CLINICAL STUDY PROTOCOL

Amendment 2.0
Date: 30 May 2022

Sponsor	Acepodia Biotech, Inc. 1600 Harbor Bay Parkway; Suite 140 Alameda, CA 94502 USA
Title	A Phase 1 Multicenter Study Evaluating the Safety and Efficacy of ACE1831, an Allogeneic CD20-Conjugated Gamma Delta T-Cell Therapy, In Adult Subjects with Relapsed/Refractory CD20-Expressing B-Cell Malignancies
Protocol Number	ACE1831-001 Amendment 2.0, 30 May 2022 Replaces Amendment 1.0, 20 Apr 2022
Indication	Relapsed/refractory (r/r) non-Hodgkin lymphoma
Investigational Product	ACE1831
Product Description	Cryopreserved human allogeneic gamma delta T-cells conjugated with anti-CD20 monoclonal antibody
IND Number	27944
Sponsor Medical Contact	Michael Kurman, MD Head of Clinical Development Email: michaelkurman@acepodiabio.com Mobile: 201-236-9730

CONFIDENTIALITY STATEMENT

INVESTIGATOR SIGNATURE PAGE

I, the undersigned, am responsible for the conduct of the trial at this site and agree to the following:

- I understand and will conduct the trial according to the protocol, any approved protocol amendments, ICH GCP and all applicable regulatory authority requirements and national laws
- I have sufficient time to properly conduct and complete the trial within the agreed trial period, and I have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely
- I will ensure that all staff at the clinical trial site who are involved in the trial conduct are adequately trained regarding the protocol and their responsibilities

Signature	**Date**

Name (printed)

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LIST OF ABBREVIATIONS

Abbreviation	Expanded Term
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AESI	adverse events of special interest
ALT	alanine transaminase
AST	aspartate transaminase
CNS	central nervous system
CRR	complete response rate
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	common terminology criteria for adverse events
DLBCL	diffuse large b-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	eastern cooperative oncology group
FiO_2	fraction of inspired oxygen
FL	follicular lymphoma
gdT	gamma delta T-cell
GvHD	graft versus host disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HGBCL	high grade B cell lymphoma
HHV	human herpesvirus
HIV	human immunodeficiency virus
HLA	human leukocyte antigens
IB	Investigator's Brochure
ITT	intent-to-treat
IUD	intrauterine device
IWG	international working group
LOQ	limit of quantification
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MAD	maximum administered dose
MCL	mantle cell lymphoma
MDRD	modification of diet in renal disease
MHC	major histocompatibility complex
mITT	modified intent-to-treat
MTD	maximum tolerated dose
MUGA	multigated acquisition
MZL	marginal zone lymphoma
NCCN	national comprehensive cancer network

NK	natural killer
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic
PET	positron emission tomography
PFS	progression free survival
PMBCL	primary mediastinal B-cell lymphoma
PRES	posterior reversible encephalopathy syndrome
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SaO_2	oxygen saturation
SAP	Statistical Analysis Plan
SRC	Safety Review Committee
TCR	T-Cell Receptor
TFL	transformed follicular lymphoma
TLS	tumor lysis syndrome
ULN	upper limit of normal
WHO	World Health Organization

Protocol Synopsis

Short Title
A Phase 1, Open-label Study of ACE1831 in Adult Subjects with Relapsed/Refractory CD20-expressing B-cell Malignancies
Background and Rationale
ACE1831 is an allogeneic gamma delta T (gdT) -cell therapy under investigation for the treatment of CD20-expressing B-cell malignancies. ACE1831 consists of human allogeneic gdT-cells that are conjugated to rituximab (an anti-CD20 monoclonal antibody [mAb]), using short complementary strand DNA linkers. Using a novel selection and expansion technology, the gdT-cells are enriched to express high levels of natural killer (NK)-activating receptors, such as CD56 and NKG2D, and low levels of inhibitory receptors to enhance their potency. Gamma delta T-cells have characteristics of both the innate and adaptive immune systems that make them an ideal platform for the development of cell therapies. This cell type can directly recognize and attack cancerous cells as well as coordinate a broad antitumor immune response by recruiting other accessory cells to the sites of disease and activating other immune factors. Gamma delta T cells do not recognize allogeneic major histocompatibility complex (MHC) restricted antigens nor do they secrete excess amounts of IL-6 (Phalke 2015), a significant driver of cytokine release syndrome (CRS), providing a potential safety advantage over other cell therapies.
Study Objectives
Phase 1 **Primary:** • To evaluate the safety and tolerability of ACE1831 as monotherapy or in combination with obinutuzumab (GAZYVA®) in subjects with relapsed/refractory B-cell lymphomas • To determine the recommended Phase 2 dose (RP2D) for further investigation **Secondary:** • To assess the pharmacokinetics of ACE1831 • To evaluate the immunogenicity of ACE1831 • To evaluate the efficacy of ACE1831, as monotherapy or in combination with obinutuzumab in subjects with relapsed/refractory B-cell lymphomas **Exploratory:** • To evaluate the pharmacodynamics of ACE1831 based on induction of cytokines and other biomarkers in the blood of subjects before and after infusion of ACE1831
Study Design
This is an open-label, multicenter, Phase 1 study designed to evaluate the safety, tolerability, and efficacy of a single dose of ACE1831 (anti-CD20 conjugated allogeneic gamma delta T cells) with or without obinutuzumab in subjects with relapsed/refractory CD20-expressing B-cell lymphomas. Subjects will be enrolled in up to 2 Treatment Groups in this study: • 3 dose levels of ACE1831 as monotherapy will be investigated (Treatment Group A) • 2 dose levels of ACE1831 in combination with obinutuzumab will be investigated (Treatment Group B) A Safety Review Committee (SRC) comprised of Principal Investigators, as well as the Sponsor's Medical Monitor, statistician, safety physician, and other ad hoc members, as appropriate, will regularly assess the safety and efficacy of ACE1831 administration throughout the trial (Section 3.3). Dose levels evaluated in this study are provide in Table S-1.

Table S-1 Dose Levels

Dose Level	Dose (cells)
3[a]	1000 × 10^6 cells
2	600 × 10^6 cells
1 (Starting Dose)	300 × 10^6 cells
-1	100 × 10^6 cells

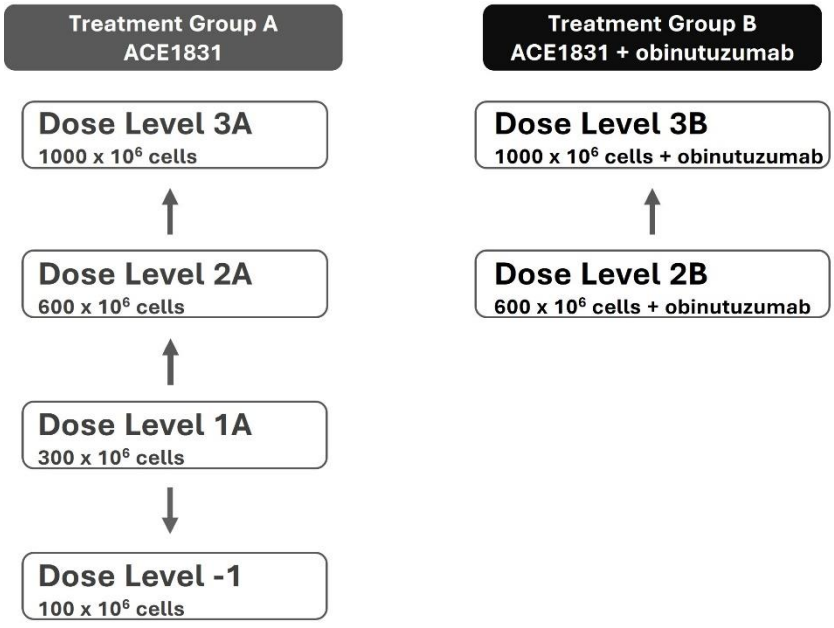
a. Dose level 3 only: subject must have a minimum weight of 55 kg or 120 lbs.

Dose Escalation

In the first stage of the dose-escalation (Treatment Group A), up to 3 different dose levels of a single dose of ACE1831 will be explored after a lymphodepletion regimen and will follow a 3+3 dose escalation design. The maximum tolerated dose (MTD)/maximum administered dose (MAD) for Treatment Group A will be defined as the highest dose level at which <33% (ie, 0 of 3 or 1 of 6) of subjects in a treatment group experience a dose limiting- toxicity (DLT) as outlined below.

In the second stage of the dose-escalation (Treatment Group B), ACE1831 will be administered in combination with obinutuzumab. A single dose of ACE1831 will be administered on Day 1; obinutuzumab will be administered on Days -5 and -4 as part of the lymphodepletion regimen, and on Days 3 and 11 post-ACE1831 infusion. This phase of the study will follow a 3+3 dose escalation design. The MTD/MAD for Treatment Group B will be defined as the highest dose level at which <33% (ie, 0 of 3 or 1 of 6) subjects in a treatment group experience a DLT. The Phase 1 study schema is provided in Figure S-1.

Figure S-1 Study Schema



The respective dose levels for monotherapy (Treatment Group A) and combination treatment (Treatment Group B) at the MTD/MAD may be expanded to a total of 12 subjects to further characterize toxicity, ACE1831 persistence, and pharmacodynamics, and to gain preliminary evidence of efficacy. Depending on findings in the expanded MTD/MAD dose level, lower dose levels may also be expanded to up to 12 subjects, to further characterize toxicity.

A staggered enrollment approach will be implemented for the first 3 subjects at each dose level.

Since acute and clinically significant adoptive cell therapy toxicities (eg, CRS, neurotoxicity, graft vs host disease [GvHD]) usually manifest up to 2 weeks after cellular infusion, the first 3 subjects at each dose level and treatment group will be enrolled with a staggered enrollment of 3 weeks from the day of ACE1831 infusion between subjects to observe for unknown potential toxicities.

The ACE1831-001 Safety Review Committee (SRC) (described in Protocol Section 3.1.4.1) will review safety data after 3 and/or 6 subjects (if applicable) have enrolled in each treatment group and have had the opportunity to be followed for at least 28 days after infusion of ACE1831. The SRC will make recommendations based on the incidence of DLTs and the overall safety profile of ACE1831, as shown in Table S-2:

Table S-2 Subject Dose Initiation Recommendations Based on DLTs

Number of Subjects with a DLT in a Treatment Group	Potential Recommendation
0 of 3 subjects or 1 of 6 subjects	Dose determined to be tolerable, enroll into next higher dose for the treatment group. If this is the highest dose level, then this will be the MTD.
1 of 3 subjects	Enroll 3 more subjects at the same dose level.
2 of 3 subjects or 2 of 6 subjects	Next lower dose level will be established as the MTD.

Abbreviations: DLT=dose limiting toxicity; MTD=maximum tolerated dose.

After completing enrollment of the Phase 1 portion of the study, the totality of the monotherapy and combination data will be used to identify the RP2D (either as monotherapy or in combination with obinutuzumab).

Study Population

Subjects with histologically confirmed, CD20-positive B-cell NHL, including the following types defined by World Health Organization (WHO) 2016 criteria (Swerdlow 2016):

- Diffuse large B cell lymphoma not otherwise specified
- High-grade B cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements
- Transformation of follicular lymphoma or marginal zone lymphoma to DLBCL
- Primary mediastinal B cell lymphoma
- Follicular lymphoma Grade 3B.

Subjects must have persistent or progressive B-cell lymphoma after having received at least 2 prior systemic therapies per National Comprehensive Cancer Network (NCCN) guidelines (NCCN 2022). Prior therapies must include at a minimum, an anthracycline and an anti-CD20 monoclonal containing chemoimmunotherapy regimen.

Up to 42 subjects will be enrolled in the study.

Centers and Study Locations

Up to a total of 6 sites in the US

Inclusion/Exclusion Criteria

Subject Population and Eligibility

Inclusion Criteria

To be eligible for this study, all the following inclusion criteria must apply:

- Signed informed consent.

- Males or Females ≥18 years of age at the time of informed consent
- A minimum weight of (55 kg or 120 lbs) is required at Dose level 3 (1000×10^6 cells)
- Histologically confirmed, CD20-positive B-cell NHL excluding the following types defined by World Health Organization (WHO) 2016 (Swerdlow 2016):
- Diffuse large B cell lymphoma not otherwise specified
- High-grade B cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements
- Transformation of follicular lymphoma or marginal zone lymphoma to DLBCL
- Primary mediastinal B cell lymphoma
- Follicular lymphoma Grade 3B.
- Subjects must have persistent or progressive B-cell lymphoma after having received at least 2 prior systemic therapies per NCCN guidelines (NCCN 2022). Prior therapies must include at a minimum, an anthracycline and an anti-CD20 monoclonal-containing chemoimmunotherapy regimen.
- At least 1 measurable lesion according to the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma (Cheson BD 2014). Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy.
- If the only measurable disease is lymph-node disease, at least 1 lymph node should be ≥2 cm.
- Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1
- Adequate hematologic function independent of platelet transfusion and growth factor support for at least 14 days prior to the planned start of the lymphodepletion regimen, defined as:
- platelet count >50,000 cells/mm^3 (50×10^9/L).
- absolute neutrophil count ≥1000 cells/mm^3 (1.0×10^9/L)
- Adequate renal, hepatic, and cardiac function defined as:
- creatinine clearance >60 mL/minute measured using the Cockcroft-Gault equation, or an estimated glomerular filtration rate (eGFR) >60 mL/minute/1.73 m^2 per 4 variable Modification of Diet in Renal Disease (MDRD) equation
- serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤3.0 × upper limit of normal (ULN) of the institution's normal range
- total bilirubin ≤2.5 × ULN of the institution's normal range, except in subjects with Gilbert's syndrome
- Albumin ≥3.5 g/dL
- Left ventricular ejection fraction (LVEF) ≥50% and no evidence of pericardial effusion as determined by an echocardiogram (ECHO)/multigated acquisition (MUGA) scan
- Oxygen saturation via pulse oxygenation ≥92% at rest on room air
- Women of childbearing potential and all male participants must agree to use at least 1 highly effective method of contraception (<1% failure rate) to avoid pregnancy during screening, for the duration of the study treatment, and 1 year after completion of the lymphodepletion regimen. Highly effective methods are defined as those that result in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The following are examples of highly effective methods of contraception including:
- Intrauterine device (IUD), hormonal (birth control pill, injections, implants), tubal ligation, and partner's vasectomy.
- Males who are not sexually abstinent and have partners of childbearing potential must agree to a condom during sexual contact with a pregnant female or a female of childbearing potential for at least 1 year after completion of the lymphodepletion regimen even if he has undergone a successful vasectomy.

Exclusion Criteria

Subjects are not eligible if any of the following apply:

- Prior treatment with a genetically modified cell therapy product targeting CD20
- Autologous stem cell transplant within 6 weeks of informed consent
- History of allogeneic stem cell transplantation
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products (eg, rituximab or obinutuzumab)
- Subjects with cardiac atrial or cardiac ventricular lymphoma involvement
- Subjects with detectable cerebrospinal fluid (CSF) malignant cells, or brain metastases, or with a history of central nervous system (CNS) lymphoma or primary CNS lymphoma
- History or presence of a clinically relevant CNS disorder such as seizure disorder (eg, epilepsy), cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, cerebral edema, posterior reversible encephalopathy syndrome (PRES), or any autoimmune disease with CNS involvement
- History of other malignancies, except:
- Malignancy treated with curative intent and with no known active disease present for ≥2 years before the first dose of study drug and felt to be at low risk for recurrence by the treating physician.
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
- Adequately treated carcinoma in situ without evidence of disease
- Clinically significant active infection currently requiring treatment with IV antibiotics or previously treated with IV antibiotics within 7 days prior to planned start of the lymphodepletion regimen. Exceptions to this exclusion criteria are simple urinary tract infection or bacterial pharyngitis, or subjects on prophylactic antibiotics, antivirals, or antifungals
- Human immunodeficiency virus (HIV) infection, based on laboratory testing performed during the screening period
- Active Hepatitis B virus (HBV) or Hepatitis C virus (HCV) infection, based on laboratory testing performed during screening period. HBV-infected subjects are considered eligible if their viral load is below the institutional limit of quantification (LOQ) and the subject is on stable viral suppressive therapy. HCV-infected subjects are considered eligible if they have completed curative antiviral treatment and their HCV RNA viral load is below the institutional LOQ
- Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class III or IV congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to the start of initial screening
- Patients with heart rate-corrected QT interval (QTcF) prolongation >470 msec at screening will be excluded from the study unless secondary to stable conduction disorders (eg, left bundle-branch block)
- Requirement for urgent therapy due to tumor mass effects such as bowel obstruction or blood vessel compression
- Primary immunodeficiency disorder
- Unresolved toxicities from prior anticancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Events (CTCAE, version 5.0), Grade ≤1 or to the levels dictated in the inclusion/exclusion criteria except for alopecia, vitiligo, and laboratory test values that meet inclusion criteria
- Concurrent systemic immunosuppressant therapy (eg, cyclosporine A, tacrolimus, etc., or chronic administration of >5 mg/day of prednisone) within 28 days of the start of the planned lymphodepletion regimen (exceptions to this exclusion criteria are topical and inhaled corticosteroids in standard doses and physiologic replacement for subjects with adrenal insufficiency)

- Any systemic anticancer therapy (chemotherapy or targeted small molecule) within 2 weeks or 5 half-lives of the drug (whichever is longer) prior to the planned start of the lymphodepletion regimen; or any investigational cellular therapy within 8 weeks prior to the planned start of lymphodepletion regimen. If the half-life of a drug is not known, then the washout period will be 4 weeks
- Live vaccine ≤6 weeks prior to initial screening
- Pregnant or lactating females and subjects of both genders who are not willing to practice birth control from the time of consent through 1 year after the completion of the lymphodepletion regimen
- Any medical, psychological, familial, or sociological conditions that, in the opinion of the Investigator or Sponsor Medical Monitor, would impair the ability of the subject to receive study treatment or comply with study requirements, including understanding and rendering of informed consent
    - Severe disease progression or health deterioration within 2 weeks prior to lymphodepletion regimen that, in the opinion of the Investigator, could impair the ability of the subject to receive study treatment or comply with study requirements.

Test Product, Dose, and Mode of Administration

Each vial contains ACE1831 cells in cryopreservation medium (10% DMSO) at a volume of 10 mL. Details on storage, preparation, and administration are provided in the study ACE1831 Cell Therapy Manual.

ACE1831 will be administered as a single IV infusion 48 hours (but no more than 7 days) after completion of the lymphodepletion regimen.

Study Treatment and Duration of Treatment

Before administration of ACE1831 on Day 1, subjects will receive a lymphodepleting regimen consisting of cyclophosphamide and fludarabine to induce lymphocyte depletion and create an optimal environment for expansion of ACE1831 in vivo. Subjects will initiate lymphodepleting chemotherapy with cyclophosphamide and fludarabine beginning on Day -5 through Day -3. The schedule of administration may be adjusted, if necessary, but the lymphodepleting regimen must be completed between 2 and 7 days before ACE1831 administration.

Treatment Group A: ACE1831 will be administered by IV infusion. Dose levels of 300×10^6 cells, 600×10^6 cells, and 1000×10^6 cells will be evaluated as monotherapy.

Treatment Group B: ACE1831 will be administered in combination with obinutuzumab. Obinutuzumab will be administered by IV infusion; 100 mg on Day-5 and 900 mg on Day-4 in combination with the lymphodepletion regimen and 1,000 mg on Days 3 and 11 post ACE1831 infusion.

Dose-limiting Toxicities

DLTs are defined as select adverse events (AEs) that are related to treatment with ACE1831 (see below). The DLT period is 28 days and starts with the dose of ACE1831 (Day 1).

The following AEs will be considered DLTs if deemed related to ACE1831:

- CRS Grade 4 of any duration (Lee 2019) (Table 12)
- CRS Grade 3 event that does not resolve to Grade ≤2 within 72 hours, with or without treatment (Table 12)
- Grade 4 infusion reaction of any duration
- Grade 3 infusion reaction lasting more than 2 hours
- Any Grade ≥2 neurotoxicity that does not resolve to Grade ≤1 within 72 hours with or without treatment
- Any Grade 3 cardiac or pulmonary toxicities that do not improve to Grade 2 or lower within 72 hours
- Any related AE requiring intubation
- Grade 4 neutropenia lasting longer than 14 days from the day of ACE1831 infusion
- Grade 4 thrombocytopenia that fails to recover to Grade ≤2 lasting longer than 14 days from the day of ACE1831 infusion
- Grade ≥3 acute GvHD (Harris 2016) (Table 15)
- Grade ≥3 autoimmune toxicities, particularly those affecting vital organs (eg, gastrointestinal tract, lung, heart, thyroid, kidneys, liver) occurring within 4 weeks of the ACE1831 infusion

- Grade 3 infection not improving to Grade 2 or lower within 2 weeks of onset.
- Grade 4 laboratory abnormalities in the presence of clinical signs or symptoms
- Any dose holds >21 days for an ACE1831-related AE
- All other related grade 3 non-hematologic toxicities lasting more than 7 days
- Any Grade 5 event, except for death due to progressive disease, will be considered a DLT.

The following will NOT be considered DLTs:

- Immediate hypersensitivity reactions occurring within 2 hours of ACE1831 cell infusion (related to cell infusion) that are reversible to a Grade ≤2 within 24 hours of cell administration with standard therapy.
- Grade ≥3 fever
- Grade 4 tumor lysis syndrome (TLS), graded as described by Cairo and Bishop (Cairo 2004) lasting <7 days (Table 13)
- Grade 4 anemia, leukopenia, or lymphopenia
- Grade 3 or 4 hypogammaglobulinemia
- Grade 3 fatigue lasting <7 days

Criteria for Evaluation

Safety Assessments

Safety will be assessed according to the schedule of evaluations (SOEs) by monitoring AEs (including DLTs, AEs of special interest [AESI] and serious AEs [SAEs]), concomitant medications, physical examinations, ECOG performance status, GvHD, vital signs, hematology and serum chemistry laboratory tests, blood coagulation tests, urinalysis, electrocardiograms (ECG), and ECHO/MUGA scan.

Anti-tumor Activity

Disease assessments will be performed according to the schedule presented in the SOEs using the IWG Criteria for Malignant Lymphoma and will include positron emission tomography-computed tomography (PET-CT) and diagnostic quality contrast enhanced CT scans, and bone marrow aspirate/biopsy if applicable.

ACE1831 Pharmacokinetics

Blood samples will be analyzed via polymerase chain reaction (PCR) and/or other assays at planned time points to assess ACE1831 pharmacokinetics.

Pharmacodynamics

Blood samples will be analyzed to assess serum levels of Interferon-γ, tumor necrosis factor (TNF)-α, IL-2, IL-6, IL-8, and IL-10. and tumor biomarker expression (CD19, CD20, CD22, CD79b, and loss of function of CD58) changes at planned time points.

Adverse Events of Special Interest (AESI)

The current AESI events are based on limited experience from an ongoing Acepodia cell therapy study without an accurate assessment of causality and reported events from other cell-based therapies (such as CAR-T). The sponsor may continuously update the AESI criteria based on data collected throughout the study.

