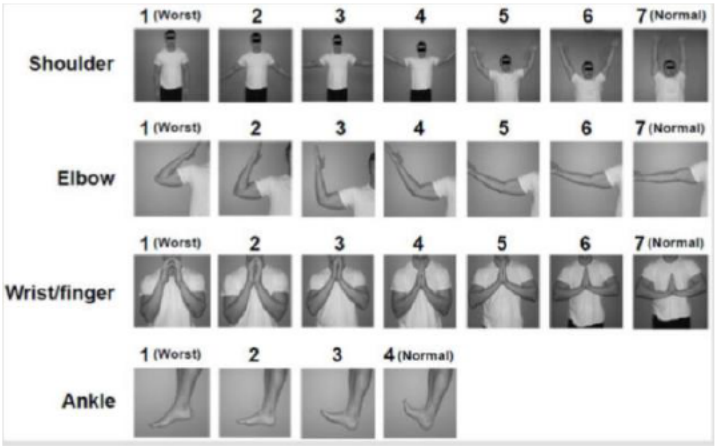
Other indicators, clinical features or complications related to chronic GvHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable: none – 0, mild -1, moderate – 2, severe – 3)

□ Ascites (serositis)	□ Myasthenia Gravis	
□ Pericardial Effusion	□ Peripheral Neuropathy	□ Eosinophilia >500µl
□ Pleural Effusion(s)	□ Polymyositis	□ Platelets <100,000 µl

□ Nephrotic syndrome	□ Weight loss>5%* without GI symptoms	□ Others (specify)

Overall GvHD Severity *(Opinion of the evaluator)*	**□ No GvHD**	**□ Mild**	**□ Moderate**	**□ Severe**

Photographic Range of Motion (P-ROM)



† Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring.
* Weight loss within 3 months.
** Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.
Abbreviations: ECOG (Eastern Cooperative Oncology Group), KPS (Karnofsky Performance Status), LPS (Lansky Performance Status); BSA (body surface area); ADL (activities of daily living); LFTs (liver function tests); AP (alkaline phosphate); ALT (alanine aminotransferase); ULN (normal upper limit).
‡ To be completed by specialist or trained medical providers.

APPENDIX 5 CYTOKINE RELEASE SYNDROME MANAGEMENT

CRS Grade	Tocilizumab *	Corticosteroids
Grade 1	N/A	N/A
Grade 2	Administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses. For CRS Grade 2 and above, a second line agent (eg, siltuximab or anakinra) may be considered for use if not responsive to initial dose of tocilizumab.	Administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (eg, 10 mg intravenously every 6 hours). Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days.
Grade 3	Per Grade 2	Per Grade 2
Grade 4	Per Grade 2 If no CRS improvement after 4 doses of tocilizumab, consider alternate anti-cytokine therapy eg, siltuximab	Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.

Subjects who experience Grade 2 or higher CRS (eg, hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For subjects experiencing Grade ≥3 CRS, an echocardiogram should be performed to assess cardiac function and subjects should be promptly considered for intensive care supportive therapy.

*In the event that tocilizumab has a pandemic-related shortage, a second line agent (eg, siltuximab or anakinra) may be considered for use if not responsive to initial dose of tocilizumab. If tocilizumab is unavailable follow institutional guidelines and use appropriate alternatives.

The treatment for CRS is not supplied by Allogene.

APPENDIX 6 MANAGEMENT OF INFUSION RELATED REACTIONS INCLUDING ALLERGIC REACTIONS OR ANAPHYLAXIS WITH ALLO-647

In the event of infusion related reactions, investigators should institute treatment measures according to best medical and nursing practice.

The following treatment guidelines should be employed:

If chills and fever (>100.4°F/38.0°C) occur, the infusion should be interrupted. Subjects may be treated symptomatically and the infusion should be restarted at 50% of the original rate.

Hypersensitivity reactions:

1. NCICTCAE Grade 1 allergic reaction
    - Monitor for worsening condition. If the reaction worsens, stop the infusion. Institute premedication for subsequent infusions as per Section 5.6.2.1.
2. NCICTCAE Grade 2 allergic reaction
    - Stop ALLO-647 infusion.
    - Administer bronchodilators, oxygen, acetaminophen, etc. as medically indicated.
    - Resume infusion at 50% of previous rate once reaction has decreased to Grade 1 in severity. Monitor closely for any worsening. If the reaction recurs, stop infusion. Institute premedication for subsequent infusions as per Section 5.6.2.1.
3. NCICTCAE Grade 3 or Grade 4 allergic reaction or anaphylaxis
    - A Grade 3 anaphylaxis (hypersensitivity reaction) consists of symptomatic bronchospasm requiring parenteral medications with or without urticaria, allergyrelated oedema/angioedema, or hypotension.
    - A Grade 4 anaphylaxis (hypersensitivity reaction) is a life-threatening event requiring urgent intervention.
4. Treatment of Grade 3 or Grade 4 allergic reaction or anaphylaxis
    - Stop the ALLO-647 infusion immediately and disconnect infusion tubing from the subject.
    - Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc. as medically indicated.
    - Telephone sponsor or designated representative to report an SAE as per Section 8.
    - For an NCICTCAE Grade 4 hypersensitivity reaction, study treatment will be discontinued.
5. Resume treatment following Grade 1 or Grade 2 allergic reactions
    - Once the ALLO-647 infusion rate has been decreased due to an allergic reaction, it will remain decreased for all subsequent infusions.
    - If the subject has a second reaction at the lower infusion rate, the infusion should be stopped and the subject should receive no further ALLO-647.