- Cytokine Release Syndrome (CRS)
- Neurotoxicity due to immune effector cell-associated neurotoxicity syndrome
- Macrophage activation syndrome (MAS)
- Acute and chronic GvHD
- Autoimmune manifestations (gastrointestinal [GI], pulmonary, thyroiditis, other])
- Tumor lysis syndrome (TLS)
- Grade 3 cytopenia that persists through the first 28 days post-ACE1831 treatment
- Severe (grade 3) infection through the first 28 days post-ACE1831 treatment

Statistical Methods and Data Analysis
Primary Safety Endpoints Treatment-emergent AEs (TEAEs) start on or after the date of the first dose of ACE1831. Adverse events that occur prior to first dose of ACE1831 will be considered pre-treatment AEs and summarized separately. The incidence of DLTs, AESIs, Grade 3 or higher TEAEs, TEAEs considered related to treatment, TEAEs by maximum grade and relationship, TEAEs resulting in death, SAEs, related SAEs, and TEAEs leading to treatment discontinuation will be summarized by treatment group and dose level. Safety laboratory data as reported by local labs (hematology, serum chemistry, coagulation, thyroid panel, and urinalysis), vital signs and ECG parameters will be summarized descriptively and presented for each timepoint, including change from baseline. Shift from baseline tables based on NCI-CTCAE grading will be created for select laboratory parameters defined in the Statistical Analysis Plan (SA). By-subject data listings of all safety data will be generated. *Efficacy Endpoints:* Disease response will be assessed throughout the study by the investigators using RECIST v1.1. The ORR will be calculated, including 95% exact confidence intervals, for each treatment group and dose level. Corresponding exact 95% confidence intervals for the ORR will also be presented. The ORR will be based only on response assessments obtained after the initial ACE1831 infusion and prior to the start of any additional non-study therapy (eg, stem cell transplant or start of other trial or anti-cancer therapy).
Sample Size Determination
Up to 42 subjects (Treatment Groups A+B) The dose-escalation part of the study will use a 3 + 3 study design. The number of subjects required will depend on the safety profile and DLT rate observed in each treatment group and dose level. Subjects who discontinue prior to completion of the 28-day DLT assessment period for reasons other than a DLT may be replaced. Subjects will be enrolled in up to 3 monotherapy dosing levels (Treatment Group A) and 2 combination therapy dosing levels (Treatment Group B). The respective dosing levels for monotherapy (Treatment Group A) and combination treatment (Treatment Group B) at the MTD/MAD may be expanded to a total of 12 subjects to further characterize toxicity, ACE1831 persistence, and pharmacodynamics to gain preliminary evidence of efficacy.
Safety Oversight
Safety Review Committee (SRC) An SRC will be established prior to the enrollment of the first subject. The SRC will be composed of Principal Investigators and the Sponsor's Medical Monitor Other members of the research team, including the study statistician, safety physician, as well as various ad hoc members may join the SRC meetings but will not have voting privileges. The SRC will regularly assess the safety and efficacy of ACE1831 administration throughout the trial. Determination of dose level escalations and opening of study treatment groups will be based on recommendations from the SRC. **Toxicity Stopping boundaries** In addition to the DLT assessment to guide dose escalation or de-escalation in each treatment group, toxicity stopping boundaries will be implemented to ensure subject safety throughout the study. These stopping bounds are defined separately for monotherapy (Treatment Group A) and combination therapy (Treatment Group B) in Section 10.3.5.3. Enrollment will be paused if a toxicity boundary is met. After a review of all available data by the SRC, a recommendation will be made as to whether enrollment in the study should resume as planned or be modified prior to additional enrollment.

1. INTRODUCTION

1.1. Disease Background

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of cancers originating in B lymphocytes, T lymphocytes, or natural killer cells. In the United States (US), B-cell lymphomas represent approximately 85% of all NHL cases (ACS 2019). NHL is the most prevalent hematological malignancy, accounting for 4% of all new cancer cases and 3% of cancer-related deaths (Howlader 2019). For 2019, an estimated 74,000 new cases of NHL and approximately 20,000 deaths due to NHL in the US were expected to occur (Howlader 2019). Subtypes of NHL include large B-cell lymphomas (LBCL) (ie, diffuse large B-cell lymphoma [DLBCL], high-grade B cell lymphoma [HGBCL], and primary mediastinal large B-cell lymphoma [PMBCL]), indolent NHL (follicular lymphoma [FL] and marginal zone lymphoma [MZL]), and mantle cell lymphoma (MCL).

Diffuse large B-cell lymphoma is the most common and is an aggressive subtype of B-cell NHL, accounting for 30% to 40% of cases (Chaganti 2016; Morton 2006; Sehn 2015) and with approximately 22,000 new diagnoses in the US each year (Elstrom 2010; Flowers 2010). Over the past 2 decades, progress has been made in understanding the biological heterogeneity of DLBCL, and the use of combination therapy has improved survival (Tilly 2015). The DLBCL population with the highest unmet need continues to consist of patients who do not respond to first-line combination chemo/immunotherapy (typically rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]) or do not respond to a subsequent course of combination chemotherapy due to chemo-insensitivity (Josting 2000).

High-grade B cell lymphoma (Swerdlow 2016) includes LBCLs with MYC and BCL2 and/or BCL6 rearrangements that are phenotypically intermediate to DLBCL or B-cell lymphoma, unclassifiable (this latter category has since been eliminated). MYC rearrangements in LBCLs are associated with a poor prognosis that is worsened in cases of concomitant BCL2 and/or BCL6 alterations (ie, double- or triple-hit lymphomas). As such, patients with HGBCL face worse outcomes.

Primary mediastinal large B-cell lymphoma has distinct clinical, pathological, and molecular characteristics compared with DLBCL and represents approximately 2% to 4% of all patients with NHL (Bhatt 2015). Initial treatment for PMBCL includes anthracycline-containing regimens with rituximab with or without involved field radiotherapy which is curative in the majority of cases. Chemosensitive patients who relapse may respond to further cytotoxic therapy followed by autologous stem cell transplantation (auto-SCT); in those that do not respond, therapeutic options are limited and with overall low response rates.

Indolent NHLs (iNHLs) include FL and MZL. FL is the most common indolent form of NHL, accounting for 10 to 22% of all cases (Howlader 2019). Although newly diagnosed, low-grade limited-stage FL is often responsive to a variety of first-line treatments; however, the disease is characterized by a pattern of relapsing and remitting disease. Relapsed or refractory (r/r) FL has limited effective therapeutic options and new therapies are needed. Furthermore, transformation from FL to DLBCL (TFL) occurs at an annual rate of approximately 3% for 15 years and is associated with poor outcomes (Al-Tourah 2008). MZL is a rare form of NHL

originating in the marginal zone of B-cells (Kahl 2008). The low incidence rates and the heterogeneous presentation make large-scale clinical trials of MZL challenging. Generally, patients respond to front-line therapy; however, patients with r/r MZL have few therapeutic options.

1.2. Relapsed/Refractory CD20-expressing B-cell Lymphomas

1.2.1. Relapsed/Refractory DLBCL

Patients with LBCL who relapse after, or are refractory to, first-line therapy have poor prognosis. For DLBCL, second-line chemotherapy regimens generally consist of cytotoxic drugs that are not cross-resistant with first-line chemotherapy to determine chemosensitivity before proceeding to auto-SCT. However, only a small fraction of patients with r/r disease benefit from auto-SCT. Poor outcomes are also observed for patients who are unable to undergo auto-SCT.

Approximately 10% of patients with r/r DLBCL have long-term survival following auto-SCT in the rituximab era (Friedberg 2011). Patients whose disease progresses after 2 or more prior lines of systemic therapy regimens are unlikely to benefit further from currently available systemic therapy options, unless they have experienced a long disease-free interval (NCCN 2022). In addition, the results of a multicenter retrospective study (Crump 2017) based on data from 3 academic centers and 2 large randomized, controlled Phase 3 studies of patients with r/r aggressive lymphomas, patients with refractory DLBCL have an objective response rate (ORR) of 26%, a complete response (CR) rate of 7%, and a median overall survival (OS) of 6.3 months. Poor outcomes were observed across all refractory subgroups (primary refractory, refractory to second-line or higher therapy, or relapse <1 year after auto-SCT) and regardless of disease stage, suggesting that these patients form a single population who lack effective treatment (Crump 2017).

The dismal prognosis for patients with refractory or third-line DLBCL has been challenged with results from pivotal studies of 3 recently Food and Drug Administration (FDA)-approved therapies and 1 study for PMBCL. Polatuzumab vedotin, a CD79b-directed antibody-drug conjugate in combination with bendamustine and rituximab (BR), resulted in an ORR of 45% (BR alone: 18%), with a CR rate of 40% (BR alone: 18%) (Sehn 2015). Pembrolizumab, a humanized monoclonal antibody (mAb) against programmed cell death protein 1 (PD1), received accelerated approval by the FDA for the treatment of PMBCL refractory to treatment or that has relapsed after 2 or more prior lines of therapy. The single-arm, multicenter KEYNOTE-170 study of pembrolizumab enrolled 53 subjects with a median of 3 prior lines of therapy, resulting in an ORR of 45% (CR: 13%) and the median OS was not reached (Armand 2019).

The FDA approved 3 autologous-based anti-CD19 chimeric antigen receptor (CAR) T-cell therapies: axicabtagene ciloleucel (YESCARTA USPI 2021), tisagenlecleucel (KYMRIAH USPI 2021), and lisocabtagene maraleuce (BREYANZI USPI 2021) for the treatment of patients with various subtypes of r/r DLBCL and r/r LBCL. These therapies have demonstrated significant improvement in disease outcomes. While these responses are significantly improved over the previous standard of care (rituximab plus chemotherapy), not all subjects who achieve an initial response with anti-CD19 CAR T-cell therapies have durable responses beyond 12 months

(Jacobson C 2020). However, therapies based on autologous cells have limitations, mainly related to the fact that the product has to be generated from each patient's cells, in a time-consuming and costly process, and with the risk of manufacturing failure (J. Zhao 2018). Thus, there is an urgent unmet need for those who relapse, do not respond or are not eligible for autologous CAR T-cell therapy.

1.2.2. Relapsed/Refractory FL

Outcomes in FL are quite varied. High-risk patients with ≥3 Follicular Lymphoma International Prognostic Index (FLIPI) criteria have a 5-year overall survival rate of 53%, whereas low-risk patients with ≤1 FLIPI criterion have a 5-year survival rate of over 90%. Advanced stage FL generally requires multiple successive lines of therapy leading to progressively shorter remission periods, chemo-refractory disease, transformation to DLBCL, or death due to repeated treatment related toxicities (Cheah 2018). Thus, regardless of disease stage at diagnosis, most patients with FL ultimately experience disease relapse, even after a long-term response to first-line therapy, representing a significant unmet need.

The National Comprehensive Cancer Network (NCCN) Treatment Guideline recommends high-dose (chemo)therapy (HDT)/auto-SCT as a consolidative therapy for patients with FL who are in second or third remission (NCCN 2022). Allogeneic (allo)-SCT may offer improved relapse rates and disease control compared with auto-SCT; however, allo-SCT is associated with higher nonrelapse mortality rates and is not a viable treatment option for most patients with FL (Freeman 2018). By one estimate, fewer than 3% of patients with FL who undergo second-line therapy receive SCT as part of their treatment strategy (Fenske 2014).

Patients with FL who experience multiple relapses tend to have incomplete or short-lived responses to treatment. New targeted mAbs, inhibitors, and immunomodulatory drugs have been developed to overcome chemotherapy and rituximab resistance. Outcomes with current therapies consisting of anti-CD20 mAbs (such as obinutuzumab + bendamustine) and phosphatidylinositol 3 kinase (PI3K) inhibitors (ie, idelalisib and copanlisib) are poor, with ORRs ranging from approximately 54% to 68% (Cheson 2018; Dreyling 2017; Gopal 2014).

Recently, the FDA approved axicabtagene ciloleucel (YESCARTA USPI 2021), an autologous based anti-CD19 chimeric antigen receptor (CAR) T-cell therapy for the treatment of patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. Axicabtagene ciloleucel demonstrated significant improvement in disease outcomes. Among the 81 patients included in the primary efficacy analysis, efficacy was established based on objective response rate (ORR 91%; CR 60%) and rate of continued remission at 12 months (76.2%) and 18 months (74.2%).

1.2.3. Relapsed/Refractory MZL

The low incidence rates and the heterogeneous presentation render large scale clinical trials of MZL challenging. To date, only a few dedicated large-scale clinical trials have been conducted in patients with relapsed or refractory MZL. Thus, there is a high unmet need for novel therapies in r/r MZL.

Currently, the FDA approved only a few therapies for patients with previously treated MZL. The only FDA approved therapies for patients with MZL who have received at least 1 prior anti-CD20-based therapy are the Bruton tyrosine kinase inhibitors (BTKi), ibrutinib and zanubrutinib. Accelerated approval was granted based on a prospective, multicenter, open-label Phase 2 study with a median of 2 prior therapies. Efficacy was established based on the ORR of 46%, with a CR rate of 3.2% for ibrutinib and ORR of 56%, with a CR rate of 20% for zanubrutinib; duration of response (DOR) was not reached for either. Toxicity profile described for both agents is in line with other therapies (Barr 2017), and is associated with a low CR rate. To this end, effective modalities to further improve on these outcomes and to keep patients disease-free are warranted.

1.3. ACE1831

ACE1831 is an allogeneic gamma delta T (gdT) -cell therapy under investigation for the treatment of CD20-expressing B-cell malignancies.

ACE1831 consists of human allogeneic gdT-cells that are conjugated to rituximab (an anti-CD20 mAb), using short complementary strand DNA linkers. Using a novel selection and expansion technology, the gdT-cells are enriched to express high levels of natural killer (NK)-activating receptors, such as CD56 and NKG2D, and low levels of inhibitory receptors to enhance their potency. Gamma delta T-cells have characteristics of both the innate and adaptive immune systems that make them an ideal platform for the development of cell therapies. This cell type can directly recognize and attack cancerous cells as well as coordinate a broad antitumor immune response by recruiting other accessory cells to the sites of disease and activating other immune factors. Gamma delta T-cells do not recognize allogeneic major histocompatibility complex (MHC) restricted antigens nor do they secrete excessive amounts of IL-6 (Phalke 2015), a significant driver of cytokine release syndrome (CRS), providing a potential safety advantage over other cell therapies.

This first-in-human study will evaluate initial drug activity and safety of ACE1831 as monotherapy and in combination with obinutuzumab (GAZYVA®) in adults subjects with relapsed/refractory CD20-expressing B-cell malignancies.

1.3.1. Gamma Delta T-Cells

Gamma delta T- cells, alongside alpha beta T lymphocytes (αβ T-cells) and B Lymphocytes, form a critical and highly conserved triumvirate of the adaptive immune system. These cells act at the interface of the innate and adaptive immune systems, recognizing molecular patterns of dysregulation in stressed, pathogen infected or transformed cells and rapidly responding to maintain homeostasis. Gamma delta T-cells are capable of eradicating cancerous or infected cells and triggering a systemic response via the adaptive immune system, without harming healthy cells.

Gamma delta T-cells comprise a relatively small subset of T lymphocytes in the peripheral blood of adult individuals. While there is substantial interindividual variability, gdT-cells usually account for anywhere between 1 and 10% of CD3+ T-cells in human blood (Parker 1990).

In contrast to conventional T-cells bearing an αβ T-cell receptor (TCR) that recognizes antigen-derived peptides loaded onto MHC molecules (human leukocyte antigen [HLA] in humans), gdT-cells typically recognize their ligands independent of antigen processing and MHC/HLA restriction (Vantourout 2013). The dominant population of gdT-cells in the blood of healthy adults expresses a TCR composed of the variable (V) gene Vγ9 paired with Vδ2. Such Vγ9Vδ2T-cells (for simplicity referred to as Vδ2 in the following sections) account for anywhere from 50 to more than 95% of peripheral blood gdT-cells, with donor-dependent variability (Hinz 1997; Wesch 1998).

Gamma delta T-cells are considered to have their niche at the crossroad of innate and adaptive immunity (Kalyan 2013). They share features of the adaptive immune system, with their expression of clonally rearranged TCR genes, but at the same time are similar to innate immune cells, with the lack of need for antigen processing to activate their effector functions. Therefore, gdT-cells rapidly respond to TCR triggering. Moreover, gdT-cells frequently coexpress functional receptors of innate immune cells, such as activating NK receptors such as NKG2D, NKp30, and/or NKp44, which directly trigger cytotoxic activity (Groh 1999), in addition to certain Toll-like receptors (TLRs), which can provide costimulatory signals (Pietschmann 2009; Wesch 1998). Activated gdT-cells have the capacity to be potent killers that can lyse a broad variety of solid tumor and leukemia/lymphoma cells and produce an array of cytokines (Di Lorenzo 2019; Kabelitz 2012; Kunzmann 2005; Wrobel 2007).

Gamma delta T-cells can distinguish between safe and dangerous tissues, such as cancerous tissues, within the body by using a combination of mechanisms including activating natural killer receptors and binding of phosphorylated isoprenoid metabolites (Kabelitz 2020; Legut 2015).The complex and polyclonal binding abilities of gamma-delta TCR and NKG2D receptor allow them to broadly target diseased tissue and cover the heterogeneity of the tumor (O'Neill 2007; Vantourout 2013). Most solid tumors as well as leukemias express at least one of the eight known NKG2D ligands, and these ligands can interact with NKG2D and trigger cytotoxic function of gdT-cells independent of TCR signaling (Kabelitz 2020). Furthermore, the non-MHC priming property of gdT activation serves an important anti-tumor safeguard mechanism as tumor cells can evade immune surveillance through MHC shedding, heterogeneous antigens and low antigen spreading (Dhatchinamoorthy 2021; Park 2021).

In addition, gdT-cells broaden the immune response both through secretion of effector cytokines and chemokines (such as IFN-γ, TNF-α, and IL-17, etc) that recruit and stimulate immune cells at the tumor (Chien 2014; Karpala 2011). A safety concern of CAR-T therapies is that these engineered T-cells can release cytokines and induce a systemic inflammatory response named as CRS, in which interleukin 6 (IL-6) plays a key role and contributes to many aspects of pathophysiology of this undesirable clinical situation (Shimabukuro-Vornhagen 2018). Multiple clinical trials have demonstrated a reliable safety profile for gdT-cell-based therapies, without showing alarming records of CRS (J. Zhao 2018).

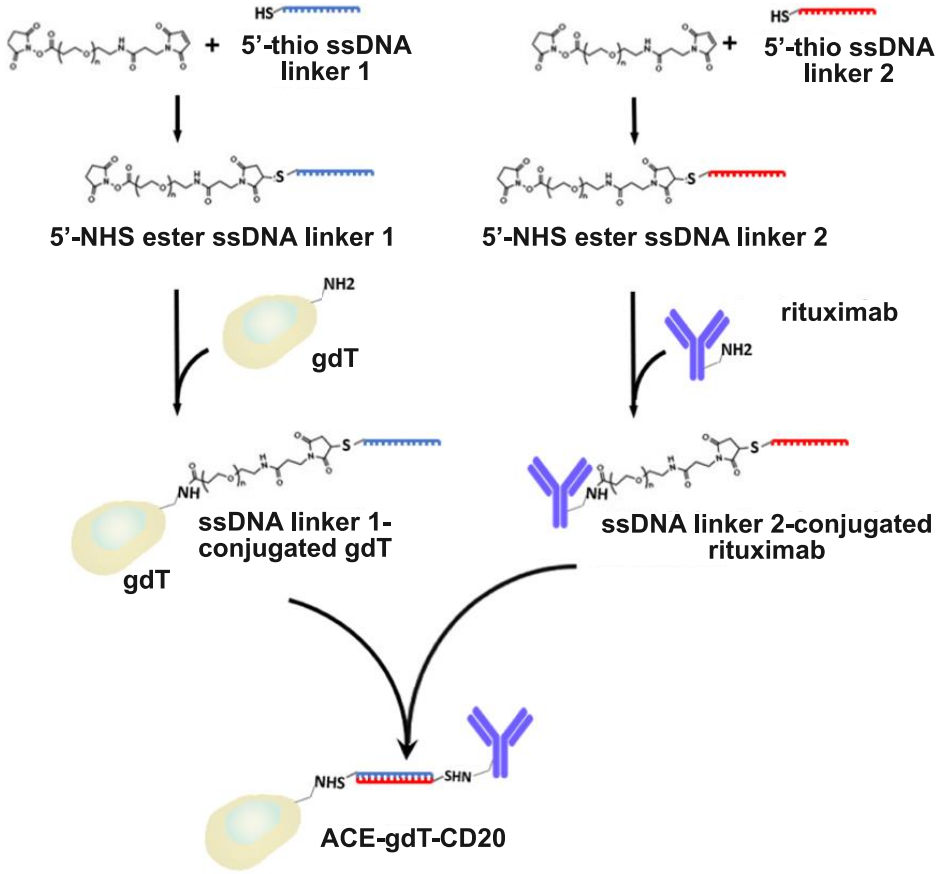
1.3.2. Rituximab Conjugation on gdT-cells Through Antibody-cell Conjugation (ACC) Platform

Other than widely used genetic engineering strategies in current cell therapy field, a biocompatible conjugation of gdT-cells with the anti-CD20 antibody rituximab (RITUXAN USPI 2019) through complementary paired single-stranded oligonucleotide linkers (ssDNA) is applied at physiological condition (Twite AA 2020).

The Antibody-cell Conjugation (ACC) strategy was applied to ACE1702 (Li 2021), which is a novel off- shelf NK cell therapy against HER2-expressing solid tumors and currently in Phase I of development (Piha-Paul 2021)(NCT04319757). The antibody and effector cells are covalently conjugated with complementary single strand DNA (ssDNA) separately and assembled through annealing of conjugated ssDNAs. The deprotected 5'-thio ssDNA linker 1 and linker 2 are activated to form the 5'-NHS ester ssDNA linker 1 and linker 2 respectively (Figure 1). The activated 5'NHS ester ssDNA linker 1 is conjugated with amino acid lysine residues in surface receptors of gdT-cells during incubation to generate the ssDNA linker 1-conjugated gdT-cells. The same reaction is also applied to generate ssDNA linker 2-conjugated rituximab. Through annealing of ssDNA linkers, ssDNA linker 1-conjugated gdT-cells and ssDNA linker 2-conjugated rituximab are linked to form the ACE-gdT-CD20 and the final product ACE1831 after cryopreservation.

Figure 1 illustrates the flow chart of rituximab conjugation with gdT-cells by ACC technology.

Figure 1: Flow Chart of Rituximab Conjugation With gdT-cells by ACC Technology



NOTES: Preparation of ssDNA linker 1-conjugated gdT-cells and ssDNA linker 2-conjugated trastuzumab is illustrated. Rituximab-conjugated gdT-cells, ACE-gdT-CD20, can be generated by co-incubation of ssDNA linker 1-conjugated gdT-cell and ssDNA linker 2-conjugated rituximab. The sequences of ssDNA linker 1 and 2 are complementary.

1.4. Summary of Relevant Nonclinical and Clinical Studies with ACE1831

Nonclinical studies show that ACE1831 can recognize and eliminate $CD20^+$ tumor cell lines in vitro and in vivo, providing proof-of-concept for use of ACE1831 in the treatment of patients with B-cell malignancies that express CD20.