- If the subject experiences a Grade 4 allergic reaction or anaphylaxis at any time, the subject should receive no further ALLO-647. Discuss with sponsor medical monitor if suspected Grade 3 infusion reaction to ALLO-647 occurs.
- If there are questions concerning whether an observed infusion-related reaction is consistent with an allergic reaction or anaphylaxis, the medical monitor should be contacted immediately to assist with grading the reaction.

PK, pharmacodynamic, and ADA sampling should continue as long as the sampling does not interfere with the medical treatment of the subject.

In cases of suspected cytokine release syndrome, a serum sample should be provided for cytokine release assay analysis so as long as the sampling does not interfere with the medical treatment of the subject.

APPENDIX 7 BONE MARROW RESERVE IN ADULTS

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
CRANIUM AND MANDIBLE	Head:			136.6		
	Cranium	165.8	0.75	124.3	13.1	**13.1**
	Mandible	16.4	0.75	12.3		
HUMERI, SCAPULAE, CLAVICLES	Upper Limb Girdle:			86.7		
	2 Humerus, head & neck	26.5	0.75	20.0	8.3	8.3
	2 Scapulae	67.4	0.75	50.5		
	2 Clavicles	21.6	0.75	16.2		
STERNUM AND RIBS	Sternum	39.0	0.6	23.4	2.3	
	Ribs:			82.6		
	1 pair	10.2	All 0.4	4.1		
	2	12.6		5.0		
	3	16.0		6.4		
	4	18.6		7.4		
	5	23.8		9.5	7.9	**10.2**
	6	23.6		9.4		
	7	25.0		10.0		
	8	24.0		9.6		
	9	21.2		8.5		
	10	16.0		6.4		
	11	11.2		4.5		
	12	4.6		1.8		
PELVIC BONES	Sacrum	194.0	0.75	145.6	13.9	
	2 os coxae	310.6	0.75	233.0	22.3	**36.2**
FEMUR	2 Femoral head and neck	53.0	0.75	40.0		**3.8**

Appendix 6 Bone Marrow Reserve in Adults (continued)

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
VERTEBRAE	Vertebrae (Cervical):			35.8		
	1	6.6	All 0.75	5.0		
	2	8.4		6.3		
	3	5.4		4.1	3.4	
	4	5.7		4.3		
	5	5.8		4.4		
	6	7.0		5.3		
	7	8.5		6.4		
	Vertebrae (Thoracic):			147.9		
	1 pair	10.8	All 0.75	8.1		
	2	11.7		8.8		
	3	11.4		8.5		
	4	12.2		9.1		
	5	13.4		10.1	14.1	**28.4**
	6	15.3		11.5		
	7	16.1		12.1		
	8	18.5		13.9		
	9	19.7		14.8		
	10	21.2		15.9		
	11	21.7		16.3		
	12	25.0		18.8		
	Vertebrae (Lumbar):			114.1		
	1 pair	27.8	All 0.75	20.8		
	2	29.1		21.8	10.9	
	3	31.8		23.8		
	4	32.1		24.1		
	5	31.4		23.6		
TOTAL		**1497.7**		**1045.7**	**100.0**	**100.0**

Adapted from Ellis RE, 1961

APPENDIX 8 ASTCT IMMUNE EFFECTOR CELL-ASSOCIATED ENCEPHALOPATHY (ICE) SCORE

ICE Encephalopathy Assessment Tool for Grading of ICANS

Orientation	Orientation to year, month, city, hospital	4 points
Naming	Ability to name 3 objects (eg, point to clock, pen, button)	3 points
Following Commands	Ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue")	1 point
Writing	Ability to write a standard sentence (eg, "Our national bird is the bald eagle")	1 point
Attention	Ability to count backwards from 100 by 10	1 point

Abbreviations: ASBMT = American Society for Bone and Marrow Transplant; ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = Immune Effector Cell-Associated Encephalopathy

Scoring: 10, no impairment;

7-9, grade 1 ICANS;

3-6, grade 2 ICANS;

0-2, grade 3 ICANS;

0 due to patient unarousable and unable to perform ICE assessment, grade 4 ICANS

APPENDIX 9 ASTCT ICANS CONSENSUS GRADING FOR ADULTS

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[a]	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness[b]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings[c]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[d]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Abbreviations: ASBMT = American Society for Bone and Marrow Transplant; CTCAE = Common Terminology Criteria for Adverse Events; ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = Immune Effector Cell-Associated Encephalopathy; ICP = intracranial pressure; N/A = not applicable

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

a A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

b Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

c Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

d Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0

APPENDIX 10 NEUROLOGIC TOXICITY MANAGEMENT GUIDANCE

Grading Assessment	Concurrent CRS	No concurrent CRS
Grade 1	Supportive care	Supportive care
Grade 2	Administer tocilizumab for management of Grade 2 CRS*. In addition, administer dexamethasone 10 mg intravenously every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days. Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days. Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis
Grade 3	Administer tocilizumab for management of Grade 2 CRS*. In addition, administer dexamethasone 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days. Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days. Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis
Grade 4	Administer tocilizumab for management of Grade 2 CRS*. Administer methylprednisolone 1000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenously per day for 2 more days; if improves, then manage as above. If no CRS improvement after 4 doses of tocilizumab, consider alternate anti-cytokine therapies eg, siltuximab Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis	Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above. Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis

Note: Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis.

*In the event of a pandemic-related tocilizumab shortage a second line agent (eg, siltuximab) may be considered for use if not responsive to initial dose of tocilizumab.

APPENDIX 11 SUMMARY OF FOLLOW-UP

Study minimum follow-up

In support of Section 6.5 Follow-up and Section 8.1.3 Time period for collecting AE/AESI/SAE, the table below is the minimum follow-up for randomized subjects who receive both ALLO-647 and/or ALLO-501A who either: 1. experience disease progression and start new anticancer therapy or 2. do not start a new anticancer therapy but decline to continue all study protocol activities.

Follow-up Activity	[redacted]	[redacted]	[redacted]
All AEs and SAEs (through Month 3 or start of new anti-cancer therapy whichever comes first)	X		
SAEs and AESIs (Grade ≥3 CRS, Grade ≥3 neurotoxicity, Grade ≥3 infection, GVHD, autoimmune disorders, secondary malignancies) through M60 or start of new anti-cancer therapy or disease progression whichever comes first.	X	X	X
Study drug-related SAEs	X	X	X
Anti-cancer therapies and survival status	X	X	X
All concomitant medications	X		
Targeted concomitant medications such as gamma globulins, immunosuppressive drugs, anti-infectives, vaccinations (through M12 or until new-anticancer therapy, whichever comes first)	X	X	
Monitoring emergence of new clinical conditions: • New malignancy(ies) • New incidence or exacerbation of a pre-existing neurologic disorder • New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder • New incidence of a hematologic disorder. • New incidence of infection (potentially product-related)	X	X	X
Physical exam/vital signs	X	X	X
RCL	X	[redacted]	[redacted]
Genomic safety biospecimen and PBMCs		[redacted]	1[redacted]

Subjects who are randomized but did not receive any study drugs should be followed for disease progression, then for anti-cancer therapies and survival until Month 60 (Section 6.5.2).

APPENDIX 12 SCHEDULE OF ACTIVITIES

The Schedule of Activities provides an overview of the protocol visits and procedures. Refer to the Assessments section (Section 7) of the protocol for detailed information on each assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the Schedule of Activities to conduct evaluations or assessments required to protect the well-being of the subject.

Schedule of Activities: Screening and Treatment

	Pre-Screening	[2] Screening and Post Randomization		Lymphodepletion			Treatment and Follow-up													
[1] Visit Identifier		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit Window				[redacted]					[redacted]											
[3] Informed consent		X																		
Tumor history		X																		
[4] Medical history		X																		
[5] Viral/bacterial/protozoal assessment		X																		
Eligibility criteria		X																		
Clinical Evaluation																				
[6] Physical examination		X		X	X	X	X			X		X	X	X	X	X	X	X	X	X
[7] Vital signs (BP/pulse rate/Temp/O_2 Sat)		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG performance status		X					X							X		X	X	X	X	X
[8] ICE assessment/ ICANS		X					As clinically indicated													
[9] 12 lead ECG		X					X							X						X
ECHO or MUGA		X		As clinically indicated																
Local Laboratory																				
[10] ALLO-501A Donor-specific anti-HLA antibodies: screening (central lab)	(X)	(X)																		
[11] CBC w/differential		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[12] Blood Chemistry		X		X			X			X		X		X		X	X	X		X
[13] Coagulation		X					As clinically indicated (e.g. CRS)													X
[14] Reflex autoantibodies				In case of suspected ALLO-647 treatment emergent autoimmunity																
Blood culture (aerobic and anaerobic)			X			X														
[15] Urinalysis		X												X		X	X	X	X	X