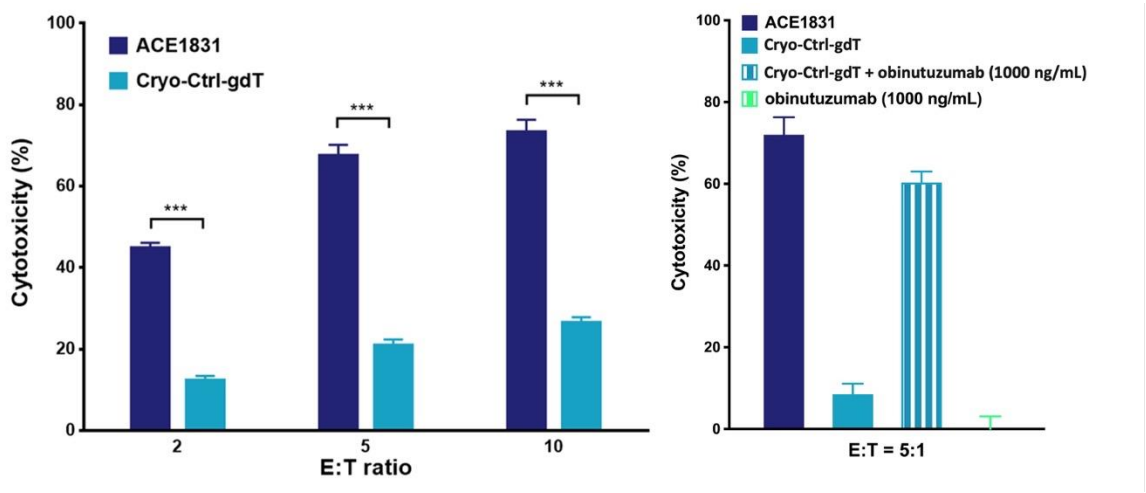
Refer to the current Investigator's Brochure (IB) for information on ACE1831 nonclinical studies.

1.4.1. Nonclinical Studies with ACE1831

In the in vitro studies, ACE1831 displayed strong cytotoxic activity against Raji cells compared to control gdT-cell (cryo-Ctrl-gdT) cells at effector to target (E:T) ratio of 2:1, 5:1 and 10:1 (Figure 2), suggesting cryopreservation did not compromise potency of ACE1831. ACE1831 also exhibited potency against CD20-expressing Daudi cells and elicited no off-target cytotoxicity against allogeneic peripheral blood mononuclear cells (PBMCs).

In addition, binding assay further supported the specificity of ACE1831 against CD20. In an in vitro combination study, the cytotoxicity of Cryo-Ctrl-gdT in the presence of anti-CD20 antibody obinutuzumab was significantly increased through ADCC (antibody-dependent cell-mediated cytotoxicity) against CD20-expressing cells, suggesting that the combination of ACE1831 with obinutuzumab may augment and persist the cytotoxic potency of ACE1831 by the ADCC-dependent manner (Figure 2).

Figure 2: ACE1831 vs Raji-luc Cells

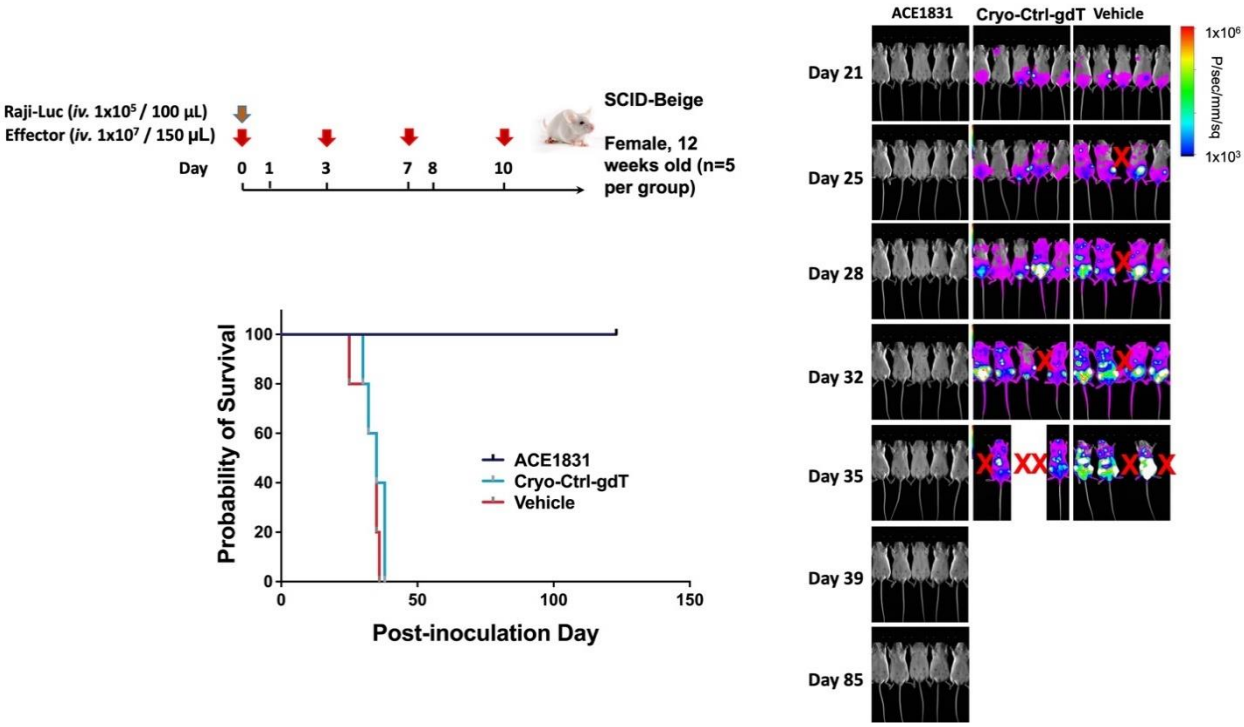


NOTES: (Left) Effector cells (E) ACE1831 and Cryo-Ctrl-gdT-cells were co-incubated with target-cells (T) Raji at E:T ratio of 2:1, 5:1 and 10:1 for four hours. (Right) Effector cells (E) ACE1831, Cryo-Ctrl-gdT in the absence and in the presence of 1,000 ng/mL of obinutuzumab were incubated with targeT-cells (T) Raji at E:T ratio of 5:1 for 4 hours. The cytotoxicity (%) of was analyzed by CellTiter(R) Glo luminescent-cell viability assay and presented as mean +/- SD.

In the toxicology study administering single dose of ACE1831 in SCID-Beige mice, there were no ACE1831 cells-related clinical signs or effects on body weight, food consumption, coagulation and gross necropsy findings. Compared to Cryo-Ctrl-gdT group animals, there were some differences in ACE1831 cells group animals. These included minimally decreased of reticulocyte (RETIRBC) in hematology, minimally increased of glucose (GLUC), alkaline phosphatase (ALP), and phosphorus (PHOS) and minimally decreased of triglyceride (TRIG) in clinical chemistry, minimally increased the ratio of brain/body weight in organ weights on Day 1. All the changes were not found or recovered on Day 14. In conclusion, all notable differences between Ctrl-gdT-cell group and ACE1831 treated animals on Day 1 were characterized by minimal change. These changes were considered non-adverse based on their small magnitude, absence of clinical correlation and the evidence of reversibility.

In the in vivo xenograft study using Raji xenograft SCID-Beige model, all mice treated with ACE1831 survived more than 120 days with complete tumor regression and no relevant signs of toxicities, while the mice with Ctrl-gdT-cell or vehicle only deceased by 38 days, suggesting the effectiveness and safety of ACE1831 in Raji SCID-Beige xenograft mouse model (Figure 3).

Figure 3: ACE1831 Against Raji in Animal Models



NOTES B cell lymphoma cell line Luciferase-expressing Raji cells (Raji-Luc) were engrafted in SCID-Beige mice on Day 0.
ACE1831 or Cryo-Ctrl-gdT cells were infused on Day 0, 3, 7 and 10.
n=5 mice per group.
The bioluminescence intensity of tumor burden and survival of mice were monitored.

1.4.2. Clinical Studies with ACE1831

ACE1831-001 is the first clinical study evaluating ACE1831 in humans.

1.5. Background on Obinutuzumab

Obinutuzumab (GAZYVA®) was initially approved by the FDA on November 16, 2017 and is currently approved:

1) In combination with chlorambucil, for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL),
2) In combination with bendamustine followed by GAZYVA® monotherapy, for the treatment of patients with FL who relapsed after, or are refractory to, a rituximab-containing regimen,
3) In combination with chemotherapy followed by GAZYVA® monotherapy in patients achieving at least a partial remission, for the treatment of adult patients with previously untreated stage II bulky, III or IV FL.

Obinutuzumab is a glycoengineered Type II anti-CD20 antibody. Compared with rituximab, obinutuzumab is characterized by more potent direct B-cell death induction and increased affinity for FcγRIII receptors expressed on NK cells, macrophages, and monocytes, resulting in enhanced antibody-dependent cellular cytotoxicity and antibody-dependent-cellular phagocytosis (Beers 2010; Herter 2014; Mossner 2010). Nonclinical xenograft experiments performed with obinutuzumab as monotherapy and in combination with chemotherapy have consistently showed that obinutuzumab has promising anti-tumor activity (Dalle 2011; Mossner 2010) and have demonstrated the superiority of obinutuzumab over rituximab. Together, these characteristics confer obinutuzumab with enhanced immune effector functions and B-cell-depleting activity compared with rituximab (Herter 2014).

Safety and efficacy of obinutuzumab monotherapy in patients previously treated with rituximab and a variety of different relapsed or refractory NHLs has been established in a variety of different relapsed or refractory NHLs (Freeman 2018; Tobinai 2017).

In addition, the GALLIUM trial (Marcus 2017) compared obinutuzumab combined with chemotherapy against rituximab plus chemotherapy in subjects with previously untreated iNHL and showed that progression-free survival was longer with obinutuzumab than with rituximab, but no significant difference was observed in the rate of response according to CT-based assessment. Overall survival was similar in the two groups. The trial was fully analyzed early after a planned interim analysis showed a significant 34% lower risk of progression, relapse, or death with obinutuzumab plus chemotherapy than with rituximab plus chemotherapy. Progression-free survival as assessed by an independent review committee and other time-to-event end points were consistent with this result. The rate of adverse events of Grade 3 to 5 and the rate of serious adverse events were higher in the obinutuzumab group than in the rituximab group, but the frequency of fatal adverse events was similar in the two groups. Clinically relevant infusion-related reactions of Grade 3 or higher occurred in 6.7% of patients who received obinutuzumab plus chemotherapy, which is similar to the rates reported in other studies involving patients with indolent lymphoma (Sehn 2015) and lower than the rates that have been reported in patients with chronic lymphoid leukemia and coexisting conditions (Goede 2014).

The GOYA trial was a randomized Phase 3 study that compared Gayzva (G)-CHOP with Rituximab (R)-CHOP in patients with previously untreated advanced-stage DLBCL. G-CHOP did not improve PFS compared with R-CHOP in patients with previously untreated DLBCL. After median observation of 29 months, the number of investigator-assessed PFS events was similar between G (201; 28.5%) and R (215; 30.2%), stratified hazard ratio was 0.92 (95% CI, 0.76 to 1.11; P = .39), and 3-year PFS rates were 70% and 67%, respectively. The incidence of grade 3 to 5 AEs, serious adverse events (SAEs), and treatment discontinuations as a result of AEs was slightly higher in the G-CHOP group than in the R-CHOP group. Analyses of AEs of particular interest showed that infections, neutropenia, IRRs, cardiac events, thrombocytopenia, and hemorrhagic events of any grade—as well as grade 3 to 5 AEs and SAEs—were more common with G-CHOP than R-CHOP (Goede 2014).

Important risks associated or potentially associated with obinutuzumab are infusion related reactions (IRR), tumor lysis syndrome (TLS), thrombocytopenia (including acute

thrombocytopenia), neutropenia (including prolonged and late-onset neutropenia), prolonged B-cell depletion, infections (including progressive multifocal leukoencephalopathy and hepatitis B virus [HBV] reactivation), worsening of preexisting cardiac conditions, gastrointestinal (GI) perforation, impaired immunization response immunogenicity, and secondary malignancies.

Detailed clinical information on obinutuzumab (GAZYVA®), is provided in the Gazyva package insert (GAZYVA USPI 2021).

1.6. Study Rationale

Cell therapies have emerged as one of the major breakthroughs in cancer immunotherapy in the last decade, particularly the use of autologous based chimeric antigen receptor (CAR) T and NK cell therapies. Outstanding results in hematological malignancies leading to multiple approvals (eg, BREYANZI®, YESCARTA®, KYMRIAH®, and ABECMA®) and encouraging pre-clinical anti-tumor activity against a wide range of solid tumors have made cell therapies one of the most promising fields for cancer therapies.

However, therapies based on autologous cells are endowed with limitations, mainly related to the fact that the product has to be generated from each patient's cells, in a time-consuming and costly process, and with the risk of manufacturing failure (J. Zhao 2018). Indeed, delay in treatment availability can be particularly problematic in patients with highly proliferative diseases (Depil 2020). In addition, the amount of functional autologous cells available in heavily pre-treated patients is often limited. For example, in the pivotal JULIET trial of CTL019, 18 subjects (12%) with r/r LBCL were not dosed due to occurrence of AEs or death during the manufacturing process and 9 subjects (6%) were not dosed because products could not be manufactured (Schuster 2017). In the ELIANA multicenter study of CTL019 for the treatment of pediatric patients with B-ALL, 7 of 92 enrolled subjects (7%) had product related issues during manufacturing and were not able to receive therapy (Maude 2018). In contrast, using cells obtained from healthy donors (allogeneic cells) provides more fully functional cells and allows generation of multiple “off-the-shelf” cell products (W. Zhao 2020).

Despite many desirable traits, allogeneic based cell therapies also come with challenges. Allogeneic cells might cause severe graft-versus-host disease (GvHD) and the host immune system might in turn induce allorejection, which will impede anti-tumor activity. Graft versus host disease occurs when donor cells (particular gdT-cells) activate and respond to HLA differences on recipient’s tissue; the responses depend on the disparity between the donor and the recipient with regard to HLA (Ferrara 2009). There are different ways to avoid GvHD when designing allogeneic CAR T or CAR NK cells, the most widely used strategy being the generation of TCR-deficient T-cells using genome editing tools such as Zinc finger nucleases (ZFN) (Provasi 2012), transcription activator-like effector nucleases (TALEN) (Poirot 2015) and CRISPR/Cas9 (Eyquem 2017). Gamma delta T-cells recognize their target-cells in an MHC/HLA-independent manner leading to low or absent risk for alloreactivity and GvHD, thus allowing the development of universal third-party allogeneic cell products for several malignancies (Minculescu 2015).

In addition to the potential reduced risk of GvHD, there are other favorable characteristics of gdT-cells, making them an appealing source for adoptive cell immunotherapy. Tumor

recognition and killing is not dependent on the expression of a single antigen. In contrast, they recognize a broad spectrum of antigens on various cancer cells through their diverse innate cytotoxicity receptors expressed on their cell membrane (Di Lorenzo 2019). This broad response reduces the chances of tumor immune escape by single antigen loss. In addition, this property provides opportunity for designing immunotherapies for tumors lacking well-defined neo-antigens and without the need of further genetic engineering. Furthermore, growing evidence indicates that gdT-cells interact with APCs (antigen-presenting cells) and other immune cells, while also playing the role of APCs by priming the antigens for αβ T-cells thereby enabling the orchestration of a cascade of immune responses against tumors (Capsomidis 2018). Furthermore, gdT-cells also do not secrete excessive amounts of IL-6 (Phalke 2015), a significant driver of CRS, which has been a fatal complication in CAR-T in acute leukemias and r/r NHL and may lead to a safer product for treating patients with specifically advanced cancers.

1.6.1. Rationale of ACE1831 in Combination with Obinutuzumab

Studies have shown that cytotoxicity of gdT-cells against target-cells can be significantly enhanced using specific monoclonal antibodies (mAbs) that induce ADCC. Antibody-dependent -cell-mediated cytotoxicity of gdT-cells is thought to depend on Fc-γ receptor III (CD16) (Couzi 2012). This mechanism can be exploited by combining mAb and gdT-cells in cancer therapy. Using tumor associated antigens (TAA)-specific Abs, gdT-cells can be directed to the tumor site.

Several lymphoma and B-cell lineage leukemia subtypes were studied using stimulated gdT-cells in combination with monoclonal anti-CD20 antibodies. Tokuyama et al. found rituximab to increase the killing of several lymphoma cell lines and to improve ADCC of gdT-cells against CLL and follicular lymphoma cells (Tokuyama 2008). One single clinical Phase 1/2a study used rituximab plus BrHPP and IL-2 for in vivo stimulation of gdT-cells in patients with relapsed follicular lymphoma. Altogether, 45 patients were treated and the treatment was generally well tolerated, with low grade pyrexia being the most common side effect and induced a 45% overall response rate (26% complete response) (Laurent G 2009). The newer anti-CD20 antibodies ofatumumab and obinutuzumab were also tested regarding the efficacy inducing ADCC in connection with gdT-cells (Braza 2011). Obinutuzumab is an Fc engineered type II monoclonal antibody and causes an increased secretion of perforin and IFN-γ compared to rituximab and ofatumumab (Mossner 2010). Highest ADCC activity against B-cell lymphoma cell lines and primary follicular lymphoma cells was found for obinutuzumab. Similar to anti-CD20 antibodies, Gertner-Dardenne found alemtuzumab, an anti-CD52 antibody, to increase gdT-cell dependent ADCC against lymphoma cell lines (Gertner-Dardenne 2009). Gamma delta T-cell mediated ADCC increases with higher numbers of CD16+ gdT-cells (Chen 2008) and the expression of CD16 is remarkably increased on ACE1831 cells compared to the CD16 expression status in freshly donor collected gdT-cells as a product of the selection and expansion protocol during the manufacturing process.

ACE1831 with or without obinutuzumab demonstrated anti-tumor activity both in vitro and in vivo, presenting promising treatment possibilities in a variety of CD20 expression malignancies. Pre-clinical studies of the pharmacology, toxicology, and pharmacokinetic profiles of ACE1831

support the initiation of Phase 1 clinical trials in in adult subjects with relapsed/refractory CD20-expressing B-cell malignancies.

1.7. Benefit/Risk Assessment for the Study

This is a first-in-human study and, therefore, there are no clinical data on the benefit/risk for humans. At this stage of development, the evaluation of benefit to patients is ongoing and the overall preliminary safety data from nonclinical studies does not show any unexpected or significant safety findings. Details of nonclinical findings are provided in the ACE1831 IB.

Clinical experiences with target directed allogeneic gdT-cells is limited and anticipated risks for ACE1831 are potentially expected to be similar to other adoptive cell therapy approaches such as anti-CD19 and anti-BCMA CAR T-cell products, namely BREYANZI® (lisocabtagene maraleucel), YESCARTA® (axicabtagene ciloleucel), KYMRIAH® (tisagenlecleucel), and ABECMA® (idecabtagene vicleucel). The risks of these anti-CD19 and anti-BCMA CAR T-cell products include CRS and neurologic events, two important identified risks that are not commonly encountered in general oncology practice. These events have an early onset, generally within 1 week after the therapy, and are manageable. Additional important identified risks include cytopenias, infection, hypogammaglobulinemia, autoimmune disorders, immunogenicity, and TLS. Since ACE1831 consists of human allogeneic gdT-cells, other important potential risks of ACE1831 include GvHD. Strategies similar to other autologous and allogeneic cell therapy approaches have been developed to monitor for and manage the potential risks associated with ACE1831 and are included in ACE1831 IB.

The eligibility criteria described in Section 4 of this protocol ensure that patients who may likely benefit from ACE1831 treatment with a lesser risk of side effects are included in the study. In addition, all subjects will be monitored frequently for signs and symptoms of the potential risks noted above. Further, this first in human Phase 1 clinical study will employ a dose escalation strategy, starting at a low cell dose and increasing the cell dose by approximately 2-fold between treatment groups, and will include staggered enrollment of subjects during this dose escalation part of the study to allow for observations of acute and subacute toxicities. In addition, a Safety Review Committee (SRC) will review the safety data and make recommendations to the sponsor on study conduct and progression of the study.

In summary, the treatment of patients with relapsed/refractory CD20-expressing B cell malignancies remains challenging and there is a significant unmet need for better and more accessible therapies in these patient populations. Because these patients are likely resistant to chemotherapy and/or chemoimmunotherapy, they may benefit from therapies with different mechanisms of action. Immunotherapy, which is based on the enhancement of a disease-targeted immune response against the cancer, is a promising approach to treating many cancer types.

Study ACE1831-001 will evaluate the use of ACE1831, an allogeneic CD20 targeting gamma delta T-cell therapy, alone and in combination with obinutuzumab (GAZYVA®) for the treatment of adult subjects with relapsed/ refractory CD20-expressing B-cell malignancies and the study design is expected to allow for an appropriate assessment of the benefits of ACE1831 while maintaining an acceptable safety profile.

1.8. Compliance

Study ACE1831-001 will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory and local legal requirements.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary:

- To evaluate the safety and tolerability of ACE1831 as monotherapy or in combination with obinutuzumab (GAZYVA®) in subjects with relapsed/refractory B-cell lymphomas
- To determine the recommended Phase 2 dose (RP2D) for further investigation

Secondary:

- To assess the pharmacokinetics of ACE1831
- To evaluate the immunogenicity of ACE1831
- To evaluate the efficacy of ACE1831 as monotherapy or in combination with obinutuzumab in subjects with relapsed/refractory B-cell lymphomas

Exploratory:

- To evaluate the pharmacodynamics of ACE1831 based on induction of cytokines and other biomarkers in the blood of subjects before and after infusion of ACE1831

2.2. Endpoints

Study endpoints for both phases of the study are provided in Table 1.

Table 1: Study Endpoints

Primary	
Objective	**Endpoints**
To evaluate the safety and tolerability of ACE1831 as monotherapy or in combination with obinutuzumab (GAZYVA®) in subjects with relapsed/refractory B-cell lymphomas	• Change from baseline in physical examination results, clinical laboratory tests, urinalysis, vital signs and ECGs • Change from baseline in ECOG status • Incidence of AEs, DLTs, AESIs, and SAEs
To determine the recommended Phase 2 dose (RP2D) for further investigation	MTD
Secondary	
To assess the pharmacokinetics of ACE1831	Persistence of ACE1831 after administration
To evaluate the immunogenicity of ACE1831	Measure of anti-ACE1831 antibodies after administration
To evaluate the efficacy of ACE1831, as monotherapy or in combination with obinutuzumab in subjects with relapsed/refractory B-cell lymphomas	Objective response of each patient's underlying lymphoma, duration of response, and progression-free survival all based on the revised IWG Response Criteria for Malignant Lymphoma (Cheson BD 2014)
Exploratory	
To evaluate the pharmacodynamics of ACE1831 based on induction of cytokines and other biomarkers in the blood of subjects before and after infusion of ACE1831	Serum levels of interferon-γ, TNF-α, IL-2, IL-6, IL-8 and IL-10, as well as other potential biomarkers, by treatment group, dose level, overall, and by time

Abbreviations: IWG=International Working Group; ORR=objective response rate; RP2D=recommended phase 2 dose.

3. STUDY DESIGN

This is an open-label, multicenter, Phase 1 study designed to evaluate the safety, tolerability, and efficacy of a single dose of ACE1831 (anti-CD20 conjugated allogeneic gamma delta T cells) with or without obinutuzumab in subjects with relapsed/refractory CD20-expressing B-cell lymphomas.

Subjects will be enrolled in 2 treatment groups in this study:

- 3 dose levels of ACE1831 as monotherapy will be investigated (Treatment Group A)
- 2 dose levels of ACE1831 in combination with obinutuzumab will be investigated (Treatment Group B)

3.1. Dose Escalation

Up to 42 subjects will be enrolled in this study in 2 stages of dose escalation.

In the first stage of the dose-escalation (Treatment Group A), up to 3 different dose levels of a single dose of ACE1831 will be explored after a lymphodepletion regimen and will follow a 3+3 dose escalation design. The maximum tolerated dose (MTD)/maximum administered dose (MAD) for Treatment Group A will be defined as the highest dose level at which <33% (ie, 0 of 3 or 1 of 6) of subjects in a treatment group experience a dose-limiting toxicity (DLT) as outlined below.

In the second stage of the dose-escalation (Treatment Group B), ACE1831 will be administered in combination with obinutuzumab at up to 2 dose levels. A single dose of ACE1831 will be administered on Day 1; obinutuzumab will be administered on Days -5 and -4 as part of the lymphodepletion regimen, and on Days 3 and 11 after ACE1831 infusion. This phase of the study will also follow a 3+3 dose escalation design. The MTD/MAD for Treatment Group B will be defined as the highest dose level at which <33% (ie, 0 of 3 or 1 of 6) of subjects at a dose level experience a dose-limiting toxicity (DLT) as outlined below. Dose levels evaluated in Phase 1 are shown in Table 2.

Table 2 Dose Levels –Dose Escalation

Dose Level	Dose (cells)
3 [a]	1000×10^6 cells
2	600×10^6 cells
1 (Starting Dose)	300×10^6 cells
-1	100×10^6 cells

a Dose level 3 only: subject must have a minimum weight of 55 kg or 120 lbs.

The respective dose levels for monotherapy (Treatment Group A) and combination treatment (Treatment Group B) at the MTD/MAD may be expanded to a total of 12 subjects to further characterize toxicity, ACE1831 persistence, and pharmacodynamics and to gain preliminary evidence of efficacy. Depending on findings in the expanded MTD/MAD dose level, lower dose levels may also be expanded to up to 12 subjects, to further characterize toxicity.

A staggered enrollment approach will be implemented for the first 3 subjects at each dose level in both treatment groups.

Since acute and clinically significant adoptive cell therapy toxicities (eg, CRS, neurotoxicity, GvHD) usually manifest up to 2 weeks after cell infusion, the first 3 subjects at each dose level and treatment group will be enrolled with a staggered enrollment of 3 weeks from the day of ACE1831 infusion between subjects to observe subjects for unknown potential toxicities.

The ACE1831-001 Safety Review Committee (SRC) (Section 3.3.1) will review safety data after 3 and/or 6 (if applicable) subjects have enrolled in each treatment group and have had the opportunity to be followed for at least 28 days after infusion of ACE1831. The SRC will make recommendations related to dose escalation based on the incidence of DLTs and the overall safety profile of ACE1831 as outlined in Table 3.

Table 3 Subject Dose Initiation Recommendations Based on DLTs

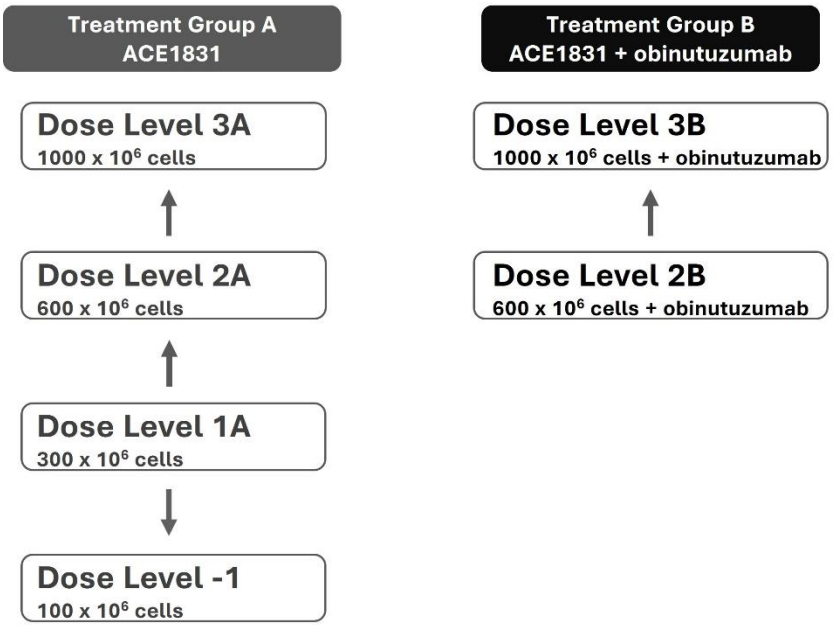
Number of Subjects with a DLT in a Treatment group	Potential Recommendation
0 of 3 subjects or 1 of 6 subjects	Dose determined to be tolerable, enroll into next higher dose for the treatment group. If this is the highest dose level, then this will be the MTD.
1 of 3 subjects	Enroll 3 more subjects at the same dose level.
2 of 3 subjects or 2 of 6 subjects	Next lower dose level will be established as the MTD.

Abbreviations: DLT=dose limiting toxicity; MTD=maximum tolerated dose.

After completing enrollment the totality of the monotherapy and combination data will be used to identify the RP2D (either as monotherapy or in combination with obinutuzumab).

The study design is shown in Figure 4.

Figure 4: Study Design – Phase 1 Dose Escalation



3.2. Dose-limiting Toxicity Criteria

DLTs are defined as select adverse events (AEs) that are related to treatment with ACE1831 (see below). The DLT period is 28 days and starts with the dose of ACE1831 (Day 1).

The following AEs will be considered DLTs if deemed related to ACE1831:

- CRS Grade 4 of any duration (Lee 2019)
- CRS Grade 3 event that does not resolve to Grade ≤2 within 72 hours, with or without treatment (Lee 2019)
- Grade 4 infusion reaction of any duration
- Grade 3 infusion reaction lasting for more than 2 hours
- Any Grade ≥2 neurotoxicity (ICANS) that does not resolve to Grade ≤1 within 72 hours with or without treatment (Lee 2019)
- Any Grade 3 cardiac or pulmonary toxicities that do not improve to Grade 2 or lower within 72 hours
- Any related AE requiring intubation
- Grade 4 neutropenia lasting longer than 14 days from the day of ACE1831 infusion
- Grade 4 thrombocytopenia that fails to recover to Grade ≤2 lasting longer than 14 days from the day of ACE1831 infusion
- Grade ≥3 acute GvHD (Harris 2016)

- Grade ≥3 autoimmune toxicities, particularly those affecting vital organs (eg, gastrointestinal tract, lung, heart, thyroid, kidneys, liver) occurring within 4 weeks of the ACE1831 infusion
- Grade 3 infection not improving to Grade 2 or lower within 2 weeks of onset
- Grade 4 laboratory abnormalities in the presence of clinical signs or symptoms
- Any dose holds >21 days for an ACE1831-related AE
- All other related grade 3 non-hematologic toxicities lasting more than 7 days
- Any Grade 5 event, except for death due to progressive disease, will be considered a DLT

The following will NOT be considered DLTs:

- Immediate hypersensitivity reactions occurring within 2 hours of ACE1831 cell infusion (related to cell infusion) that are reversible to a Grade ≤2 within 24 hours of cell administration with standard therapy.
- Grade ≥3 fever
- Grade 4 TLS lasting <7 days (Cairo 2004)
- Grade 4 anemia, leukopenia, or lymphopenia
- Grade 3 or 4 hypogammaglobulinemia
- Grade 3 fatigue lasting <7 days

3.3. Safety Oversight

3.3.1. Safety Review Committee

An SRC will be established prior to the enrollment of the first subject. The SRC will be composed of Principal Investigators and the Sponsor's Medical Monitor. Other members of the research team, including the study statistician, safety physician, as well as various ad hoc members may join the SRC meetings but will not have voting privileges. The SRC will regularly assess the safety and efficacy of ACE1831 administration throughout the trial. Determination of dose level escalations and opening of study treatment groups will be based on recommendations from the SRC. Following the completion of enrollment at each dose level within a treatment group (3 subjects if no DLTs are observed, or 6 subjects if a DLT is observed in the first 3 subjects), the SRC will meet to all available data for that dose level. The SRC will then decide if enrollment to the next higher dose is permitted, if a dose level should be expanded to provide additional subject observations, or if further dose escalation should cease, and a lower dose further explored. The highest dose level of ACE1831 deemed by the SRC to be safe in each treatment group will be expanded to 12 subjects. If that dose level did not previously contain 6 subjects, the SRC will meet after 6 subjects have been enrolled, and will again decide if enrollment may continue, or if modifications to the protocol (exploring a lower dose or holding enrollment) are required. The SRC may also recommend temporary suspension of enrollment pending further data evaluation at any time.

The SRC will also be consulted if a toxicity stopping boundary is met.

Further details regarding the constitution of the SRC and its specific roles and responsibilities and timing of reviews will be provided in the SRC charter.

3.3.2. Toxicity Stopping Boundaries

In addition to the DLT assessment to guide dose escalation or de-escalation, toxicity stopping boundaries will be implemented to ensure subject safety throughout the study. These stopping bounds are defined in Section 10.3.5.3. Enrollment will be paused if a toxicity boundary is met. The SRC will review all available data and make a recommendation as to whether enrollment in the study should resume as planned or be modified prior to additional enrollment.

3.4. Rationale for Study Design Elements

Refer to the current IB for detailed information on ACE1831 nonclinical studies and Section 1.4.1.

3.4.1. Rationale for Administration of ACE1831

The starting dose is conservatively planned based on a well-established safety profile when targeting CD20-positive hematological malignancies and due to the absence of appropriate animal models to perform preclinical safety studies. Further, increasing the cell doses by 2-fold for each successive treatment group will provide adequate margins of safety for subjects enrolled in this study.

3.4.2. Rationale for Lymphodepleting Chemotherapy

Before administration of ACE1831, subjects will receive a lymphodepleting regimen consisting of cyclophosphamide and fludarabine in order to induce lymphocyte depletion and create an optimal environment for expansion of ACE1831 in vivo. Subjects will initiate lymphodepleting chemotherapy with cyclophosphamide and fludarabine beginning on Day −5 through Day −3 (refer to Section 5.1).

Increasing levels of lymphodepleting chemotherapy have been shown to correlate with clinical response to adoptive cellular therapy (Dudley 2008). Specifically, there appears to be a link between adequate lymphodepletion and adoptively transferred cell expansion and function in nonclinical models. The depth and duration of the lymphodepletion in nonclinical models correlate with antitumor activity of the adoptively transferred tumor-specific CD8+ T-cells (Gattinoni 2005). Lymphodepletion may function by eradicating cytokine sinks for the transferred cells, eliminating T regulatory cells, or enhancing antigen presenting cell activation (Klebanoff 2005). Cyclophosphamide and fludarabine are an effective lymphodepleting regimen.

Cyclophosphamide is a nitrogen mustard-derivative alkylating agent that also possesses potent immunosuppressive activity. Fludarabine phosphate is a synthetic purine antagonist antimetabolite.

Administration of cyclophosphamide (500 mg/m^2) and fludarabine (30 mg/m^2) for 3 consecutive days has been studied and tolerated in subjects with B-cell malignancies. This regimen has been evaluated at the National Cancer Institute (NCI) and is one of the most commonly used regimens utilized in adoptive cell therapy studies in B-cell malignancies. Allogeneic based gamma delta T-cells studies have not been well studied at this time and to reduce site effects and the depth/duration of cytopenias the sponsor decided to utilize a less intensive schedule of cyclophosphamide (300 mg/m^2) and fludarabine (30 mg/m^2) for 3 consecutive days.

3.5. Duration of Subject Participation

The total time of participation for each subject (from the time of the signing of informed consent through the last study visit) will be approximately 25 months, this includes approximately a 4-week screening period, a 1-week lymphodepletion regimen, a 1-month treatment period, and an 23-month post-treatment follow-up period.

4. SUBJECT POPULATION

4.1. Inclusion Criteria

To be eligible for this study, all of the following inclusion criteria must apply:

1. Signed informed consent.
2. Males or Females ≥18 years of age at the time of informed consent
3. A minimum weight of 55 kg (120 lbs.) is required at Dose level 3 (1000×10^6 cells)
4. Histologically confirmed, CD20-positive B-cell NHL including the following types defined by World Health Organization (WHO) 2016 (Swerdlow 2016):
    - Diffuse large B cell lymphoma not otherwise specified
    - High-grade B cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements
    - Transformation of follicular lymphoma or marginal zone lymphoma to DLBCL
    - Primary mediastinal B cell lymphoma
    - Follicular lymphoma Grade 3B
5. Subjects must have persistent or progressive B-cell lymphoma after having received at least 2 prior systemic therapies per NCCN guidelines (NCCN 2022). Prior therapies must include at a minimum, an anthracycline and an anti-CD20 monoclonal-containing chemoimmunotherapy regimen.
6. At least 1 measurable lesion according to the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma (Cheson BD 2014). Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy.
    - If the only measurable disease is lymph-node disease, at least 1 lymph node should be ≥2 cm.
7. Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1
8. Adequate hematologic function independent of platelet transfusion and growth factor support for at least 14 days prior to the planned start of lymphodepletion, defined as:
    - Platelet count >50,000 cells/mm^3 (50×10^9/L).
    - Absolute neutrophil count ≥1000 cells/mm^3 (1.0×10^9/L)
9. Adequate renal, hepatic, and cardiac function defined as:
    - Creatinine clearance >60 mL/minute measured using the Cockcroft-Gault equation (see Appendix 6), or an estimated glomerular filtration rate (eGFR) >60 mL/minute/1.73 m^2 per 4 variable Modification of Diet in Renal Disease (MDRD) equation
    - Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤3.0 × upper limit of normal (ULN) of the institution's normal range

- Total bilirubin ≤2.5 × ULN of the institution's normal range, except in subjects with Gilbert's syndrome
- Albumin ≥3.5 g/dL
- Left ventricular ejection fraction (LVEF) ≥50% and no evidence of pericardial effusion as determined by an echocardiogram (ECHO)/multigated acquisition (MUGA) scan

10. Oxygen saturation via pulse oxygenation ≥92% at rest on room air
11. Women of childbearing potential and all male participants must agree to use at least 1 highly effective method of contraception (<1% failure rate) to avoid pregnancy during screening, for the duration of the study treatment, and 1 year after receiving lymphodepleting chemotherapy. Highly effective methods are defined as those that result in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The following are examples of highly effective methods of contraception including:
    - Intrauterine device (IUD), hormonal (birth control pill, injections, implants), tubal ligation, and partner's vasectomy.
    - Males who are not sexually abstinent and have partners of childbearing potential must agree to a condom during sexual contact with a pregnant female or a female of childbearing potential for at least 1 year after lymphodepleting chemotherapy even if he has undergone a successful vasectomy.

4.2. Exclusion Criteria

Subjects are not eligible if any of the following apply:

1. Prior treatment with a genetically modified cell therapy product targeting CD20
2. Autologous stem cell transplant within 6 weeks of informed consent
3. History of allogeneic stem cell transplantation
4. History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products (eg, rituximab or obinutuzumab)
5. Subjects with cardiac atrial or cardiac ventricular lymphoma involvement
6. Subjects with detectable CSF malignant cells, or brain metastases, or with a history of central nervous system (CNS) lymphoma or primary CNS lymphoma
7. History or presence of a clinically relevant CNS disorder such as seizure disorder (eg, epilepsy), cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, cerebral edema, posterior reversible encephalopathy syndrome (PRES), or any autoimmune disease with CNS involvement
8. History of other malignancies, except:
    - Malignancy treated with curative intent and with no known active disease present for ≥2 years before the first dose of study drug and felt to be at low risk for recurrence by the treating physician.

- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
- Adequately treated carcinoma in situ without evidence of disease

9. Clinically significant active infection currently receiving IV antibiotics or have received IV antibiotics within 7 days prior to planned start of lymphodepletion. Exceptions to this exclusion criteria are simple urinary tract infection or bacterial pharyngitis, or subjects on prophylactic antibiotics, antivirals, or antifungals.
10. Human immunodeficiency virus (HIV) infection, based on laboratory testing performed during the screening period
11. Active HBV or Hepatitis C virus (HCV) infection, based on laboratory testing performed during screening period. HBV-infected subjects are considered eligible if their viral load is below the institutional limit of quantification (LOQ) and the subject is on stable viral suppressive therapy. HCV-infected subjects are considered eligible if they have completed curative antiviral treatment and their HCV RNA viral load is below the institutional LOQ
12. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or class III or IV congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months initial screening
13. Patients with heart rate-corrected QT interval (QTcF) prolongation >470 msec at screening will be excluded from the study unless secondary to stable conduction disorders (eg, left bundle-branch block)
14. Requirement for urgent therapy due to tumor mass effects such as bowel obstruction or blood vessel compression
15. Primary immunodeficiency disorder
16. Unresolved toxicities from prior anticancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Events (CTCAE, version 5.0), Grade ≤1 or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia, vitiligo, and laboratory test values that meet inclusion criteria
17. Concurrent systemic immunosuppressant therapy (eg, cyclosporine A, tacrolimus, etc., or chronic administration of >5 mg/day of prednisone) within 28 days of the start of the planned lymphodepletion regimen (exceptions to this exclusion criteria are topical and inhaled corticosteroids in standard doses and physiologic replacement for subjects with adrenal insufficiency)
18. Any systemic anticancer therapy (chemotherapy or targeted small molecule) within 2 weeks or 5 half-lives of the drug (whichever is longer) prior to the planned start of lymphodepletion regimen; or any investigational cellular therapy within 8 weeks prior to the planned start of lymphodepletion. If the half-life of a drug is not known, then the washout period will be 4 weeks
19. Live vaccine ≤6 weeks prior to initial screening

20. Pregnant or lactating females and subjects of both genders who are not willing to practice birth control from the time of consent through 1 year after the completion of the lymphodepletion regimen
21. Any medical, psychological, familial, or sociological conditions that, in the opinion of the Investigator or Sponsor Medical Monitor, would impair the ability of the subject to receive study treatment or comply with study requirements, including understanding and rendering of informed consent
22. Severe disease progression or health deterioration within 2 weeks prior to lymphodepletion regimen that, in the opinion of the Investigator, could impair the ability of the subject to receive study treatment or comply with study requirements

5. STUDY TREATMENTS

5.1. Lymphodepleting Regimen

The Investigational Product (ACE1831) must be available at the site before initiation of lymphodepleting regimen.

Before administration of ACE1831 on Day 1, subjects will receive a lymphodepleting regimen on Day -5 through Day -3 consisting of: cyclophosphamide and fludarabine. The schedule of administration may be adjusted, if necessary, but the lymphodepleting regimen must be completed between 2 and 7 days before ACE1831 administration.

The lymphodepleting chemotherapy regimen will consist of

- Cyclophosphamide 300 mg/m2 IV over approximately 60 minutes on Day −5, Day −4, and Day −3; and
- Fludarabine 30 mg/m^2 IV over approximately 30 minutes on Day −5, Day −4, and Day −3.

Subjects will receive the following 3-day chemotherapy regimen per the order identified below:

1. Cyclophosphamide 300 mg/m^2/day IV over approximately 60 minutes on Day −5, Day −4, and Day −3
2. Fludarabine 30 mg/m^2/day IV over approximately 30 minutes on Day −5, Day −4, and Day−3
3. (Optional) Mesna (sodium 2-mercaptoethanesulfonate; a detoxifying agent used to inhibit the hemorrhagic cystitis induced by chemotherapy) and antiemetics should be administered per institutional guidelines

The lymphodepleting regimen will be supplied by the investigative site unless otherwise noted. Refer to the current product label for guidance on packaging, storage, preparation, administration, and toxicity management associated with the administration of chemotherapy agents.

Delay of the lymphodepleting regimen by more than 14 days requires discussion with the Sponsor's Medical Monitor and may require rescreening.

For Treatment Group B only

The lymphodepleting regimen on Day –5 and Day –4 should be administered approximately 30 minutes following the obinutuzumab infusion (Section 5.3).

5.1.1. Requirements for Initiating Lymphodepletion Regimen

Administration of ACE1831 cells to subjects with ongoing infection or inflammation, even if asymptomatic, may increase the risk of severe and fatal toxicities. All efforts should be made to rule out such conditions before the start of both lymphodepleting chemotherapy and ACE1831 infusion (Section 5.1.1 and Section 5.2.2).

All of the following criteria must be met within the last 24 hours leading up to the initiation of the lymphodepleting regimen, the initiation of the lymphodepleting chemotherapy must be held until the event resolves before the initiation of lymphodepleting chemotherapy.

- no evidence of an active fever (≥38.0°C),
- no clinically significant active infection, and
- no clinical or laboratory clinical signs of decompensation or severe health deterioration within the last 24 hours leading up to the initiation of the lymphodepleting regimen.

For subjects that experience a fever, ACE1831 may only commence if 24 hours elapse after the fever resolves (<38.0°C).

5.2. Investigational Product ACE1831

The ACE1831 investigational drug product is provided frozen in a formulation containing DMSO for IV administration. Additional details of product formulation, packaging, labeling, storage, tracking, accountability, preparation, administration, disposal and destruction are provided in the ACE1831 Cell Therapy Manual.

5.2.1. Dosage and Administration

ACE1831 will be administered as an IV infusion at the dose level to which the subject is assigned. The infusion should be administered through a dedicated line in an environment in which full resuscitation facilities are immediately available. The list of planned ACE1831 dose levels to be investigated is provided in Section 3.1.

5.2.2. Requirement for ACE1831 Infusion

ACE1831 will be administered IV on Day 1 at least 48 hours (but no more than 7 days) after the subject has completed the lymphodepletion regimen. Within the last 24 hours leading up to ACE1831 administration, subjects must meet ACE1831 treatment criteria and have:

- no evidence of an active fever (≥38.0°C),
- no clinically significant active infection, and
- no clinical or laboratory clinical signs of decompensation or severe health deterioration within the last 24 hours leading up to ACE1831 administration.

Should an event exceed these criteria immediately prior to receiving ACE1831, the ACE1831 infusion must be held until the event resolves. For subjects who experience a fever, ACE1831 may only commence if 24 hours elapse after the fever resolves (<38.0°C).