	Pre-Screening	[2] Screening and Post Randomization		Lymphodepletion			Treatment and Follow-up													
[1] **Visit Identifier**		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**9**
Visit Window				[redacted]					[redacted]									[redacted]	[redacted]	[redacted]
[16] Pregnancy test and contraception check		X																	X	X
[17] RCL			X															X	X	X
TSH		X																X		X
CMV Antigen by PCR							X			X		X	X	[redacted]	[redacted]	X				
EBV and adenovirus monitoring				Per institutional practices																
[18] Quantitative serum immunoglobulins (local)			X				X					X		X		X	X	X	X	X
[19] Lymphodepletion																				
[19] Fludarabine (FC and FCA)				X	X	X														
[19] Cyclophosphamide (FC and FCA)				X	X	X														
[19] ALLO-647: FCA-90 (FCA only)				X	X	X														
Treatment																				
ALLO-501A							X													
Anti-infection prophylaxis				Based on Section 5.12.3; NCCN guidelines																
Tumor Assessments																				
[20] PET/CT		X												X		X	X		X	X
[21] Brain MRI		X		As clinically indicated																
[22] Bone marrow aspirate and biopsy		X		If positive at [redacted], or as clinically indicated																
[23] Lymphoma biopsy		X								As clinically indicated										
[24] MRD assessment		X												X		X	X		X	X
Other Clinical assessments																				
Serious and non-serious adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant treatments		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Pre-Screening	[2] Screening and Post Randomization		Lymphodepletion			Treatment and Follow-up													
[1] Visit Identifier		Day -34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit Window				[redacted]					[redacted]											
[25] EQ-5D (PRO)		X												X		X	X		X	X
[25] QLQ-C30 (PRO)		X												X		X	X		X	X
Cellular kinetics/PK assessments – central laboratory testing																				
[26] ALLO-501A in blood (flow cytometry)				X						X	X	X	X	X	X	X	X	X		
[27] ALLO-501A in blood (transgene)							X EOI only	X	X	X	X	X	X	X	X	X	X	X	X	X
[28] ALLO-501A in BM aspirate							As clinically indicated													
[28] ALLO-501A in lymph node biopsy									X	As clinically indicated										
[28] ALLO-501A and viral in CSF							As clinically indicated													
[29] ALLO-647 serum concentration				X	X	X	X		X		X									
[30] Fludarabine and Cyclophosphamide serum concentration				X	X	X	X	X												
[31] Cytokines and soluble proteins (serum)			X			X	X	X	X	X	X	X		X	X	X	X			
Immunogenicity assessments																				
[32] Anti-ALLO-501A ADA				X										X		X	X	X		X
[33] Anti-ALLO-647 ADA				X										X		X	X	X		X
[34] ALLO-501A donor-specific anti-HLA antibodies(serum)														X			X	X		X
Pharmacodynamic assessments																				
[35] TBNK (blood)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[36] Gene expression profile (blood RNA)			X							X		X		X		X				X
[37] TCR sequencing (blood DNA)			X							X		X		X		X				X

	Pre-Screening	[2] Screening and Post Randomization		Lymphodepletion			Treatment and Follow-up													
[1] Visit Identifier		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit Window				[redacted]					[redacted]											
Other assessments																				
[38] Genomic safety biospecimen			X																X	
[39] Banked serum and plasma			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[40] PBMCs			X								X		X		X		X		X	X
[41] Focal CNA or Risk Score		X																		

Abbreviations: + = positive; → = ongoing/continuous event; ADA = anti-drug antibody; BM = bone marrow; BP = blood pressure; CBC = complete blood count; CMV = cytomegalovirus; CSF = cerebral spinal fluid; CT = computed tomography; d = days; DNA = deoxyribonucleic acid; EBV = Epstein-Barr virus; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS = end of study; EQ 5D = EuroQol 5-Dimension questionnaire; FC = fludarabine, cyclophosphamide; FCA = fludarabine, cyclophosphamide, and ALLO-647; HLA = human leukocyte antigen; ICANS = Immune effector cell-associated neurotoxicity syndrome; ICE = Immune Effector Cell-Associated Encephalopathy; MRI = magnetic resonance imaging; mos = months; MRD = minimum residual disease; MUGA = multi-gated acquisition scan; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; qPCR = quantitative polymerase chain reaction; PRO = patient reported outcomes; RCL= replication competent lentivirus; RNA = ribonucleic acid; TBNK = T, B, NK cells; TCR = T cell receptor; TSH = thyroid-stimulating hormone; wks = weeks.

1 [redacted].

2 **Screening and Post Enrollment (Randomization):** Screening procedures are to be obtained within[redacted]. Specific procedures to be completed[redacted] are listed under[redacted] Visit.

3 **Informed Consent:** Pre-screening or Screening Consent for this study must be obtained prior to undergoing any study specific procedures.

4 **Medical History:** Includes history of disease process other than the cancer under study (active or resolved) and concurrent illness. Includes any current medical treatments for any condition. Demographic data collection will take place as part of the Screening Visit and will include the collection of sex, age, race and ethnicity.

5 **Viral/bacterial/protozoal assessment** by IgG and IgM serology tests, and reflex PCR in case of IgM seropositive result whenever clinically appropriate, except for CMV for which IgG serology test and DNA PCR (instead of IgM serology test) should be performed: Cytomegalovirus (CMV), Epstein Barr virus (EBV), human immunodeficiency virus (HIV)-1, HIV-2, hepatitis B (HBV, HbsAG, antiHBc, antiHbs), hepatitis C (HCV). IGRA for Latent TB. For subjects living in or travelling to endemic areas screening should be considered for West Nile Virus, Strongyloides, Cocciomycosis, and, Histoplamosis. Serum Aspergillus galactomannan antigen should be sent in high-risk patients.