5.2.3. ACE1831 Pre-medications

All subjects will receive the following pre-medications approximately 30 to 60 minutes prior to ACE1831 infusion:

- Acetaminophen 500 to 1,000 mg given orally or equivalent

and/or

- Diphenhydramine 12.5 to 25 mg IV or 25 mg given orally or equivalent

5.2.4. Monitoring During and After ACE1831 Infusion

Subjects must be continuously monitored during each IV administration of ACE1831. Vital signs (temperature, respiratory rate, heart rate, blood pressure, and oxygen saturation [SaO_2] by pulse oximetry) will be measured within 15 (± 5) minutes prior to and after the ACE1831 IV administration, and then every 15 (± 5) minutes thereafter for the first hour, and hourly (within a ±15-minute window) for the next 3 hours. If the subject's vital signs are not stable 4 hours following the IV administration, vital signs should be monitored as clinically indicated until stable. Assessments performed on the day of administration are described in Appendix 1.

5.3. Obinutuzumab

5.3.1. Dosage and Administration

Obinutuzumab will be administered by IV infusion at an absolute (flat) dose of 100 mg on Day –5 and of 900 mg on Day –4. On Days –5 and –4, obinutuzumab will be administered prior to administration of the lymphodepletion regimen. Two additional infusions of obinutuzumab 1000 mg will occur on Days 3 and 11 post ACE1831 IV infusion.

5.3.2. Pre-medication

Pre-medication with a corticosteroid (prednisone or prednisolone are preferred for this study due to shorter half-lives compared to dexamethasone or methylprednisolone), analgesic/antipyretic, and antihistamine, as outlined in Table 4, is recommended to reduce the incidence and severity of IRRs. Please refer to the Full Prescribing Information for Gazyva® (obinutuzuamb injection) for additional information regarding premedication for obinutuzumab. Reference to institutional guidelines for the use of pre-medications prior to the administration of obinutuzumab is also recommended.

Table 4 Suggested Pre-medication Prior to Obinutuzumab Administration

Timepoint	Patients Requiring Pre-medication	Pre-medication	Administration
Day –5 and Day –4	All patients	corticosteroid [a]	Administer ≥1 hour prior to obinutuzumab infusion
	All patients	Analgesic/anti-pyretic [b] Antihistamine drug [c]	Administer ≥30 minutes prior to obinutuzumab infusion
	Patients at risk for TLS (eg, because of bulky diseaseor renal impairment (creatinine clearance <70 mL/min)	Allopurinol or suitable alternative such as rasburicase, along with adequate hydration	Administer prior to obinutuzumab infusion
Day 3 and Day 11	Patients with Grade 1 or 2 IRR or no IRR during the previous infusion	Analgesic/anti-pyretic [b] Antihistamine drug [c]	Administer at least 30 minutes prior to Obinutuzumab infusion
	Patients with Grade 3 IRR, wheezing, urticaria, or other symptoms of anaphylaxis during the previous infusion Patients with bulky disease	Intravenous glucocorticoid: 20 mg dexamethasone or 80 mg methylprednisolon [a]	Administer <1 hour prior to obinutuzumab infusion
		Analgesic/anti-pyretic [b] Antihistamine drug [c]	Administer <30 minutes prior to obinutuzumab infusion
	Patients still at risk for TLS	Allopurinol or suitable alternative such as rasburicase, along with adequate hydration	Administer prior to obinutuzumab infusion

Abbreviations: IRR = infusion-related reaction; TLS = tumor lysis syndrome.

a. Treat with 100 mg of prednisone or prednisolone (as an alternative: 20 mg of dexamethasone, or 80 mg of methylprednisolone may be administered). See Section 5.7, Prohibited Medications, for more details. Hydrocortisone should not be used because it has not been effective in reducing rates of IRR.
b. For example, 1000 mg of acetaminophen/paracetamol.
c. For example, 50 mg of diphenhydramine.

5.3.2.1. Infusion Rate

Obinutuzumab should be administered as an IV infusion through a dedicated line in an environment in which full resuscitation facilities are immediately available. Obinutuzumab infusions will be administered per as outlined in Table 5.

Do not administer as an intravenous push or bolus.

No dose modification for obinutuzumab is allowed.

Vital signs will be obtained at 15, 30, and 60 minutes (±5 minutes prior to obinutuzumab administration or after the completion of the obinutuzumab infusion for each timepoint).

Table 5 Obinutuzumab Infusion Rate

Treatment Days	Dose of Obinutuzumab	Rate of infusion
Day –5	100 mg	Administer at 50 mg/hour. In the absence of IRR, the rate of the infusion can be escalated to 100 mg/hour for the remaining infusion.
Day –4	900 mg	If no infusion-related reaction occurred during the previous infusion and the final infusion rate was 100 mg/hour, infusions can be started at a rate of 100 mg/hour and increased by 100 mg/hour increments every 30 minutes to a maximum of 400 mg/hour. If an infusion-related reaction occurred during the previous infusion, administer at 50 mg/hour. The rate of infusion can be escalated in increments of 50 mg/hour every 30 minutes to a maximum rate of 400 mg/hour
Day 3	1,000 mg	If no infusion-related reaction or an infusion-related reaction of Grade 1 occurred during the previous infusion and the final infusion rate was 100 mg/hour or faster, infusions can be started at a rate of 100 mg/hour and increased by 100 mg/hour increments every 30 minutes to a maximum of 400 mg/hour. If an infusion-related reaction of Grade 2 or higher occurred during the previous infusion, administer at 50 mg/hour. The rate of infusion can be escalated in increments of 50 mg/hour every 30 minutes to a maximum of 400 mg/hour.
Day 11	1,000 mg	

5.4. Concomitant Medications

During the study, investigators may prescribe any concomitant medications deemed necessary to provide adequate supportive care or to treat concomitant medical conditions except those medications listed in Section 5.7.

All medications taken by the subject will be recorded from informed consent until 30 days after the last dose of ACE1831 or obinutuzumab (whatever comes later). Thereafter, until the end of study visit, only concomitant medications used at the time of ACE1831 or obinutuzumab related AEs will be recorded.

Subjects should be discouraged from use of illicit drugs, herbal remedies, self-prescribed drugs, tobacco products, or excessive alcohol at any time during the clinical study.

5.5. COVID-19 Vaccination

Multiple studies have revealed that patients with cancer have an increased risk of complications and mortality from COVID-19, including 30-day mortality of 30% in hospitalized patients with COVID-19 and cancer compared with 21% in those without cancer. Therefore, the Sponsor recommends that all subjects considered for participation in the study should be fully vaccinated prior to enrollment (Desai 2021).

The last dose of the planned COVID-19 vaccination should be completed for at least 7 days prior to initiating the lymphodepletion regimen and all potential vaccine-related AEs have improved to Grade ≤1 for at least 72 hours prior to the initiation of lymphodepletion.

COVID-19 testing should be performed according to local institutional policy.

5.6. Concomitant Medication Collection During Hospitalization

For subjects requiring hospitalization during the study, a targeted concomitant medication collection approach will be utilized for the case report form (CRF). Therefore, the following medications should NOT be entered on the Concomitant Medication CRF during inpatient and Intensive Care Unit (ICU) stays:

- IV fluids
- Heparin flushes
- Stool softeners
- Pneumocystis pneumonia (PCP) prophylaxis
- Vitamins, minerals, health supplements
- Saline
- Lotions

Enter the following treatments on the Concomitant Medications CRF during inpatient and ICU stays:

- Vasopressor – enter the maximum infusion rate/day
- Antibiotics
- Oxygen – enter the maximum fraction of inspired oxygen (FiO_2)/day

5.7. Prohibited Medications

The following medications are prohibited during the treatment and follow-up periods:

- Corticosteroid therapy at a pharmacologic dose (≥10 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for at least 5 days before ACE1831 administration unless used as an anticancer agent after progression of lymphoma. The use of topical, inhalational, ophthalmic or intra-otic corticosteroids is permitted.

  Exceptions

  – Treatment Group B (combination with obinutuzumab): Premedication with 100 mg of prednisone or prednisolone on Day -5 and -4 during the Lymphodepletion regimen is recommended to reduce frequency and severity of potential infusion-related reactions (IRR). Subjects with a Grade 3 IRR on the first or second infusion should also receive intravenous glucocorticoid: 20 mg dexamethasone or 80 mg methylprednisolone on Day 3 and Day 11 following the ACE1831

administration. Prednisone or prednisolone are recommended over dexamethasone or methylprednisolone due to a short half-life time.

- Physiologic replacement dosing of steroids (≤10 mg/m^2/day prednisone or equivalent [≤30mg/m^2/day hydrocortisone or ≤0.45 mg/m^2/day dexamethasone]) is allowed. The use of topical, inhalational, ophthalmic or intra-otic corticosteroids is permitted as well as administration of intrathecal steroids for CNS relapse prophylaxis.
- Corticosteroids and other immunosuppressive drugs should also be avoided for 2 months following ACE1831 administration unless used to manage ACE1831-related toxicities or discussed with the Sponsor Medical Monitor. Other medications that might interfere with the evaluation of ACE1831, such as nonsteroidal anti-inflammatory agents, should also be avoided for the same period unless medically necessary.

- GvHD therapies (eg, calcineurin inhibitors, methotrexate or other chemotherapeutics, mycophenolyate, rapamycin, thalidomide, immunosuppressive antibodies such as anti-TNF, anti IL6, or anti-IL6R), unless needed for treatment of newly developed acute or chronic GvHD following ACE1831 administration.
- Treatments for underlying disease, such as chemotherapy, immunotherapy, targeted agents, radiation, and high-dose corticosteroids (other than those defined/allowed in this protocol) and other investigational agents are prohibited, except as needed for treatment of disease progression following ACE1831 administration.
- Therapeutic doses of systemic anticoagulants, such as unfractionated heparin and low-molecular weight heparin, as well as warfarin, should be avoided whenever possible for subjects who are at risk of bleeding due to thrombocytopenia. The use of heparin flush to maintain the patency of central indwelling venous catheters is permitted.

If permissibility of a specific medication/treatment is in question, contact the Sponsor Medical Monitor.

6. STUDY PROCEDURES

6.1. Clinical Procedures

6.1.1. Demographic and Safety Assessments

The clinical procedures to be conducted during this study related to the evaluation of population demographics and safety are provided in Table 6. Clinical laboratory assessments are to be performed at time points detailed in the Schedule of Evaluations (SOE). The time windows for each type of assessment are detailed in Section 7.

Table 6: Study Procedures: Demographic and Safety Assessments

Evaluation	Description
Demographics	• Age • Sex • HLA typing[b] • Race/ethnicity • Reproductive status
Medical History	• Clinically significant medical condition and/or surgeries • Cancer history to include: • Date of initial diagnosis • Histology • Most recent biopsy • Tumor type • Disease grade at diagnosis • Known mutations • Prior anticancer treatment to include: systemic therapies, radiation, and surgical procedures
Pregnancy Test [a]	Urine or blood test for choriogonadotropin beta, as indicated for women of childbearing potential. A blood test will be performed at Screening and urine tests will be performed per the SOE (Appendix 1).
Physical Examination	Complete physical examination to include: • Height (screening only • Cardiovascular • Respiratory • Weight • Dermatological • Gastrointestinal • Head, eyes, ears, nose and throat • Musculoskeletal • Routine neurological exam • Peripheral neuropathy Symptom directed examination as per the Investigator's discretion
Cardiac Function	• ECG • ECHO/MUGA
Vital Signs	• Blood pressure (systolic and diastolic) • Body temperature • Respiratory rate • SaO_2 by Pulse oximetry • Heart rate
Hematology [a]	• CBC with differential
Clinical Chemistry [a]	• Albumin • Blood urea nitrogen • Potassium • Alkaline phosphatase • Calcium • Protein (total) • Alanine aminotransferase • Chloride • Sodium • Aspartate aminotransferase • Creatinine • Uric acid

Evaluation	Description
	• Bilirubin (total) • C-reactive protein • Phosphorus • Lactate dehydrogenase • Magnesium • Bicarbonate • Ferritin • Glucose
Coagulation [a]	• Activated partial thromboplastin time • International normalized ratio
Virus Testing	• HIV-1 and HIV-2[a] • Hepatitis panel (Hepatitis B core Ab, Hepatitis B sAg, Hepatitis C Ab)[a] • HHV-6 [b] • HHV-7 [b]
Thyroid Function [a]	• Free T_3 • Free T_4 • Thyroid-stimulation hormone
Urinalysis	• Ketones • pH • Microscopic examination (if dipstick determinations are 2+ or greater) • Protein • Specific gravity • Glucose & Blood (dipstick)

Abbreviations: Ab=antibody; CBC=complete blood count; ECG=electrocardiogram; ECHO=echocardiogram; HHV=human herpesvirus; HLA=human leukocyte antigen; MUGA=multigated acquisition scan.

a. Performed by a local lab.
b. Performed by a central lab.

6.1.2. Physical Examination

The physical examination must include at a minimum a routine neurological, cardiovascular, pulmonary, abdominal, and extremity examination. In addition, symptom-directed exams should be performed as appropriate.

The routine neurological exam should include an evaluation of the cranial nerves, motor and sensory skills, coordination, and balance, as well as mental status examination.

6.1.3. Vital Signs

Vital signs including temperature, respiratory rate, heart rate, blood pressure, and SaO_2 by pulse oximetry.

6.1.4. ECG

The date and time of the electrocardiogram (ECG) and the following parameters will be collected and assessed: PR, QRS, QT, and QTcF interval, and heart rate. Subjects should be resting and in a supine position for 12-lead ECG recording. Reference the SOEs (Appendix 1) and study procedures for collection timepoints. Additional ECGs may be performed if clinically indicated. Any abnormality observed during screening should be documented in the Medical History eCRF. Any ECG changes post-screening determined as clinically significant by the Investigator should be recorded as AEs on the AE eCRF.

6.1.5. ECHO/MUGA

Echocardiogram (ECHO) or multigated acquisition scan (MUGA), which includes an assessment of LVEF, should be completed during Screening and if clinically indicated during the study period. Any abnormal ECHO/MUGA assessments determined as clinically significant by the Investigator should be documented in the Medical History/Adverse Events eCRF.

An ECHO/MUGA scan completed within 8 weeks prior to initial Screening may be used for screening rather than repeating the assessment.

Subjects must have left ventricular ejection fraction (LVEF) ≥50% and no evidence of pericardial effusion as determined by an ECHO/MUGA scan during screening to be eligible for the study.

6.1.6. ECOG Performance Status

The ECOG performance status is a scale used to assess how a patient's disease is progressing and assess how the disease affects the daily living abilities of the patient (Oken 1982). The ECOG grading scale is shown in Table 7. ECOG Performance Status will be collected at the timepoints outlined in the SOE (Appendix 1).

Table 7: ECOG Performance Status Grading

Grade	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry outwork of a light or sedentary nature (eg, light house work or office work)
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

6.1.7. HHV-6 and HHV-7

A screening sample from each subject will be submitted to the central laboratory for the assessment of HHV-6 and HHV-7 by quantitative polymerase chain reaction (qPCR), and additional samples will be collected on Day 15 and 29. If a Grade 3 or higher neurologic event emerges, additional samples should be collected at first onset and upon resolution of the event to test for HHV-6 and HHV-7 by qPCR, and/or viral genotyping.

6.1.8. HLA typing

A screening sample is collected from each subject for HLA typing. A minimum of five (5) loci (A, B, C, DRB1, DQB1) will be determined using a Next Generation Sequencing platform. Output sequences are assembled for each sample and HLA types are determined for each locus by allele-assignment software with trained and certified histocompatibility experts.

6.2. Radiographic Assessments

Disease assessments will be performed according to the schedule presented in the SOE (Appendix 1) for all subjects.

6.2.1. Positron Emission Tomography/Computed Tomography scans

For all positron emission imaging (PET)-computed tomography scans:

- The computed tomography (CT) must be of diagnostic quality with IV-iodinated contrast, performed by either of the following modalities, depending on the site's capability:
  - as part of a combined PET-diagnostic CT; or
  - as a separate diagnostic quality CT (with IV-iodinated contrast)
- The PET-diagnostic CT scan must include the neck, chest, abdomen, and pelvis, along with the appropriate imaging of all other sites of disease

- If IV-iodinated contrast is contraindicated per the Investigator, then the diagnostic CT can use non-iodinated contrast. If non-iodinated contrast is not available or not recommended by the Investigator, then the diagnostic CT can be nonenhanced

Screening/Baseline:
To confirm eligibility and/or to establish a baseline, PET-diagnostic CT scans of the neck, chest, abdomen, and pelvis, along with the appropriate imaging of all other sites of disease, are required at screening.

PET-diagnostic CT scans should be performed as close to enrollment as possible:

- A PET-diagnostic CT scan performed after the subject's last line of therapy and before signing the ICF may be used for confirmation of eligibility if within 28 days before initiation of the lymphodepleting regimen and no other anticancer treatment has been administered.
- If a PET-diagnostic CT scan is performed >28 days before the initiation of the lymphodepleting regimen or if the subject receives any anticancer therapy with therapeutic intent (eg, radiation, supraphysiologic doses of steroids, chemotherapy) between the last PET-diagnostic CT scan and the initiation of lymphodepleting chemotherapy, the PET-diagnostic CT scan must be repeated before lymphodepleting regimen to establish a new baseline.

Disease Assessment:
The PET-diagnostic CT scans will be performed at the time points outlined in the SOE (Appendix 1) through Month 12 or until disease progression, whichever comes first. A PET-diagnostic CT scan can be performed at any time disease progression is suspected even if this requires an unscheduled visit.

An MRI of the head should be completed prior to study enrollment if CNS involvement is suspected per Investigator judgment. Additional MRI of the head may be performed post-baseline if clinically indicated per local institutional guidelines.

Additional radiographic assessment should be completed at Day 29 and thereafter at Months 3, 6, 9, and 12 or per Investigator judgment.

Other additional radiographic assessments deemed necessary to assess suspected area(s) of disease should be performed at the discretion of the Sponsor and according to the local standard of care.

All known sites of disease should be documented in the subject eCRF.

Tumor burden will be evaluated by the Investigator using the revised IWG Response Criteria for Malignant Lymphoma (Cheson BD 2014) to assess scans to evaluate disease status.

6.2.2. Bone Marrow Aspirate/Biopsy

Refer to Appendix 2 for treatment response assessment requirements per the IWG Response Criteria for Malignant Lymphoma (Cheson BD 2014). If bone marrow aspirate and biopsies are collected, they will be analyzed by the local laboratory.

Screening/Baseline:
For fluorodeoxyglucose (FDG)-avid lymphoma, a subject's bone marrow involvement must be assessed by PET-diagnostic CT (Section 6.2.1) or bone marrow aspirate and biopsy at screening. For non-FDG-avid lymphoma, a subject's bone marrow involvement should be assessed by bone marrow aspirate and biopsy at screening.

Disease/Response Assessment:
If there is evidence of baseline bone marrow involvement, if PET-diagnostic CT is not available, if the lymphoma is not FDG avid, or if there are unexplained cytopenias or suspicion of bone marrow involvement, a bone marrow aspirate and biopsy will be performed in subjects who are being assessed for CR in order to confirm CR (Cheson BD 2014).

To confirm a CR, 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 (IHC).

Subjects with Unexplained Cytopenias or Suspicion of Hemophagocytic Lymphohistiocytosis
A bone marrow aspirate and biopsy should be considered for any subject with unexplained or prolonged (>30 days after ACE1831 infusion) cytopenias Grade ≥3 or where there is suspicion of hemophagocytic lymphohistiocytosis (HLH). The samples will be reviewed at the local laboratory.

6.3. ACE1831 Pharmacokinetic Assessments

Blood samples will be drawn according to the schedule presented in the SOE (Appendix 1).

The genomic DNA of PBMCs will be extracted and will be analyzed by qPCR/ddPCR-based assay. Gamma delta T-cell markers (CD3 and TCRVδ2) will be monitored by flow cytometry analysis. ACE1831 assessments will include but are not limited to monitoring of ACE1831 persistence in blood over time to understand ACE1831 behavior in patients.

6.4. Pharmacodynamic Assessments

Blood samples for pharmacodynamic assessments will be drawn according to the schedule presented in the SOE (Appendix 1).

Pharmacodynamic assessments will include monitoring levels of key analytes in blood over time. Key analytes can include, but are not limited to, the following:

- Interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), interleukin (IL)-2, IL-6, IL-8, and IL-10
- B-cell, T-cell and NK cell subset monitoring will be analyzed by flow cytometry analysis.

6.5. Immunogenicity

Anti-drug Antibody (ADA): Anti-ACE1831 antibody assay will be based on the recognition of ADA using fluorescence-conjugated anti-human Fc antibody by flow cytometry-based analysis.

6.6. Biomarkers of Disease

Blood samples for tumor marker assessments will be drawn according to the schedule presented in the SOE (Appendix 1).

Tumor marker assessments will include, but are not limited to, the following:

Tumor markers: CD19, CD20, CD22, CD79b and loss-of-function of CD58

6.7. Exploratory Assessments

For subjects who provide consent, remaining samples will be banked for future exploratory assessments. Exploratory assessments may include nucleic acids, proteins, and lipids. Samples may also be used to develop new diagnostic test therapies, research methods or technologies.

6.8. Sample Storage

Subject tumor (including bone marrow) or blood samples, as well as any derivatives from these samples, may be stored for 10 years from last subject dosed with ACE1831 to address exploratory research questions related to the treatment or disease under study.

Each subject will have the right to have their sample material destroyed at any time by contacting the Investigator who in turn can contact the sponsor. The Investigator should provide the sponsor the study and subject ID number so that the sample can be located and destroyed. For subjects who withdraw consent, any samples that were not requested to be returned or destroyed will remain with the sponsor and any data that may be generated will be entered in the study database.

6.9. Instructions for Follow-up and Data to be Collected for Subjects Withdrawn from Treatment/Study

If withdrawal of consent occurs (defined in Section 8.2), the Investigator is to discuss with the subject appropriate procedures for withdrawal from the study. If a subject withdraws consent, subject data collected up to withdrawal of consent will be retained and included in the analysis of the study, and where permitted by local regulations, publicly available data (eg, death records) can be included after withdrawal of consent.

As part of the study, sites may be asked to conduct searches of public records such as those establishing survival status (eg, for subjects lost to follow-up), per the applicable local laws if available, to obtain survival data for any subject for whom the survival status is not known. Sites may be also asked to retrieve autopsy reports to confirm status of disease at the time of death, if possible, per the local laws.

7. STUDY VISIT SCHEDULE

7.1. Screening

The following evaluations will be conducted at the Screening visit (may be performed up to 4 weeks following informed consent):

- Informed consent
- Eligibility criteria review — Refer to Section 4
- Medical, surgical, cancer history — Refer to Section 6.1.1
- Demography — Refer to Section 6.1.1
- PET/diagnostic CT — Refer to Section 6.2.1
- Bone marrow aspirate/biopsy — Refer to Section 6.2.2
- Physical examination — Refer to Section 6.1.2
- Vital signs — Refer to Section 6.1.3
- 12-lead ECG — Refer to Section 6.1.4
- ECHO/MUGA — Refer to Section 6.1.5
- ECOG Performance Status — Refer to Section 6.1.6
- Hematology — Refer to Section 6.1.1
- Serum chemistry — Refer to Section 6.1.1
- Coagulation panel — Refer to Section 6.1.1
- Urinalysis — Refer to Section 6.1.1
- Serum Pregnancy test — Refer to Section 6.1.1
- Thyroid function — Refer to Section 6.1.1
- COVID-19 testing — Refer to Section 5.5
- Viral testing (HIV, HBV, HCV serology) — Refer to Section 6.1.1
- HHV-6 and HHV-7 — Refer to Section 6.1.7
- HLA typing — Refer to Section 6.1.8
- Prior/concomitant medications — Refer to Section 5.4
- Adverse events — Refer to Section 9

7.2. Lymphodepletion Regimen Visits

The evaluations in Table 8 will be conducted during lymphodepletion regimen on Days -5, -4, and -3.

Table 8 Lymphodepletion Evaluations

	Day –5 Before initiation of lymphodepletion regimen	Day -4	Day -3
Re-confirm eligibility	X [a]		
Physical examination	X	X	X
Vital signs	X	X	X
Hematology	X		
Serum chemistry	X		
Urinalysis	X		
Urine pregnancy test	X		
Anti-drug antibodies	X		
B-, T-, and NK cells	X		
Cytokines	X		
Biomarkers	X		
ACE1831 persistency	X		
Lymphodepleting regimen	X	X	X
Obinutuzumab infusion [b] (Treatment Group B only)	X	X	

Abbreviations: NK=natural killer cells;
a. Refer to Section 5.1.1
b. On Days –5 and –4, obinutuzumab will be administered prior to administration of the lymphodepletion regimen.

7.3. Treatment Visits

7.3.1. Study Day 1

The ACE1831 infusion will occur on Day 1. Evaluations must be conducted for all subjects pre- and/or post-dose as shown in Table 9. Additional post-ACE1831 evaluations may be conducted at the discretion of the Investigator. Subject eligibility will be re-confirmed within 24 hours prior to the ACE1831 infusion.

Table 9 Study Day 1 Evaluations

Evaluation	Pre-ACE1831 infusion	Post-ACE1831 infusion
Re-confirm eligibility [a]	X	
Hematology	X	
Serum chemistry	X	
Urinalysis	X	
Physical examination	X	
Urine pregnancy test (WOCBP only)	X	
Vital signs	X	X
ECOG performance status	X	
B-, T-, and NK cells	X	
Cytokines	X	X
ACE1831 persistency	X	X
Concomitant medications	X	X
Adverse events	X	X

Abbreviations: ECOG=Eastern Cooperative Oncology Group; NK=natural killer; WOCBP=women of childbearing potential.
[a] Refer to Section 5.2.2

7.3.2. Study Day 3

The following evaluations will be conducted on Day 3 (± 1day) for all subjects.

- Physical examination
- Vital signs
- Hematology
- Serum chemistry
- Cytokines
- ACE1831 persistency
- Concomitant medications
- Adverse events

Treatment Group B: The evaluations in Table 10 will be conducted on Day 3 (± 1 day) for subjects who receive an obinutuzumab infusion on Day 3:

Table 10 Study Day 3 Evaluations (Treatment Group B)

Evaluations	Pre-obinutuzumab Infusion	Post-obinutuzumab Infusion
Physical examination	X	
Vital signs	X	X [a]
Hematology	X	
Serum chemistry	X	
Cytokines	X	
ACE1831 persistency	X	
Concomitant medications	X	X
Adverse events	X	X

a. Vital signs will be obtained 15, 30, 60 minutes (±5 minutes) after the completion of the obinutuzumab infusion.

7.3.3. Study Day 5

The following evaluations will be conducted for all subjects on Day 5 (± 1 day):

- Physical examination
- Vital signs
- Hematology
- Serum chemistry
- B-, T-, and NK cells
- Cytokines
- ACE1831 persistency
- Concomitant medications
- Adverse events

7.3.4. Study Day 8

The following evaluations will be conducted for all subjects on Day 8 (± 1 day)

- Physical examination
- Vital signs
- Hematology
- Serum chemistry
- Cytokines
- Biomarkers
- ACE1831 persistency
- ECOG performance status
- Concomitant medications
- Adverse events

7.3.5. Study Day 11

The following evaluations will be conducted on Day 11 (± 1 day) for subjects in **Phase 1**.

- Physical examination
- Vital signs
- Hematology
- Serum chemistry
- B-, T-, and NK cells
- Cytokines
- ACE1831 persistency
- ECOG performance status
- Concomitant medications
- Adverse events

Treatment Group B: The evaluations in Table 11 will be conducted on Day 11 (± 1 day) for subjects who receive an obinutuzumab infusion on Day 11.

Table 11 Study Day 11 Evaluations (Treatment Group B)

Evaluation	Pre-obinutuzumab infusion	Post-obinutuzumab infusion
Physical examination	X	
Vital signs	X	X [a]
Hematology	X	
Serum chemistry	X	
B-, T-, and NK cells	X	
Cytokines	X	
ACE1831 persistency	X	
ECOG performance status	X	
Concomitant medications	X	X
Adverse events	X	X

Abbreviations: ECOG=Eastern Cooperative Oncology Group; NK=natural killer.

a. Vital signs will be obtained 15, 30, 60 minutes (±5 minutes) after the completion of the obinutuzumab infusion.

7.3.6. Study Days 15 and 22

The following evaluations will be conducted for all subjects on Days 15 and 22 (± 2 days):

- Physical examination
- Vital signs
- Hematology
- Serum chemistry
- B-, T-, and NK cells (Study Day 15 only)
- Cytokines
- HHV-6 and HHV-7 (Study Day 15 only)
- ACE1831 persistency
- ECOG performance status
- Concomitant medications
- Adverse events

7.3.7. Study Day 29 (End of Treatment)

The following evaluations will be conducted for all subjects on Day 29 (± 2 days):

- Physical examination
- Vital signs
- 12-lead ECG
- Hematology
- Serum chemistry
- Urinalysis
- Coagulation panel
- PET/diagnostic CT
- B-, T-, and NK cells
- HHV-6 and HHV-7
- Cytokines
- Anti-drug antibodies
- Biomarkers
- ACE1831 persistency
- ECOG performance status
- Concomitant medications
- Adverse events

7.3.8. Follow-up (Months 3, 6, 9, 12)

The following evaluations will be conducted for all subjects at Months 3, 6, 9, and 12 (±14 days):

- Bone marrow aspirate/biopsy
- Serum chemistry
- Vital signs
- Hematology
- ECOG Performance Status
- Subsequent anticancer therapy for NHL
- Biomarkers (Months 3, 6, and 12)
- Adverse events
- Concomitant medications
- Physical Examination

7.3.9. Follow-up (Months 18 and 24)

The following evaluations will be conducted for all subjects at Months 18 and 24 (± 14 days):

- Adverse events
- Subsequent anticancer therapy for NHL
- Concomitant medications

7.3.10. Unscheduled Visits

If the Investigator feels that a subject needs to be evaluated at a time other than the protocol-specified visit, the subject may be asked to come into the clinic for an unscheduled evaluation.

8. SUBJECT COMPLETION AND WITHDRAWAL

8.1. End-of-Study Definition

A subject is considered to have completed the study if he/she has completed the last scheduled visit shown in the SOE (Appendix 1), has not been lost to follow up, or has not withdrawn consent before the end of the study.

8.2. Subject Withdrawal

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution. However, subjects will be encouraged to continue all study evaluations through the End of Study visit. Acepodia Biotech, Inc. must be notified if a subject is withdrawn from the study, and the reason(s) for withdrawal must be documented.

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

Withdrawal of consent from 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. The Investigator is to discuss with the subject appropriate procedures for withdrawal from the study (Section 8.3).

The Investigator and/or sponsor can also decide to withdraw a subject from the investigational product (IP) and/or other protocol-required therapies, protocol procedures, or the study as a whole, or at any time before study completion.

Every effort should be made to obtain information on subjects who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, subjects will not be followed for any reason after consent has been withdrawn. If a patient withdraws consent, this request must be documented in the source documents and signed by the investigator. Study personnel may use a public information source (eg, county records) to obtain information about survival status.

8.3. Reasons for Removal from Study

Reasons for removal of a subject from the study are as follows:

- Subject did not receive ACE1831
- Lost to follow-up
- Other
- Withdrawal by subject
- Death
- Progression (clinical or objective)

Subjects who have been screened but do not receive lymphodepleting chemotherapy or ACE1831 will be withdrawn and replaced.

The Sponsor reserves the right to discontinue the study or suspend the study either at a particular site or at all study sites at any time. Reasons for discontinuation may include but are not limited to: a request to discontinue the study from a regulatory/health authority, inability to continue to supply study treatment, business conditions that make further development of

ACE1831 no longer feasible, inadequate enrollment, issues with GCP at a site(s). If such action is taken, the Sponsor will discuss this with the Investigator at each study site and notify the Investigator in writing. If the study is terminated for safety reasons, all Investigators and the relevant regulatory agencies will be immediately notified of the action, as well as the reason. The Investigator at each study site will inform the IRB overseeing the study at his/her site.

8.4. Reasons for Removal from Treatment

Reasons for removal from protocol-required IP treatment or procedures include any of the following:

- Adverse Event (AE)
- Subject becomes pregnant
- Lost to follow-up
- Other (eg, noncompliance)
- Withdrawal by subject
- Death
- Termination of study by Sponsor or IRB
- Disease progression

8.5. Replacement of Subjects

Subjects who discontinue prior to completion of the DLT assessment period for reasons other than a DLT may be replaced.

9. ADVERSE EVENTS

9.1. Definitions of Adverse Events and Serious Adverse Events

9.1.1. Adverse Events

An AE is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The Investigator is responsible for ensuring that any AEs observed by the Investigator or reported by the subject are recorded in the subject's medical record.

The definition of AEs includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition has increased in severity, frequency, and/or duration or has an association with a worse outcome. When recording such events, descriptions that the pre-existing condition has changed (eg, more frequent headaches for a subject with pre-existing headaches or increased blood pressure in a subject with pre-existing hypertension) must be provided.

An AE does not include the following:

- A pre-existing condition that has not worsened during the study or involves an intervention (such as elective cosmetic surgery or a medical procedure) while on study is not considered an AE. Interventions for pretreatment conditions (such as elective cosmetic surgery) or medical procedures that were planned before study participation are not considered AEs.
- Hospitalization for study treatment infusions or study-mandated procedures, for elective procedures, for respite care, or hospitalization as a precautionary measure per institutional policy are not considered AEs (refer also to Section 9.5).
- The term "disease progression" as assessed by measurement of malignant lesions on radiographs or other methods is not considered to be an AE. Worsening of signs and symptoms of the malignancy under study are considered to be AEs.

Refer to Section 9.6.2 for information and instructions for recording and reporting AEs. Refer to Section 9.6.5 for information and instructions for recording and reporting AEs due to disease progression.

9.1.2. Serious Adverse Events

An SAE is defined as an AE that meets at least one of the following serious criteria:

- Results in death
- Is life-threatening (ie, an event that places the subject at immediate risk of death; it does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of planned hospitalization (refer to Section 9.5 for definition of prolongation of planned hospitalization for this study)
    - An AE would meet the criterion of "requires hospitalization" if the event necessitated an admission to a healthcare facility

  - Events that require an escalation of care when the subject is already hospitalized should be recorded as an SAE. Examples of such events include movement from routine care in the hospital to the intensive care unit or if that event resulted in a prolongation of the planned hospitalization
  - Refer to Section 9.5 for hospitalizations that are not considered to be SAEs
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a medically important serious event as determined by the Investigator. If an Investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as an SAE with the criterion of "other medically important serious event."

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE according to the CTCAE; the event itself may be of relatively minor medical significance and, therefore, may not meet the seriousness criteria. Severity and seriousness need to be independently assessed for each AE recorded in the eCRF.

Progression of the malignancy during the study is not considered to be an SAE; signs and symptoms of disease progression can be considered to be SAEs (and documented as being due to disease progression).

Refer to Section 9.6.3 for information and instructions for recording and reporting SAEs. Refer to Section 9.6.5 for information and instructions for recording and reporting SAEs due to disease progression.

9.1.3. Adverse Events of Special Interest

The current AESI events are based on limited experience from an ongoing Acepodia cell therapy study without an accurate assessment of causality and reported events from other cell-based therapies (such as CAR-T). The sponsor may continuously update the AESI criteria throughout the study based on data collected throughout the study.

- Cytokine Release Syndrome (CRS)
- Neurotoxicity due to immune effector cell-associated neurotoxicity syndrome
- Macrophage activation syndrome (MAS) as defined in Appendix 7, Table 25
- Acute and chronic GvHD
- Autoimmune manifestations (gastrointestinal [GI], pulmonary, thyroiditis, other)
- Tumor lysis syndrome (TLS)
- Grade 3 cytopenia that persists through the first 28 days post- ACE1831 treatment
- Severe (grade 3) infection through the first 28 days post- ACE1831 treatment

Refer to Sections 9.6.2 and 9.6.3 for information and instructions for recording and reporting AESIs, respectively.

9.2. Clinical Laboratory and Vital Sign Abnormalities

9.2.1. Abnormal Clinical Laboratory Findings

The Investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) are not to be recorded as AEs. However, abnormal laboratory findings that result in new or worsening clinical sequelae or that require therapy or adjustment in current therapy, are considered AEs. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.

An abnormal laboratory test result must be reported as an AE if it is a change from baseline and meets any of the following criteria:

- Is associated with clinical signs and/or symptoms
- Requires medical or surgical intervention (eg, potassium supplementation for hypokalemia or iron replacement therapy for anemia) or a change in concomitant therapy
- Is clinically significant in the Investigator's judgment

Whenever possible, the clinical diagnosis, rather than the laboratory result, should be reported by the Investigator (eg, anemia versus low hematocrit).

Clinically significant abnormal laboratory values occurring during the study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant

9.2.2. Abnormal Vital Sign Values

Not all vital sign abnormalities qualify as an AE. A vital sign result must be reported as an AE if it is a change from baseline and meets any of the following criteria:

- Is accompanied by clinical signs and/or symptoms
- Requires medical or surgical intervention or a change in concomitant therapy
- Is clinically significant in the Investigator's judgment

It is the Investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding if an isolated vital sign abnormality should be classified as an AE. However, if a clinically significant vital sign abnormality is a sign of a disease or syndrome (eg, high blood pressure), only the diagnosis (ie, hypertension) should be recorded in the eCRF.

9.3. Assessments of Adverse Event and Serious Adverse Event Severity and Causality

The Investigator or delegated sub-investigator is responsible for assessing AEs and SAEs for causality and severity and for final review and confirmation of accuracy of event information and assessments.

The severity of AEs will be graded according to the NCI CTCAE version (v)5.0, with the exception of the adverse events noted below. A copy of the grading scale can be downloaded from the Cancer Therapy Evaluation Program home page (http://ctep.cancer.gov).

9.3.1. Cytokine Release Syndrome

CRS may be induced by ACE1831 cells upon engagement with the CD20 antigen target antigen. The severity of CRS events will be assessed by American Society for Transplantation and Cellular Therapy (ASTCT) grading (Lee 2019) (Table 12).

The severity of individual signs/symptoms of CRS (including organ toxicities potentially associated with CRS) will be graded according to the NCI CTCAE version 5.0 for those signs/symptoms that are not part of the grading scale.
Guidance for management of CRS events is provided in Appendix 3.

9.3.2. Tumor Lysis Syndrome

TLS may be induced by ACE1831 cells upon engagement with the CD20 antigen target. The severity of the TLS event will be assessed by the Cairo-Bishop TLS Grading (Cairo 2004) (Table 13).

The severity of individual signs/symptoms of TLS will be graded according to the NCI CTCAE version 5.0 for those signs/symptoms not part of the grading scale.

9.3.3. Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)

ICANS may be induced by the activated gdT-cells targeting CD20 antigen. The severity of ICANS will be assessed by American Society for Transplantation and Cellular Therapy (ASTCT) grading (Lee 2019) (Table 14).

The severity of individual signs/symptoms of neurologic events will be graded according to the NCI CTCAE version 5.0 for those signs/symptoms that are not part of the grading scale.
Guidance for management of ICANS is provided in Appendix 4.

9.3.4. GvHD

Given that ACE1831 is an allogeneic product, there is a potential risk of acute GvHD and chronic GvHD. All cases of suspected and diagnosed acute and chronic GvHD should be discussed with the Sponsor Medical Monitor.

The diagnosis and grading of:

- acute GvHD should follow the Mount Sinai Acute GvHD International Consortium (MAGIC) criteria (Harris 2016) (Table 15) and
- chronic GvHD should follow the National Institutes of Health 2014 criteria (Jagasia 2015) (Table 16).

Guidance for management of acute and chronic GvHD is provided in Appendix 5.

Table 12: 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)

Abbreviations: ASTCT=American Society for Transplantation and Cellular Therapy; BiPAP=bilevel positive airway pressure; CPAP=continuous positive airway pressure; CRS=cytokine release syndrome.

a. Fever is defined as temperature ≥38°C not attributable to any other cause. In patients 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 patient 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 ≤6L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6L/minute.

Table 13 Cairo-Bishop Clinical Tumor Lysis Syndrome Definition [a] & Grading

Complication	Grade					
	0	1	2	3	4	5
Creatinine	<1.5 × ULN	1.5 × ULN	>1.5 to 3.0 × ULN	>3.0 to 6.0 × ULN	>6.0 × ULN	Death
Cardiac Arrhythmia [b]	None	Intervention not indicated	Nonurgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (eg, defibrillator)	Life-threatening (eg, arrhythmia associated with HF, hypotension, syncope, shock)	Death
Seizure [b]	None	-	One brief, generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which are prolonged, repetitive, or difficult to control (eg, status epilepticus, intractable epilepsy)	Death

Abbreviations: ADL=activities of daily living ULN=upper limit of normal; HF=heart failure.

a. Clinical tumor lysis syndrome defined as laboratory tumor lysis syndrome plus at least one clinical complication

b. Not directly or probably attributable to therapeutic agent

c. If no institutional ULN is specified, age/sex ULN creatinine may be defined as follows: 1 to 12 years of age, both male and female, 61.6 mmol/L; 12 to 16 years, both male and female, 88 mmol/L; 16 years female 105.6 mmol/L, male 114.4 mmol/L.

Table 14: ASTCT ICANS Consensus Grading for Adults

Neurotoxicity domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score [a]	7 to 9	3 to 6	0 to 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 minutes), 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, cranial nerve VI palsy, papilledema, or Cushing triad
ICE score definitions				
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: ASTCT=American Society for Transplantation and Cellular Therapy; CTCAE=common terminology criteria for adverse events; ICANS=immune effector cell associated neurotoxicity; ICE=immune effector cell-associated encephalopathy; ICP=intracranial pressure; N/A=not applicable

a. A patient with an ICE score of 0 (ie, not oriented, can't name 3 objects, can't follow simple commands, unable to write a sentence, and can't hold attention) 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 Version 5.0, 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 version 5.0.

Table 15: Clinical Grading of Acute GvHD

Overall clinical grade (based upon most severe target organ involvement):				
Grade 0	No stage 1–4 of any organ			
Grade 1	Stage 1–2 skin without liver, upper GI or lower GI involvement			
Grade 2	Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI			
Grade 3	Stage 2–3 liver and/or stage 2–3 lower GI, with stage 0–3 skin and/or stage 0–1 upper GI			
Grade 4	Stage 4 skin, liver or lower GI involvement, with stage 0–1 upper GI			
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).

Abbreviations: ASTCT=American Society for Transplantation and Cellular Therapy; BSA=body surface area; CTCAE=common terminology criteria for adverse events; GvHD=graft vs host disease; ICANS=immune effector cell associated neurotoxicity; ICE=immune effector cell-associated encephalopathy; ICP=intracranial pressure; NA=not applicable

Table 16 NIH Global Severity of Chronic GvHD

Mild cGvHD	1 or 2 organs involved with no more than score 1 plus Lung score 0
Moderate cGvHD	3 or more organs involved with no more than score 1 OR At least 1 organ (not lung) with a score of 2 OR Lung score of 1
Severe cGvHD	At least 1 organ with a score of 3 OR Lung score 2 or 3
Key Points: 1 In skin: higher of the two scores to be used for calculating global severity. 2 In Lung: FEV1 is used instead of clinical score for calculating global severity 3 If the entire abnormality in an organ is noted to be unequivocally explained by a non-GvHD documented cause, that organ is not included for calculation of the global severity. 4 If the abnormality in an organ is attributed to multifactorial causes (GvHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).	

Abbreviations: cGvHD=chronic graft vs host disease; FEV1=forced expiratory volume at 1 second; GvHD=graft vs host disease; NIH=National Institutes of Health.

9.4. Assessment of Adverse Event/Serious Adverse Event Relationship to Study Treatment and Study Procedures:

In reviewing AEs, investigators must assess whether the AE is possibly related to:

1) the study treatment (ACE1831 and/or obinutuzumab),
2) lymphodepleting regimen, and/or
3) any protocol-required study procedure.

The relationship is indicated by a “related” or “not related” response and entered in the eCRF. In assessing causality, the Investigator or delegated sub-investigator will use clinical judgment and the following considerations:

- **Not Related:** Evidence exists that the AE has an etiology other than the study drug or study procedure. For SAEs, an alternative causality must be provided (eg, disease progression, concurrent disease[s], concomitant medications, or other).
- **Related:** There is reasonable possibility and/or evidence to suggest that the event may have been caused by the study drug or as a result of a study procedure.

9.5. Hospitalization and Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE as described in Section 9.6.2.

The following hospitalization scenarios are not considered to be SAEs:

- Hospitalization for palliative care or hospice care
- Planned hospitalization required by the protocol (eg, for monitoring of the subject or to perform an efficacy measurement for the study)
- Planned hospitalization for a pre-existing condition
- Hospitalization due to progression of the underlying malignancy. (Refer to Section 9.6.5 for instructions on reporting underlying signs/symptoms of the underlying malignancy/disease progression as AEs/SAEs.)
- Hospitalization for routine treatment, eg, platelet transfusion or monitoring of the condition under study that is not associated with any deterioration in condition

9.6. Investigator Requirements and Instructions for Reporting Adverse Events, Serious Adverse Events, and Deaths to the Sponsor

9.6.1. Reporting Adverse Events and Serious Adverse Events

The Investigator or delegated sub-investigator must address the following for AEs/SAEs:

- AE diagnosis or syndrome (if not known, signs or symptoms)
- Dates of onset and resolution
- Severity (Section 9.3)
- Assessment of relatedness to study treatment, lymphodepleting regimen, or study procedures (Section 9.4)
- Action taken

Additional relevant data with respect to describing the AE/SAE will be collected in the eCRFs. For AEs/SAEs, a diagnosis (if known) rather than individual signs and symptoms should be recorded on the eCRF AE form.

When manifestations of neurological toxicities appear in the presence of CRS, those manifestations should be reported as separate AEs.

The Investigator is expected to follow reported AEs/SAEs until stabilization or resolution. If a subject begins a new anticancer therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started.

Refer to Section 9.6.5 for instructions on reporting AEs/SAEs associated with disease progression.

The Investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an AE/SAE. In the event a subject request to withdraw from protocol-required- therapies or the study due to an AE/SAE, the subject should undergo the procedures outlined in the end of treatment visit of the SOE (Appendix 1).

Refer to Section 9.6.2 and Section 9.6.3 for additional information on reporting AEs and SAEs, respectively.