6 **Physical examination (PE):** Physical examination (with neurologic exam) will include weight and height. Height will only be required[redacted].

7 **Vital Signs:** Includes temperature (oral, tympanic, temporal or axillary), blood pressure (BP), pulse rate and oxygen saturation level. Oxygen saturation will be evaluated by pulse oximetry. On [redacted], to be performed [redacted].

8 **ICE Assessment/ ICANS**. Conduct immune effector cell-associated encephalopathy (ICE) score at screening. Conduct ICE score and immune effector cell-associated neurotoxicity syndrome (ICANS) grading as clinically indicated, starting on [redacted] ICE and ICANS grading scales are provided in Appendix 8.

9 **12 Lead electrocardiogram (ECG):** At each time point, 12 lead ECG will be performed to determine cardiac safety and QTcF interval. On [redacted], ECG will be performed prior to investigational product administration. If the QTcF is prolonged (>500 msec), the ECG should be re-evaluated by a qualified person at the institution for confirmation.

10 **Donor-specific anti-human leukocyte antigen (HLA) antibodies (DSA): Screening:** Samples will be collected and sent to a central laboratory for processing and analysis after the subject signs the pre-screening or screening informed consent form. Donor-specific anti-HLA antibodies must be repeated prior to [redacted] if subject receives blood transfusion (ie, red blood cells, platelets, plasma) after an initial negative result to confirm eligibility.

11 **CBC Hematology:** complete blood count (CBC) with differential (should include % and absolute number of neutrophils, lymphocytes, monocytes, eosinophils, basophils, and reticulocyte count), hemoglobin, hematocrit, platelet counts. On[redacted], hematology will be performed [redacted]. On [redacted], samples will be collected [redacted] infusion.

12 **Blood Chemistry (fasting not required):** should include: alanine aminotransferase (ALT), albumin, alkaline phosphatase, aspartate aminotransferase (AST), bicarbonate, total bilirubin, blood urea nitrogen (BUN), chloride, serum calcium, creatinine, creatinine clearance, glucose, lactate dehydrogenase, magnesium, sodium, phosphorus or phosphate, total protein, potassium, uric acid, serum ferritin, C-reactive protein (CRP). On [redacted], chemistry will be performed prior to start of lymphodepletion treatment. On [redacted] samples will be collected prior to ALLO-501A infusion.

13 **Coagulation:** fibrinogen and D-dimer, partial thromboplastin time (PTT) and International Normalized Ratio (INR) or prothrombin time.

14 **Reflex auto-antibodies** will be evaluated in case of suspected ALLO-647 treatment emergent autoimmunity AE. Depending on the type of AE, the tests should include (but not limited to) serum antiphospholipid antibodies (APA), platelet-bound APA, anti-Factor VIII antibodies, anti-Thyroid Peroxidase (anti-TPO), anti-Thyroglobulin (anti-TG) and anti-thyroid stimulating hormone (anti-TSH receptor), Coombs test, antinuclear antibodies (ANA), perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA), anti-neutrophil cytoplasmic antibodies (cANCA), and/or anti-Sjogren's syndrome type B (anti-SSB).

15 **Urinalysis:** Urine dipstick for protein, glucose, and blood: If positive collect 24 hr and/or microscopic cell count (Reflex Testing).

16 **Pregnancy test and contraception check:** Serum or urine pregnancy test for females of childbearing potential. Follicle stimulating hormone test may be performed for post-menopausal women. Contraception use will be checked to confirm that contraception is used consistently and correctly.

17 **Replication competent lentivirus (RCL):** Whole blood samples will be collected to monitor for the presence of RCL-specific DNA sequences by a validated PCR-based assay. Samples may be analyzed for RCL only [redacted]; if negative, then remaining samples [redacted] may be collected and archived. Assess for RCL upon diagnosis of a new (secondary) malignancy.

18 **Quantitative serum immunoglobulins (local analysis):** Humoral immunity will be monitored by the measurement of serum IgG, IgA, and IgM levels. On [redacted], samples will be collected prior to investigational product administration.

19 **Lymphodepletion:**

- **Fludarabine (FC and FCA arms):** 30 mg/m^2/day fludarabine will be administered IV over approximately 15 to 30 minutes for 3 days, from Day -5 to Day -3. The fludarabine dose should be adjusted based on renal function; for subjects with creatinine clearance <80 mL/min, the fludarabine dose should be 20 mg/m^2 on each of the 3 dosing days or as per institutional guidelines.
- **Cyclophosphamide (FC and FCA arms):** 300 mg/m^2/day cyclophosphamide will be administered by IV over approximately 1 hr for 3 days, from Day -5 to Day -3.
- **ALLO-647 (FCA arm only):** Administer 30 mg/d IV over approximately 4 hrs each day. For FCA-90, 30 mg/day x 3 days, from Day -5 to Day -3.