9.6.2. Reporting Adverse Events

The Investigator is responsible for reporting all AEs observed by the Investigator or reported by the subject during the AE-reporting period described in Table 17. Refer to Section 9.6.5 for instructions on reporting AEs associated with disease progression.

Table 17 Reporting Requirements for Adverse Events

Time Period	Events to Record
Informed consent to start of lymphodepleting regimen [a]	Only AEs/SAEs related to protocol-mandated procedures will be collected.
From start of lymphodepleting regimen through 30 days after the last study treatment, either ACE1831 or obinutuzumab, whichever is later.	All AEs/SAEs (including complications that arise from any procedure, whether or not the procedure was considered protocol-mandated) will be collected, including AEs ongoing at the start of lymphodepleting chemotherapy
>30 days after the last study treatment, either ACE1831 or obinutuzumab, whichever is later	Only AESI (Section 9.1.3) and secondary malignancies will be reported through the end of the study (24 months) or time of disease progression or initiation of subsequent therapy, whichever occurs first.
All AEs deemed related to ACE1831 should be recorded in the eCRF and reported regardless of study period.	

Abbreviations: AE=adverse event(s); AESI=adverse event(s) of special interest; SAE=serious adverse events.
a. If a subject receives lymphodepleting therapy but not ACE1831, all AE/SAEs should be recorded/reported for 30 days following the last dose of lymphodepleting regimen.

9.6.3. Reporting Serious Adverse Events

The Investigator is responsible for reporting all SAEs observed by the Investigator or reported by the subject during the SAE-reporting periods described in Table 17. Refer to Section 9.6.5 for instructions on reporting SAEs associated with disease progression.

Unless otherwise indicated in Table 17:

The following must be submitted via email within 24 hours after the Investigator's knowledge of the event:

- All SAEs
- Pregnancy or lactation exposure

The SAE must be submitted using the paper SAE Report Form and sent via email to the SAE reporting mailbox: **icon-mads@iconplc.com**.

All SAEs will be reported to the health authorities per local reporting guidelines.

AESIs that do not qualify as SAEs must be entered into the EDC within 48 hours after the Investigator's knowledge of the event.

9.6.4. Reporting Deaths

Death must be reported if it occurs during the AE reporting period, irrespective of any intervening treatment. Refer to Section 9.6.5 for instructions on reporting deaths associated with the underlying malignancy/disease progression.

Any death occurring after the signing the study ICF and within 30 days following ACE1831 infusion, regardless of attribution to treatment, requires expedited reporting within 24 hours after the Investigator's knowledge of the event. Any death occurring after the 30 days SAE reporting period requires expedited reporting within 24 hours only if it is considered related to treatment, ACE1831 infusion, and/or study-required treatments (eg, lymphodepleting regimen).

Death is an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded on the eCRF AE form with entries including the start date of the event and the death date as the stop date of the event. Every effort should be made to capture the established cause of death, which may become available later on (eg, after autopsy).

9.6.5. Reporting Adverse Events/Serious Adverse Events/Deaths Associated with Disease Progression

Progression of the malignancy ("disease progression") as assessed by the measurement of malignant lesions on radiographs or other methods during the study, should not be reported as an AE or SAE.

For situations when an AE or SAE is due to the malignancy under investigation, the sign(s) and symptom(s), including worsening of sign(s) and symptom(s), of the malignancy under study should be reported as an AE/SAE.

If the malignancy has a fatal outcome within 30 days following the last ACE1831 or obinutuzumab infusion (whichever occurs later), the event leading to death must be recorded as an SAE with CTCAE severity of Grade 5 and outcome of "fatal". Within this 30 day period, the death that is due to the underlying disease/disease progression must be reported immediately to the sponsor as an SAE, as follows:

- If there are no signs and symptoms of alternate underlying disease associated with the death (although the death has been determined to be due to disease progression), the death should be reported immediately to the sponsor as an SAE with the primary tumor type (eg, "NHL" or "LBCL") as the event term.
- If the death is due to a sign or symptom of the underlying disease/disease progression and the sign or symptom is an AESI/SAE

9.7. Sponsor-reporting Requirements (Includes Reporting of SAEs and Deaths)

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations and relevant updates, and other country-specific legislation or regulations, Acepodia may be required to expedite to worldwide regulatory agencies

reports of serious adverse drug reactions or suspected unexpected serious adverse reactions (SUSARs). Acepodia or a specified designee will notify regulatory authorities and the relevant IRBs of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Acepodia using reference safety information specified in the current IB or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The Investigator should notify the IRB of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

9.8. Pregnancy Guidance and Reporting Information

There is no relevant clinical experience with ACE1831 in pregnant or lactating women, and animal reproductive studies have not been performed. This experimental therapy should not be administered to pregnant women or women who are breastfeeding. Women of childbearing potential must have a negative pregnancy test before enrollment because of the potentially dangerous effects of the preparative chemotherapy on the fetus. Women of childbearing potential should be monitored according to local and country-specific regulations.

9.8.1. Definition of Women of Childbearing Potential

Childbearing Potential and Contraception Requirements

Any woman who does not meet at least one of the following criteria will be considered to have reproductive potential:

- Naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 12 consecutive months (ie, has had menses at any time in the preceding 12 consecutive months)
- Undergone a sterilization procedure (hysterectomy, salpingectomy, or bilateral oophorectomy; tubal ligation is not considered a sterilization procedure)

Female study participants of reproductive potential must have a negative pregnancy test at the screening evaluation and throughout the study as outlined in the SOE (Appendix 1). Female subjects with reproductive potential who are not sexually abstinent must agree to use one highly effective method of contraception from screening and for at least 1 year following the lymphodepleting regimen. True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. In contrast, periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Highly effective methods are defined as those that result in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The following are examples of highly effective methods of contraception including IUD, hormonal (birth control pill, injections, implants), tubal ligation, and partner's vasectomy.

Males who are not sexually abstinent and have partners of childbearing potential must agree to a condom during sexual contact with a pregnant female or a female of childbearing potential for at least 1 year after lymphodepleting chemotherapy even if he has undergone a successful vasectomy. Subjects must agree not to breastfeed, or to donate blood, organs, sperm or semen, and egg cells for usage in other individuals for at least 1 year following lymphodepleting chemotherapy. There are insufficient exposure data to provide any recommendation concerning the duration of contraception and the abstaining from breastfeeding following treatment with ACE 1831. Any decision regarding contraception, breastfeeding, or donating reproductive tissue after ACE 1831 should be discussed with the treating physician.

9.8.2. Instructions for Reporting Pregnancies

All pregnancies or suspected pregnancies (including elevated βhCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring at any time after receipt of ACE 1831, in a female subject or in the female partner of a male subject, must be reported to the Sponsor within 24 hours of learning of its occurrence (for reporting a pregnancy in the female partner of a male subject, authorization from the pregnant partner must first be obtained). The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to **icon-mads@iconplc.com** immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

Pregnancy follow-up, including all perinatal and neonatal outcomes, should be recorded on a Pregnancy Follow-up Form and should be submitted to the Sponsor within 24 hours of awareness. Any SAE experienced during pregnancy must be reported on the SAE Report Form. Abortion, whether accidental, therapeutic, or spontaneous, should be reported as an SAE. Congenital anomalies or birth defects should be reported as SAEs.

9.9. Overdose

An overdose is defined as an accidental or intentional administration of a quantity of an IP (eg, lymphodepleting chemotherapy or other study-specified IP) given per administration or cumulatively that is above the maximum recommended dose as per protocol for ACE1831 or in the obinutuzumab product labeling (as it applies to the daily dose of the subject in question).

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size Determination

Up to 42 subjects

The dose-escalation part of the study will use a 3 + 3 study design. The number of subjects required will depend on the safety profile and DLT rate observed in each treatment group and dose level. Subjects who discontinue prior to completion of the 28-day DLT assessment period for reasons other than a DLT may be replaced. Subjects will be enrolled in up to 3 monotherapy dosing levels (Treatment Group A) and 2 combination therapy dosing levels (Treatment Group B).

The respective dosing levels for monotherapy (Treatment Group A) and combination treatment (Treatment Group B) at the MTD/MAD may be expanded to a total of 12 subjects to further characterize toxicity, ACE1831 persistence, and pharmacodynamics to gain preliminary evidence of efficacy.

10.2. Analysis Sets

The primary study analysis sets are defined in this section. Additional analysis sets may be defined in the SAP:

- Screened Analysis Set – all subjects who provide written informed consent, including screen failures
- All Enrolled Set - all subjects who go through lymphodepletion
- Intent-to-Treat/Safety Analysis Set - all subjects who receive at least 1 dose of ACE1831
- Efficacy Evaluable Analysis Set – all subjects who receive at least 1 dose of ACE1831 and have at least 1 post-baseline disease assessment, or discontinue prior to having a post-baseline disease assessment due to disease progression
- ACE1831 Pharmacokinetics Analysis Set – all subjects in the mITT Analysis Set who have at least 1 quantifiable pre- and post-ACE1831 persistence sample
- Pharmacodynamic Analysis Set – all subjects in the mITT Analysis Set who have at least 1 quantifiable pre- and post-ACE1831 dose pharmacodynamic assessment

10.3. Statistical Analyses

10.3.1. General Considerations

Categorical variables will be summarized as the number and percentage of subjects within each category (with a category for missing, if applicable). Continuous variables will be presented as n, mean standard deviation, median and range (minimum and maximum).

Data from all investigational sites will be pooled in the analyses.

Data will be analyzed separately by treatment group (A or B) and ACE1831 dose level group using the analysis sets defined above. Given the small sample sizes in each dosing level within a treatment group, data analyses and summaries will be descriptive in nature only.

A detailed SAP will be finalized before database lock and will document the analysis methods, data handling procedures, and other statistical analysis issues.

Statistical analyses will be performed using SAS® version 9.4 or higher.

10.3.2. Prior and Concomitant Medications

Medications will be coded using the World Health Organization drug dictionary (WHO-DDE) and summarized according to the Anatomical Therapeutic Chemical classes and preferred term for the Safety Analysis Set. Subjects will be counted only once for a given concomitant medication for each Anatomical Therapeutic Chemical class and preferred term in the summary tables.

Medications will be presented in a by-subject data listing, with a flag indicating prior medications.

10.3.3. Study Treatment Exposure and Compliance

Exposure to ACE1831 and obinutuzumab will be summarized descriptively for the Safety Analysis Set. Treatment information will be presented in by-subject data listings.

Details of lymphodepletion will be presented in a by-subject data listing.

10.3.4. Efficacy Analyses

All efficacy endpoints will be determined based on the Investigator's assessment using the revised IWG Response Criteria for Malignant Lymphoma (Cheson BD 2014). These endpoints will be based on response assessments obtained after the initial ACE1831 infusion and prior to the start of any additional non-study therapy (eg, stem cell transplant or start of other trial or anti-cancer therapy).

Efficacy analyses will be descriptive in nature. The number and percentage of subjects with a complete response (CR), partial response (PR), stable disease (SD), and progressive disease will be summarized for the Efficacy Evaluable Analysis Set separately for monotherapy and combination therapy, overall and by dose level.

The ORR will be calculated as the number of subjects with a CR or PR divided by the number of subjects in the analysis set. Corresponding 95% Clopper Pearson confidence intervals will be calculated for the ORR.

Duration of Response (DOR) will be summarized for responders (subjects with a CR or PR) and defined as the time between the date of first documented CR or PR (whichever occurs first) to date of disease progression, relapse, or death due to disease progression or relapse. Median DOR and corresponding 95% confidence intervals will be calculated using the Kaplan-Meier method. Censoring rules will be defined in the SAP.

Progression Free Survival (PFS) is defined as the time from the date of lymphodepletion to the date of disease progression or death from any cause. Median PFS and corresponding 95% confidence intervals will be calculated using the Kaplan-Meier method. Censoring rules will be defined in the SAP.

Subjects who discontinue due to disease progression or death due to disease progression prior to having a post-baseline disease assessment will be classified as having a response of progressive disease and considered evaluable. Subjects who discontinue prior to having a post-baseline disease assessment for other reasons will be exclude from the Efficacy Evaluable analyses.

10.3.5. Safety Analyses

10.3.5.1. Adverse Events (AEs)

AEs will be coded using MedDRA, and severity/grading assessed using NCI-CTCAE v5.0, with the exception of:

- CRS (Table 12) and ICANS (Table 14) which will be graded according to Lee et al. (Lee 2019)
- TLS (Table 10) which will be graded according to Cairo-Bishop (Cairo 2004)
- Acute GvHD (Table 15) which will be graded according to Harris et al (Harris 2016)
- Chronic GvHD (Table 16), which will be graded according to the National Institutes of Health 2014 criteria (Jagasia 2015)

AEs that occur prior to first dose of ACE1831 will be considered pre-treatment AEs and summarized separately. Treatment-emergent AEs (TEAEs) start on or after the date of first dose of ACE1831.

TEAEs will be summarized for the Safety Analysis Set. The incidence of TEAEs will be summarized as the number and percent of subjects reporting each TEAE. A subject with 2 or more TEAEs within the same level of summarization (ie, system organ class [SOC] or preferred term) will be counted only once in that level using the most severe event or most related (for the relationship to study treatment tables). Additional TEAE summaries tables will be generated for DLTs, AESIs, Grade 3 or higher TEAEs, TEAEs considered related to treatment, TEAEs by maximum grade and relationship, TEAEs resulting in death, serious AEs (SAEs), related SAEs, and TEAEs leading to treatment discontinuation.

A by-subject AE data listing, including verbatim term, MedDRA SOC and preferred term, grade, outcome, and relationship to treatment for ACE1831, will be generated. Separate listings will also be generated for DLTs, AESIs, Grade 3 or higher TEAEs, TEAEs considered related to study treatment, TEAEs resulting in death, SAEs, and TEAEs leading to treatment discontinuation.

10.3.5.2. Other Safety Assessments

Safety laboratory data as reported by local labs (hematology, serum chemistry, thyroid panel, coagulation, and urinalysis), vital signs and ECG parameters will be summarized descriptively and presented for each timepoint, including change from baseline, for the Safety Analysis Set. Shift from baseline tables based on NCI-CTCAE grading will be created for select laboratory parameters defined in the SAP. By-subject data listings of all safety data will be generated.

10.3.5.3. Safety Stopping Bounds

As an additional safety measure, rule-based stopping bounds will be employed.

Bayesian stopping bounds are based on the occurrence of >33% subject incidence of the following AEs:

- Grade 4 nonhematologic AE (regardless of whether is related or not to ACE1831 treatment) that do not decrease to a Grade 2 or lower within 7 days.
- Any cerebral edema
- Any ACE1831 related AE requiring intubation,
- All ACE1831 related Grade 3 nonhematologic toxicities lasting >7 days
- Grade 3 CRS
- Grade 3 cardiac and pulmonary toxicities that do not improve to Grade 2 or lower within 72 hours,
- Grade 4 infusion reaction of any duration
- Grade 3 infusion reaction of more than 2 hours

Separate stopping boundaries for deaths unrelated to disease progression will also be employed.

Refer to Appendix 8 for the full stopping bounds tables to be referenced during the study.

Enrollment will be paused if the stopping boundary is met. The SRC will review all available data and make a recommendation as to whether enrollment in the study will be allowed to resume as planned or modified prior to additional enrollment.

10.3.6. Pharmacodynamics

Pharmacodynamic data will be summarized descriptively for the Pharmacodynamic Analysis Set.

Details on the pharmacodynamic analyses will be included in the SAP.

10.3.7. ACE1831 Pharmacokinetic Studies

ACE1831 PK studies will be summarized descriptively for the PK Population.

11. RESPONSIBILITIES

11.1. Investigator Responsibilities

The Investigator is responsible for ensuring that all study site personnel, including Sub-Investigators and other responsible study staff members, conduct the study in compliance with the Declaration of Helsinki and the ICH E6 Guideline for GCP, including the archiving of essential documents.

The Investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, Subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, Part 50, 1998, and 21 CFR, Part 56, 1998.

The Investigator will sign and return the Investigator Signature Page of the original protocol and any protocol amendment, provide current medical licenses, curriculum vitae, and the US FDA form 1572 "Statement of Investigator." All forms must be updated as applicable throughout the study.

11.1.1. Access to Information for Monitoring

In accordance with regulations and guidelines, the Sponsor appointed CRA must have direct access to the Investigator's source documentation in order to verify the accuracy of the data recorded in the CRF.

The monitoring CRA is responsible for routine review of the CRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitoring CRA should have access to any subject records needed to verify the entries on the CRFs. The Investigator agrees to cooperate with the monitoring CRA to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

11.1.2. Financial Disclosure

Investigators, Sub-Investigators, and study staff will comply with 21 CFR, Part 54, 1998, providing documentation of any financial conflict of interest. This documentation must be provided prior to the Investigator's (and any Sub-Investigators') participation in the study. The Investigator and Sub-Investigator(s) agree to notify the Sponsor of any change in reportable interests during the study and for 1 year following completion of the study at the Investigator's site. Study completion is defined as the date when the study database is locked.

11.1.3. IRB/IEC Approvals

A copy of the protocol, Investigator's Brochure, ICF, and any additional subject or trial information, such as subject recruitment materials, must be submitted to each site's respective IRB/IEC for approval. After approval is obtained from the IRB/IEC, all documents must be provided to the key sponsor contact before subject recruitment can begin.

If the protocol, Investigator's Brochure, or ICF are amended during the study, per local regulations the Investigator is responsible for ensuring that the IRB/IEC has reviewed and approved these amended documents. In addition, IRB/IEC approval of the amended documents must be obtained before implementation and before new subjects are consented to participate in the study using the amended version of the ICF.

During the course of the study, investigators are to submit site-specific and study SAEs (provided to the site by the key sponsor contact) along with any protocol deviations to their IRB/IEC in accordance with their respective IRB/IEC policies.

11.1.4. Informed Consent

Before a subject can participate in the study, the Investigator, or a qualified person designated by the Investigator, is responsible for obtaining written informed consent from the subject after adequate explanation of the study design, purpose, anticipated benefits, and potential risks of participation in the study. Written informed consent must be obtained prior to the subject entering the study (before initiation of any study-related procedure). Sufficient time will be allowed to discuss any questions raised by the subject. The consent process and the subject's agreement or refusal to participate in the study is to be documented in the subject's medical records. The Investigator, or a qualified person designated by the Investigator, must use the current IRB/IEC-approved consent form for documenting written informed consent. If the subject agrees to participate, the most current IRB/IEC approved ICF is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed ICF will be retained in accordance with the institution's policy and IRB/IEC requirements and a copy of the ICF will be provided to the subject.

The process of obtaining the informed consent will be in compliance with all federal regulations, International Conference of Harmonisation (ICH) requirements (ICH E6 4.8) and local laws.

If the ICF is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IRB/IEC. The investigative site must use the amended ICF for all new subjects and repeat the consent process with the amended ICF for any ongoing subjects.

11.1.5. Confidentiality

The Investigator must assure that the subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an ID code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to the Sponsor or the laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject (refer to specific laboratory instructions for further information). Subject data will be processed in accordance with all applicable regulations.

The Investigator agrees that all information received from the Sponsor, including but not limited to the IB, this protocol, eCRFs, the study drug, and any other study information, remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the Sponsor. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

Per federal regulations and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)/GCP guidelines, investigators and institutions are required to permit direct access to the sponsor, CRO, IRB/IEC, and regulatory agencies to subject's original source documents for verification of study data. The Investigator is responsible for informing potential subjects that such individuals will have access to their medical records, which include personal information.

Subject confidentiality must be maintained on all material submitted to the key sponsor contact. The following rules are to be applied:

- Subjects will be identified by a unique ID number

11.1.6. Study Files and Retention of Records

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. Records of subjects, source documents, monitoring visit logs, inventory logs of study investigational product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. This includes any electronic records. These records will be retained in a secure file for the period required by the institution or site policy but not less than 25 years. Prior to the transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

11.1.7. Data Collection: Electronic Case Report Forms

An electronic data capture (EDC) system provided by the Sponsor will be used for data collection. The EDC system is a fully validated, secure system that conforms to 21 CFR Part 11 requirements. Access to the EDC system is role-based, and login credentials will be provided only after completion of the assigned role-based training.

All entries in the EDC must be completed in English and concomitant medications should be identified by generic names except for combination medications. For further details surrounding the completion of eCRFs captured in the EDC, refer to the eCRF completion guidelines.

For each subject consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in the EDC system. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures. The inclusion/exclusion criteria and enrollment eCRFs should be completed only after all data related to eligibility have been received. Data entry should be performed in accordance with the eCRF completion guidelines provided by the sponsor.

Subsequent to data entry, a study monitor will perform source data verification within the EDC system. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the monitor or the Sponsor's staff, who routinely review the data for completeness, correctness, and consistency. The site Investigator or site coordinator or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. At a minimum, before any interim time points or database lock (as instructed by the Sponsor), the Investigator will use his/her log-in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents.

The Principal Investigator is responsible for ensuring that the data entered into the eCRFs are complete and accurate and will electronically sign the CRFs for each subject prior to database lock.

This archive must be stored in accordance with the records retention requirements outlined in Section 11.1.6.

11.1.8. Access to Study Information

The Investigator will make available all source documents and other records for this study to the Sponsor or the Sponsor's designee appointed study monitors, to IRBs/IECs, or to regulatory authority or health authority inspectors. By signing the Investigator statement, the Investigator agrees to cooperate with the monitor to address and resolve issues identified during monitoring visits, audits, and regulatory authority inspections.

11.1.9. Protocol Compliance

The Investigator is responsible for ensuring that the study is conducted in accordance with the procedures and evaluations described in this protocol.

11.2. Sponsor Responsibilities

11.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by the Sponsor. The Investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive

documented approval before modifications can be implemented. Documentation acknowledging agreement with the protocol amendment from the Investigator and approval from the IRB/IEC are to be submitted to the key sponsor contact.

11.2.2. Study Report and Publications

The Sponsor is responsible for the ACE1831-001 final clinical study report (CSR) prepared according to ICH guidelines. A final CSR will be prepared and will include any subject who has signed informed consent, regardless of whether the study is completed or prematurely terminated. If appropriate, an abbreviated report may be prepared.

Interim data from this study may be presented at scientific meetings.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of the Sponsor in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.
- The Investigator will submit to the Sponsor any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.
- No such communication, presentation, or publication will include the Sponsor's confidential information (Section 11.1.5).
- The Investigator will comply with the Sponsor's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 90 days in order to obtain patent protection if deemed necessary.

11.2.3. Financing and Insurance

The Sponsor has insurance that provides compensation for study-related illness or injury pursuant to the information outlined in the injury section of the ICF.

Investigators and their study staff may be asked to provide services performed under this protocol (eg, attendance at Investigator meetings). If required under the applicable statutory and regulatory requirements, the Sponsor will capture and disclose to federal and state agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

11.3. Joint Investigator/Sponsor Responsibilities

11.3.1. Regulatory Authority Review

The study will be conducted in accordance with ICH Good Clinical Practice (GCP), the protocol, and any other applicable Federal, state, and/or local regulatory requirements.