20 **Lymphoma assessments by positron emission tomography (PET)/computerized tomography (CT):** tumor assessments will include all known or suspected disease sites. Disease-specific imaging as clinically appropriate will be performed as described in the study imaging manual. All scans will also be sent to a central radiology vendor, as specified in the study imaging manual. If a PET/CT was performed within [redacted] prior to Screening, then the results may be used for Screening disease assessment and a Screening PET/CT does not need to be done, providing there was no intervening therapy between the time of the PET/CT and Screening. Radiographic disease assessment will not be required after documented disease progression per Lugano criteria or initiation of subsequent anti-cancer therapy.

21 **Brain MRI:** Subjects with a history of CNS disease: screening brain MRI must be stable as compared to previous brain MRI scan.

22 **Bone Marrow Biopsy and Aspirate:** Bone marrow biopsy and aspirate will be completed [redacted], and at the time complete response (CR) is suspected only if bone marrow infiltration is positive or unknown at screening. Samples (screening; others as indicated) will be banked, and may be analyzed for insertion site analysis, molecular analysis, and other similar analyses. Proceduralist should aim to achieve a 2cm core to best assess cellularity.

23 **Lymphoma biopsy:** An archival formalin-fixed paraffin-embedded (FFPE) cancer tissue block from initial diagnosis, or previously obtained cancer tissue biopsy obtained prior to screening, may be submitted in place of a fresh sample, if obtained within [redacted] and if the subject received no intervening systemic anti-cancer treatment during this period. Cancer tissue from cytological sampling (eg, fine needle aspirates, including FFPE cell pelletthe material) is not adequate and should not be submitted. The FFPE tissue blocks must be of sufficient size to obtain approximately 22-26 unstained slides which should be submitted to the central laboratory. For subjects who undergo a fresh biopsy [redacted], or an on-treatment biopsy, a total of 3 core biopsies are to be obtained when possible for translational analyses.

24 **MRD assessment**: A plasma sample will be collected for MRD analysis using ClonoSeq or equivalent testing.

25 **EQ-5D-5L (PRO) and QLQ-C30 (PRO):** Completion of these instruments is not required after documented disease progression per Lugano criteria or initiation of subsequent anti-cancer therapy.

26 **ALLO-501A in blood (flow cytometry):** A blood sample will be collected to quantify ALLO-501A by a validated flow cytometry-based cellular-kinetics assay on [redacted], and at the indicated time points by central laboratory. Phenotypic subsets of CAR + T cells such as memory, activated and exhausted populations may also be characterized.

27 **ALLO-501A in blood (transgene levels):** A blood sample will be collected into a tube optimized for DNA isolation on [redacted], at the end of infusion on [redacted] (ie, within 30 min after infusion), and at the indicated time points to quantify ALLO-501A transgene levels by a validated qPCR-based transgene assay, performed by central laboratory.

28 **ALLO-501A detection in lymph node, BM, and CSF:** A sample of the indicated tissues will be evaluated to investigate the quantity of ALLO-501A in tissue compartments that may harbor tumor cells as clinically indicated. ALLO-501A may be measured by flow cytometry and/or qPCR-based assays by central laboratory. If subject experiences prolonged (>42 days) cytopenia a bone marrow aspirate will be collected for TCR clonality assessment, central CAR flow cytometry analysis, VCN and potential RNASeq. CSF will be collected, as clinically indicated, at any time if Grade 3 and above ALLO-501A related neurological AEs and/or suspected encephalitis are observed. In addition to the ALLO-501A detection, infectious workup (including HHV) may also be performed with the CSF sample collected.

29 **ALLO-647 pharmacokinetics (PK) assessment (FCA arm only):** Blood samples will be collected at each time point for PK analysis of ALLO-647. ALLO-647 serum concentration will be measured by immunoassay during and following ALLO-647 infusions at the following time-points: FCA-90: on [redacted] pre-dose, and end of infusion (within 15 minutes), [redacted] pre-dose, and end of infusion (within 15 minutes), [redacted] pre-dose, and end of infusion (within 15 minutes). [redacted] collect sample pre-ALLO-501A infusion, and at subsequent days as shown in the schedule. Testing will be performed at a central laboratory.

30 **Fludarabine and cyclophosphamide pharmacokinetics (PK) assessment (FC and FCA arms):** Blood samples will be collected at each time point for PK analysis of fludarabine and cyclophosphamide. Fludarabine and cyclophosphamide concentration will be measured by immunoassay during and following fludarabine and cyclophosphamide infusions at the following time-points: on [redacted] pre-dose, end of fludarabine infusion (within 15 minutes), end of cyclophosphamide infusion (within 15 minutes), [redacted] pre-dose, end of fludarabine infusion (within 15 minutes), end of cyclophosphamide infusion (within 15 minutes), [redacted] pre-dose, and end of fludarabine infusion (within 15 minutes), end of cyclophosphamide infusion (within 15 minutes). [redacted] collect sample pre-ALLO-501A infusion, and at subsequent days as shown in the schedule. Testing will be performed at a central laboratory.

31 **Cytokines and Soluble Proteins:** Analysis will be completed at a central lab. Serum cytokines assessed for cytokine release syndrome (CRS) safety management will be managed locally. On [redacted], the cytokine assessment (blood) will be performed prior to start of lymphodepletion treatment. On [redacted], samples will be collected prior to ALLO-501A infusion.

32 **Anti-ALLO-501A Antibodies (anti-scFv and anti-TALEN antibodies):** A blood sample will be collected into a tube optimized for serum isolation to monitor for the development of ALLO-501A and TALEN-specific antibodies. Testing will be performed at a central laboratory.

33 **Anti-ALLO-647 Anti-Drug-Antibodies (FCA arm only):** circulating levels of human anti-ALLO-647 antibodies will be assessed in serum by immunoassays up to [redacted] or up to 2 consecutive negative tests post-dosing completion whichever is the latest. Neutralizing antibody testing will be performed only in case of positive anti-drug antibody (ADA). Testing will be performed at a central laboratory.

34 **Donor-specific anti-human leukocyte antigen (HLA) antibodies (DSA): (On study):** Binding of C1q to HLA Class I and II DSA will be tested in case of positive DSA results following [redacted].

35 **TBNK Assay:** A blood sample will be collected for the enumeration of T, B, and natural killer (NK) cells by a flow cytometry-based assay to monitor the depth and duration of lymphodepletion. Samples will be collected before administration of ALLO-647 ([redacted]) or ALLO-501A ([redacted]). Testing will be performed at a central laboratory.

36 **Gene expression (RNA) profile:** Gene expression in whole blood associated with CART cell phenotype, activation state, and anti-tumor activity will be measured by RNA sequencing in blood, and bone marrow if bone marrow is collected to monitor response. Testing will be performed at a central laboratory.

37 **TCR sequencing:** Whole blood samples will be collected into a tube optimized for isolation of DNA at the indicated time point to assess the clonality of ALLO-501A, the subject T cell repertoire by TCR sequencing analysis by a central laboratory. Testing will be performed at a central laboratory.

38 **Genomic safety biospecimen:** Unless prohibited by local regulations or ethics committee decision, a blood sample will be collected during [redacted], and [redacted], for assays related to treatment response in the disease under study, e.g. insertion site analysis, malignancy panels, microbial cell–free DNA (mcfDNA) for pathogens that cause infections, etc.

39 **Banked serum and plasma samples:** Serum and plasma samples will be collected at the indicated timepoints and banked for future studies including endemic infectious diseases (e.g. HHV-6/7).

40 **PBMCs:** Peripheral blood mononuclear cells (PBMCs) will be collected at the indicated timepoints and cryopreserved for future cytogenetics, cellular, molecular or proteomic studies.

41 **Focal CNA or risk score**: A plasma sample will be collected for focal copy number alteration (CNA) or risk score (Cherng et al, 2022).

SCHEDULE OF ACTIVITIES: Follow-up and End of Study

	Follow-up		EOS
Visit Identifier	[redacted]		
[1] **Visit Window**	[redacted]		
[2] Physical examination	X	X	X
ECOG performance status	X	X	X
[3] CBC w/differential	X	X	X
[4] Blood Chemistry	X	X	X
[5] TSH (FCA arm only)	[redacted]	X	X
[6] Urinalysis (FCA arm only)	[redacted]	X	X
[7] Pregnancy test and contraception check	[redacted]		
[8] Reflex autoantibodies	As clinically indicated		
[9] EQ-5D (PRO)	X	X	X
[9] QLQ-C30 (PRO)	X	X	X
Tumor assessments			
[10] PET/CT	X	X	X
Brain MRI	As clinically indicated		
[11] Bone marrow aspirate and biopsy	As clinically indicated		
[12] Lymph node biopsy	As clinically indicated		
Other assessments			
Serious and non-serious adverse event monitoring	See Section 8		
Concomitant treatment(s)	See Section 5.11		
[13] Follow-up for survival and subsequent anticancer treatment (telephone contact if visits are discontinued)	X	X	X
[14] RCL	[redacted]	[redacted]	X
[15] Genomic safety biospecimen	[redacted]	X	X
[16] PBMCs	[redacted]	X	X

1 [redacted].

2 **Physical examination (PE):** Physical examination will include weight. Not required after documented disease progression per Lugano criteria or initiation of subsequent anti-cancer therapy.

3 **CBC Hematology:** complete blood count (CBC) with differential (should include % and absolute number of neutrophils, lymphocytes, monocytes, eosinophils, basophils, and reticulocyte count), hemoglobin, hematocrit, platelet counts. Not required after documented disease progression per Lugano criteria or initiation of subsequent anti-cancer therapy.

4 **Blood Chemistry (fasting not required):** should include: alanine aminotransferase (ALT), albumin, alkaline phosphatase, aspartate aminotransferase (AST), bicarbonate, total bilirubin, blood urea nitrogen (BUN), chloride, serum calcium, creatinine, creatinine clearance, glucose, lactate dehydrogenase, magnesium, sodium, phosphorus or phosphate, total protein, potassium, uric acid, serum ferritin, C- reactive protein (CRP). Not required after documented disease progression per Lugano criteria or initiation of subsequent anti-cancer therapy.

5 **TSH (FCA arm only)**

6 **Urinalysis (FCA arm only):** Urine dipstick for protein, glucose, and blood: If positive collect 24 hr and/or microscopic cell count (Reflex Testing)

7 **Pregnancy test and contraception check:** Serum or urine pregnancy test for females of childbearing potential. Follicle stimulating hormone test may be performed for post-menopausal women. Contraception use will be checked to confirm that contraception is used consistently and correctly.

8 **Reflex auto-antibodies** will be evaluated in case of suspected ALLO-647 treatment emergent autoimmunity AE. Depending on the type of AE, the tests should include (but not limited to) serum antiphospholipid antibodies (APA), platelet-bound APA, anti-Factor VIII antibodies, anti-Thyroid Peroxidase (anti-TPO), anti-Thyroglobulin (anti-TG) and anti-thyroid stimulating hormone (anti-TSH receptor), Coombs test, antinuclear antibodies (ANA), perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA), anti-neutrophil cytoplasmic antibodies (cANCA), and/or anti-Sjogren's syndrome type B (anti-SSB).

9 **EQ-5D-5L (PRO) and QLQ-C30 (PRO):** Not required after documented disease progression per Lugano criteria or initiation of subsequent anti-cancer therapy.

10 **PET/CT Lymphoma assessments by positron emission tomography (PET)/computerized tomography (CT):** tumor assessments will include all known or suspected disease sites. Disease-specific imaging as clinically appropriate will be performed as described in the study imaging manual. Radiographic disease assessment will not be required after documented disease progression per Lugano criteria or initiation of subsequent anti-cancer therapy.

11 **Bone Marrow Biopsy and Aspirate:** Bone marrow biopsy and aspirate will be completed at the time complete response (CR) is suspected only if bone marrow infiltration is positive or unknown at screening, and as clinically indicated. Samples (screening; others as indicated) will be banked, and may be analyzed for insertion site analysis, molecular analysis, and other similar analyses. Proceduralist should aim to achieve a 2cm core to best assess cellularity. Not required after documented disease progression per Lugano criteria or initiation of subsequent anti-cancer therapy.

12 **Lymph node biopsy:** To be performed as clinically indicated. Not required after documented disease progression per Lugano criteria or initiation of subsequent anti-cancer therapy.

13 **Follow-up for survival:** All randomized subjects will be followed in the follow-up period for survival and disease status. As part of the study sites may be asked to conduct searches of public records, such as those establishing survival status, if available, to obtain survival data if the subject survival status is not already known. Sites may be also asked to also retrieve autopsy reports to confirm status of disease at the time of death and as per FDA Guidance: Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up (July 2018)

14 **Replication competent lentivirus (RCL):** Whole blood samples will be collected to monitor for the presence of RCL-specific DNA sequences by a validated PCR-based assay. Samples may be analyzed for RCL only [redacted]; if negative, then remaining samples [redacted] may be collected and archived. Assess for RCL upon diagnosis of a new (secondary) malignancy.

15 **Genomic safety biospecimen:** Unless prohibited by local regulations or ethics committee decision, a blood sample will be collected during [redacted] and every [redacted], for assays related to treatment response in the disease under study, eg, insertion site analysis, malignancy panels, etc.

16 **PBMCs:** Peripheral blood mononuclear cells (PBMCs) will be collected at the indicated timepoints and cryopreserved for future cytogenetics, cellular, molecular or proteomic studies.

SPONSOR SIGNATURE PAGE

By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

Name:	[redacted]
Title:	[redacted]
Signature: (Electronic signature)	[redacted]
Date signed:	[redacted]

INVESTIGATOR SIGNATURE PAGE

Allogene Therapeutics

A Randomized, Open-label, Phase 2 Study Evaluating Lymphodepletion with Fludarabine, Cyclophosphamide, and ALLO-647, vs Fludarabine and Cyclophosphamide alone, in Subjects with Relapsed/Refractory Large B-cell Lymphoma (LBCL) Receiving ALLO-501A Allogeneic CAR T Cell Therapy

Protocol Number:	ALLO-647-201
Protocol Date:	13 October 2022
Protocol Version:	Amendment 1

Signature of Agreement for Protocol ALLO-647-201 (EXPAND Study)

I have read this protocol and agree to conduct the study as outlined herein, in accordance with all applicable regulations including the International Conference on Harmonization guidelines on Good Clinical Practices (ICH-E6).

_____	_____
Site Number	Print Site Name

_____	_____
Investigator Signature	Date

_____
Print Investigator Name and Title