11.3.2. Quality Control and Quality Assurance

The Sponsor or its designee will perform quality control and quality assurance checks of all clinical studies that it sponsors. Before the enrollment of any subject in this study, the Sponsor's personnel will review and provide training as needed to the Investigator, Sub-Investigators, and study site personnel regarding the following: protocol, IB, CRFs and procedures for their completion, informed consent process, and procedures for reporting SAEs. The monitor is responsible for source document verification of eCRF data at regular intervals during the study. Protocol adherence and accuracy and consistency of study conduct and data collection with respect to local regulations will be confirmed.

In accordance with ICH GCP and the audit plan, a site may be chosen for a Sponsor Quality Assurance site audit. The Sponsor's Quality Assurance site audit would include, but is not limited to, an inspection of the facility(ies), review of subject and study-related records, and compliance with protocol requirements as well as ICH GCP and applicable regulatory policies. Investigators will provide the Sponsor's Quality Assurance auditors access to subject records.

Representatives of regulatory authorities, the Sponsor or IRB/IEC may conduct inspections of the clinical study. If the Investigator is notified of an inspection by a regulatory authority, the Investigator agrees to notify the Sponsor's Medical Monitor immediately. The Investigator agrees to provide to representatives of a regulatory agency or Acepodia, access to records, facilities, and personnel for the effective conduct of any inspection or audit.

11.3.3. Ethics

Study ACE1831-001 will be conducted under a US Investigational New Drug (IND) application or equivalent and in accordance with recognized international scientific and ethical standards, including but not limited to the ICH guideline for GCP, and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US Code of Federal Regulations Title 21, Part 312, and the European Community Directive 27/05/2014, as well as other local legislation.

11.3.4. Study Discontinuation

Both the Sponsor and the Investigator reserve the right to terminate the Investigator's participation in the study as per the terms of the agreement in the study contract. In addition, the Sponsor reserves the right to temporarily suspend or prematurely terminate this study for any reason. Study termination and follow-up will be performed in compliance with the conditions set forth in 21 CFR Parts 312.50 and 312.56 and local regulation.

Upon completion or early termination of the study, the following activities, when applicable, must be conducted by the monitoring CRA and the Investigator:

11.3.5. Public Notification of Study Conduct

Consistent with Section 113 of the Food and Drug Modernization Act of 1997 (FDAMA) and with requirements of the International Committee of Medical Journal Editors (ICMJE) as a condition of consideration for publication of study results, the Sponsor will be responsible for ensuring that this protocol is listed at the ClinicalTrials.gov website per the US FDA requirement and that information at the website relating to study design and conduct is appropriately updated during the course of the study.

If the study is suspended or terminated for safety reasons, the Sponsor will promptly inform the Investigator and will also inform the regulatory authorities of the suspension or termination of the study and the reasons for the action. The Investigator is responsible for promptly informing the IRB/IEC and providing the reasons for the suspension or termination of the study.

The Investigator is to provide written communication to the IRB/IEC of the trial completion.

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APPENDIX 1. SCHEDULE OF EVALUATIONS

Table 18: Schedule of Evaluations - Screening, Lymphodepletion Regimen, and Treatment Periods

	Screening	*Lymphodepletion Regimen*			*Treatment*								
	Day												
						3	5	8	11	15	22	29	
Assessment	**-33 to -6**	**-5**	**-4**	**-3**	**1**	**(±1 day)**				**(±2 days)**			***Notes***
Informed consent	X												Written study informed consent must be signed within 33 days prior to start of lymphodepletion.
Eligibility criteria review	X[1]	X[2]			X[3]								1 Refer to Section 4 2 Refer to Section 5.1.1. 3 Refer to Section 5.2.2
Medical, surgical, cancer history	X												Cancer history includes date and stage of diagnosis, CD19 and CD20 expression statuses, known mutations, and prior anticancer treatment. Surgical history includes both cancer-related and non-cancer related surgeries.
Demography	X												Demographics include age at time of informed consent, sex, self-reported race/ethnicity, and reproductive status.
PET/ diagnostic CT	X											X	Tumor assessments via whole body PET-CT or FDG-PET+CT should be conducted within 28 days prior to lymphodepletion). Refer to Section 6.2.1
Bone marrow aspirate/ biopsy	X												Refer to Section 6.2.2.

Table 18: Schedule of Evaluations - Screening, Lymphodepletion Regimen, and Treatment Periods (Continued)

	Screen	Lymphodepletion Regimen			Treatment								
	Day												
Assessment	-33 to -6	-5	-4	-3	1	3 (± 1 day)	5 (± 1 day)	8 (± 1 day)	11 (± 1 day)	15 (± 2 days)	22 (± 2 days)	29 (± 2 days)	Notes
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	The physical examination must include at a minimum a routine neurological, cardiovascular, pulmonary, abdominal, and extremity examination. In addition, symptom-directed exams should be performed as appropriate. Refer to Section 6.1.2
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	Vital signs include respiratory rate, heart rate, blood pressure, temperature, and pulse oxygenation. Refer to Section 6.1.3
12-lead ECG	X											X	The date and time of the ECG and the following parameters will be collected and assessed: PR, QRS, QT, and QTcF interval, and heart rate. Refer to Section 6.1.4
ECHO/ MUGA	X												ECHO/MUGA must include assessment of left ventricular ejection fraction. Refer to Section 6.1.5
ECOG Performance Status	X				X			X	X	X	X	X	Refer to Section 6.1.6
Hematology	X	X			X	X	X	X	X	X	X	X	Assessment should be completed pre-dose when applicable. Tests to be performed locally. Refer to Section 6.1

Table 18: Schedule of Evaluations - Screening, Lymphodepletion Regimen, and Treatment Periods (Continued)

Assessment	Screening	Lymphodepletion Regimen			Treatment								Notes
	Day												
	-33 to -6	-5	-4	-3	1	3 (± 1 days)	5 (± 1 days)	8 (± 1 days)	11 (± 1 days)	15 (± 2 days)	22 (± 2 days)	29 (± 2 days)	
Serum chemistry	X	X			X	X	X	X	X	X	X	X	Assessment should be completed pre-dose when applicable. Tests to be performed locally. Refer to Section 6.1
Coagulation panel	X											X	Tests to be performed locally. Refer to Section 6.1
Urinalysis	X	X			X							X	Assessment should be completed pre-dose when applicable. Tests to be performed locally. Refer to Section 6.1
Pregnancy test (WOCBP only)	X	X			X								Pregnancy test (for female subjects of childbearing potential only) should be performed on Day 1. Refer to Section 6.1
Thyroid function	X												Tests to be performed locally. Refer to Section 6.1
COVID-19 testing	X												According to local institutional policy Refer to Section 5.5
Viral Testing													
HIV, HBV, and HCV serology	X												Subjects will be tested for HIV, HBV, and HCV prior to study entry. Tests to be performed locally. Refer to Section 6.1
HHV6 and HHV7	X									X		X	Samples will be taken for HHV6 and HHV7 prior to lymphodepletion. Refer to Section 6.1.7

Table 18: Schedule of Evaluations - Screening, Lymphodepletion Regimen, and Treatment Periods (Continued)

Assessments	Screen	Lymphodepletion Regimen			Treatment								Notes
	Day												
	-33 to -6	-5	-4	-3	1	3 (± 1 days)	5 (± 1 days)	8 (± 1 days)	11 (± 1 days)	15 (± 2 days)	22 (± 2 days)	29 (± 2 days)	
Anti-drug antibodies		X										X	Tests to be performed centrally. Refer to Section 6.4
HLA typing	X												Tests to be performed prior to lymphodepletion. Refer to Section 6.1.8
B-, T-, and NK cells		X			X		X		X	X		X	Assessment should be completed pre-dose when applicable Refer to Section 6.4
Cytokines		X			X *	X	X	X	X	X	X	X	*Samples will be collected pre- and post-dose on Day 1. Pre-ACE1831 samples may be collected any time on Day 1 prior to dosing and post-ACE1831 samples must be collected at 4 hours (+/- 30 minutes) after ACE1831. Refer to Section 6.4
ACE1831 persistency		X			X *	X	X	X	X	X	X	X	*Samples will be collected pre- and post-dose on Day 1. Pre-ACE1831 samples may be collected any time on Day 1 prior to dosing and post-ACE1831 samples must be collected at 4 hours (+/- 30 minutes) after ACE1831. Refer to Section 6.3
Biomarkers		X						X				X	Refer to Section 6.6
Lymphodepleting regimen		X	X	X									Refer to Section 5.1
ACE1831 infusion					X								Refer to Section 5.2 and/or Cell Therapy Manual for details on preparation and administration of ACE1831.
Prior/ concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	Prior medication collected at screening. Refer to Section 5.4 and Section 5.7.
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	Refer to Section 9.1

Abbreviations: d=day; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HHV6=human herpesvirus 6; HHV7=human herpesvirus 7; HLA=human leukocyte antigen; LD=lymphodepletion; MUGA=multigated acquisition scan; NK=natural killer; PS=performance status; WOCBP=women of child-bearing potential.

Table 19: Schedule of Evaluations - End of Treatment and Follow-up

Assessment	Follow-up		Notes
	Months 3, 6, 9, and 12 (± 14 days)	Months 18 and 24 (± 14 days)	
PET/diagnostic CT	X		End-of-Treatment tumor assessments may be omitted if another tumor assessment was completed within 28 days prior to that visit. Refer to Section 6.2.1
Physical examination	X		Refer to Section 6.1.2 and 7.3.8
Bone marrow aspirate/biopsy	X		To confirm CR if applicable or if clinical indicated. Refer to Section 6.2.2 .
ECOG Performance Status	X		ECOG Performance Status scale and criteria, Section 6.1.6.
Vital signs	X		Vital signs include respiratory rate, heart rate, blood pressure, temperature, and pulse oxygenation.
Hematology	X		Refer to Section 6.1. Tests to be performed locally.
Serum chemistry	X		Refer to Section 6.1. Tests to be performed locally.
Adverse events	X	X	AE/SAEs potentially associated with study treatment to be collected through Month 12 or until disease progression, whichever occurs first.
Concomitant medications	X	X	Targeted concomitant medications defined as ongoing or newly added concomitant medications associated with the study treatment will be collected through Month 12 or until disease progression, whichever occurs first.
Biomarkers	X		3, 6, and 12 months only. Refer to Section 6.6.
Subsequent anticancer therapy for NHL	X	X	Subsequent anticancer therapy administered after ACE1831 infusion for a subject's disease will be collected until 1 of the following occurs: subject completes the study procedures, is considered lost to follow-up, withdraws consent, or dies. Refer to Section 8.2.

Abbreviations: AE=adverse event; ECOG=Eastern Cooperative Oncology Group; NHL=non-Hodgkin lymphoma; PET=positron emission tomography; SAE=serious adverse event.

APPENDIX 2. DISEASE RESPONSE CRITERIA: INTERNATIONAL WORKING GROUP LUGANO CLASSIFICATION

Table 20: International Working Group Lugano Classification

Score [a]	Description
1	No uptake above background
2	Uptake ≤mediastinum
3	Uptake >mediastinum but ≤liver
4	Uptake moderately higher than liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

a. The Deauville score uses a patient's fludeoxyglucose (FDG) uptake in the mediastinal blood pool and liver as an internal control. The Deauville score (also known as the 5-point scale) is a purely visual method of standardizing the interpretation of post-treatment positron emission tomography (PET) scans for lymphoma.

Source: (Cheson 2014)

Disease Response Definitions

	PET–CT-based Response	CT-based Response
Complete Remission	The designation of complete metabolic response requires all of the following: • A 5PS (5-point scale) score of 1, 2, or 3, with or without a residual mass. • In Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow, uptake may be greater than normal in the mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake. • No new sites of disease should be observed • No evidence of fluorodeoxyglucose (FDG)-avid disease in bone marrow	The designation of complete radiologic response requires all of the following: • Target nodes/nodal masses must regress to ≤1.5 cm in longest transverse diameter (LDi) of a lesion • No extra lymphatic sites of disease • Absent nonmeasured lesion • Organ enlargement regress to normal • No new sites of disease should be observed • Bone marrow normal by morphology; if indeterminate, negative by immunohistochemistry

Partial Remission	The designation of partial metabolic response requires all of the following:
	• A 5PS score of 4 or 5, with reduced uptake compared to baseline (screening), and residual mass(es) of any size. Note:
	  • At interim, these findings suggest responding disease.
	  • At end of treatment, these findings suggest residual disease.
	• No new sites of disease should be observed
	• Residual uptake is higher than uptake in normal bone marrow but reduced compared with baseline (diffuse uptake is compatible with reactive changes from chemotherapy allowed).
	If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with magnetic resonance imaging or biopsy or an interval scan.
		The designation of partial radiologic response requires all of the following:
		• Greater than or equal to 50% decrease in sum of the product of the perpendicular diameters of up to 6 target measurable nodes and extranodal sites.
		  • When a lesion is too small to measure on a computed tomography scan, assign 5 mm × 5 mm as the default value
		  • When no longer visible, 0 × 0 mm
		  • For a node >5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
		• Absent/normal, regressed, but no increase of nonmeasured lesions
		• Spleen must have regressed by >50% in length beyond normal
		• No new sites of disease should be observed

Stable Disease	The designation of no metabolic response requires all of the following: • A 5PS score of 4 or 5, with no significant change in FDG uptake compared to baseline (screening) at an interim time point or end of treatment • No new sites of disease should be observed • No change from baseline in bone marrow	The designation of stable radiologic disease requires all of the following: • <50% decrease from baseline in the sum of the product of the perpendicular diameters of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met • No increase consistent with progression in nonmeasured lesion and organ enlargement • No new sites of disease should be observed

Progressive Disease	The designation of progressive metabolic disease requires at least one of the following:
	• A 5PS score 4 or 5 with an increase in intensity of uptake from baseline nadir and/or
	• New FDG-avid foci consistent with lymphoma at interim or end of treatment assessment
	• New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered
	• New or recurrent FDG-avid foci in bone marrow
		The designation of progressive radiologic disease requires at least one of the following:
		• An individual node/lesion must be abnormal with:
		  • LDi >1.5 cm and
		  • Increase by ≥50% from cross product of LDi and perpendicular diameter nadir and
		  • An increase in LDi or shortest transverse diameter, shortest axis perpendicular to the LDi, (shortest transverse diameter) from nadir
		  ■ 0.5 cm for lesions ≤2 cm
		  ■ 1.0 cm for lesions >2 cm
		  • In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, spleen must increase by at least 2 cm from baseline
		  • New or recurrent splenomegaly
		• New or clear progression of preexisting nonmeasured lesions
		• New lesion
		  • Regrowth of previously resolved lesions
		  • A new node >1.5 cm in any axis
		  • A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma
		  • Assessable disease of any size unequivocally attributable to lymphoma
		• New or recurrent bone marrow involvement

APPENDIX 3. MANAGEMENT OF CYTOKINE RELEASE SYNDROME

ACE1831 is an allogeneic cell therapy product with a potential risk of cell-associated CRS. CRS is a constellation of physiologic changes and symptoms that occur after treatment with immune effector cell (IEC) therapy and other immunotherapies. Clinical features associated with CRS include fevers, tachycardia, myalgias, capillary leak, hypotension, and hypoxia. In severe cases, CRS can be associated with multiorgan failure, including cardiac arrhythmias, respiratory failure, renal failure, liver dysfunction, and consumptive coagulopathy. Incidence and severity of CRS is variable between ICE therapies and different malignancies. Whereas there have been differences in what specific cytokines and serum biomarkers have been predictive across study populations, interleukin (IL) -6, IL-8, IL-10, IL-15, interferon gamma (IFNg), monocyte chemoattractant protein- 1 (MCP-1), granulocyte macrophage colony-stimulating factor (GM-CSF), C-reactive protein, and ferritin have been associated with the development of more severe CRS. Currently, there are no randomized trial data to guide toxicity management for CRS, and specific strategies differ between trials, products, and across institutions. Low-grade CRS is typically managed using supportive care. For CRS Grade ≥2, tocilizumab and corticosteroids are key therapies in addition to supportive care. Tocilizumab is an anti–IL-6 receptor antibody used for CRS caused by CAR T-cells and other T-cell–activating therapies and can result in rapid symptomatic improvement. Tocilizumab is the only medication approved for the management of CRS on the basis of analyses of tisa-cel trials (Le RQ 2018).

ACE1831-001 will be conducted as an outpatient clinical trial, the Investigator and/or designated staff members should counsel participating subjects to seek immediate medical intention should signs or symptoms of CRS occur at any time.

Table 21 summarizes current recommendations for toxicity management of CRS based on the ASTCT grading criteria (Reagan PM et al 2021).

Table 21 Suggested Management of CRS

ASTCT[a] Grade	Recommended Management[b]
Grade 1	• Evaluation for infectious causes of symptoms • Empirical treatment of neutropenic fever with antibiotics • Supportive care with acetaminophen and IV hydration to maintain fluid balance • Consider cardiac telemetry and pulse oximetry depending on the patient's risk • Symptomatic management of constitutional symptoms and organ toxicities • If fever is refractory to supportive measures after 72 hours, or if there are medical comorbidities, consider tocilizumab[c] 8 mg/kg (maximum 800 mg)
Grade 2	• Supportive care as per grade 1 • Initiate cardiac telemetry and pulse oximetry • Fluid resuscitation for hypotension • Supplemental oxygen as needed • Tocilizumab 8 mg/kg (maximum 800 mg), which may be repeated every 8 hours for up to three doses in a 24-hour period • If patient does not respond to tocilizumab, initiate dexamethasone 10 mg every 12 hours (or methylprednisolone equivalent)
Grade 3	• Supportive care as per grades 1 and 2 • Assess cardiac function using ECG • Transfer to ICU for vasopressor and/or supplemental oxygen management • Tocilizumab 8 mg/kg (maximum 800 mg) as per grade 2 • Dexamethasone 10 mg every 6 hours (or methylprednisolone equivalent) • If patient does not respond in 24 hours, escalate to dexamethasone 20 mg every 6 hours (or methylprednisolone equivalent)
Grade 4	• Supportive care as per grades 1-3 • Transfer to ICU for vasopressor and/or supplemental oxygen management • Tocilizumab 8 mg/kg (maximum 800 mg) as per grade 2 • Methylprednisolone 1,000 mg every 24 hours • If patient does not respond, consider alternative immune suppression with anakinra, antithymocyte globulin, or cyclophosphamide

[a] Lee et al, 2019; [b] Reagan et al 2021; [c] Refer to tocilizumab Prescribing Information for details (ACTEMRA[å] Prescribing Information 2017).
Abbreviations: ASTCT, American Society of Transplant and Cellular Therapy; CRS, cytokine release syndrome; ICU, intensive care unit; IV, intravenous.

APPENDIX 4. MANAGEMENT OF ICANS

ACE1831 is an allogeneic cell therapy product with a potential risk of immune effector cell–associated neurotoxicity syndrome (ICANS).

Along with CRS, another common toxicity observed after immune effector cell (IEC) therapy is neurotoxicity. Common clinical symptoms experienced by patients include encephalopathy, tremor, myoclonus, aphasia, and focal weakness. Cerebral edema is a rare but potentially lethal complication. Imaging with computed tomography and magnetic resonance imaging is typically normal, even in patients with severe ICANS, although a few studies have reported white matter changes in a subset of patients. Lumbar puncture may show a mild pleocytosis, and ICE are typically detected. EEG findings are commonly consistent with encephalopathy, although epileptic events do occur. Corticosteroids are used at most centers for the management of ICANS in addition to supportive care. Tocilizumab does not likely achieve therapeutic concentrations in CSF when administered intravenously and is not recommended for the management of ICANS unless there is concomitant CRS. There is some concern that tocilizumab use in the absence of concomitant CRS may potentiate the severity of ICANS through transient increases in serum IL-6 (Nishimoto, 2008).

Table 22 summarizes current recommendations for toxicity management of ICANS based on the ASTCT grading criteria (Reagan PM et al 2021).

Table 22 Suggested Management of ICANS

ASTCT[a] Grade	Recommended Management[b]

Grade 1	• Supportive care, including:
	  ○ Aspiration precautions
	  ○ Avoidance of sedating medications
	  ○ If not on seizure prophylaxis, initiate prophylactic levetiracetam
	• CT and/or MRI head, EEG, neurologic consultation
	• Consider lumbar puncture if other causes of encephalopathy are suspected
	• Consider dexamethasone 10 mg every 24 hours
	• Consider tocilizumab[c] 8 mg/kg (max 800 mg) if there is concurrent CRS

Grade 2	• Supportive care as per grade 1 • Diagnostic workup as per grade 1 • Continuous pulse oximetry and telemetry • Dexamethasone 10 mg every 12 hours • Tocilizumab 8 mg/kg (max 800 mg) if there is concurrent CRS
Grade 3	• Supportive care as per grades 1 and 2, and consider management in the ICU setting or 1:1 monitoring • Diagnostic workup as per grade 1 • Dexamethasone 10 mg every 6 h • Tocilizumab 8 mg/kg (max 800 mg) if there is concurrent CRS • If there is no improvement after 24 hours, consider escalation to dexamethasone 20 mg every 6 hours
Grade 4	• Supportive care as per grades 1 and 2 • Management in the ICU setting • Methylprednisolone 1,000 mg every 24 hours • If patient does not respond, consider alternative immune suppression with anakinra, antithymocyte globulin, or cyclophosphamide • Additional supportive measures for seizures or cerebral edema as needed

Abbreviations: ASTCT=American Society for Cellular Therapy and Transplant; CRS=cytokine release syndrome; CT=computed tomography; EEG=electroencephalogram; ICANS=immune effector cell–associated neurotoxicity syndrome; ICU= intensive care unit; MRI=magnetic resonance imaging.

a. Lee et al, 2019;
b. Reagan et al 2021
c. Refer to tocilizumab Prescribing Information for details (ACTEMRA Prescribing Information 2017).

APPENDIX 5. RECOMMENDED MANAGEMENT OF ACUTE AND CHRONIC GRAFT-VERSUS-HOST DISEASE

ACE1831 is an allogeneic cell therapy product with a potential risk of acute graft-versus-host disease (aGvHD) and chronic GvHD (cGvHD). Recommendations how to manage acute and chronic GvHD are described below.

All cases of potential aGvHD and cGvHD should be discussed with the Sponsor's Medical Monitor.

Acute GvHD

If aGvHD is suspected clinically, a histological diagnosis (biopsy) should be obtained before initiating treatment. However, treatment should not be delayed if suspected GvHD is Grade 2 or higher.

Grade 1: If skin GvHD is Grade 1, topical steroids should be applied after biopsy of the lesion. Decision to treat should not depend on the biopsy result.

Grade ≥2: Methylprednisolone 2 mg/kg/day IV for 7 days. No dose reduction is allowed during the first 7 days. Tapering of the dose is done slowly and depending on the response. No marked corticosteroid dose reductions are allowed in the early phase and methylprednisolone is not discontinued until all signs of GvHD have disappeared. Nonabsorbable oral steroids (budesonide 9mg/day, 1 daily dose via oral administration) is given for gastrointestinal GvHD, along with systemic corticosteroid.

If there is clear progression after 3 days or if there is no improvement (ie, if the aGvHD has not been downgraded) after 7 days, initiate second-line treatment with horse antithymocyte globulin (ATG) 15 mg/kg IV every other day (6 doses) or rabbit ATG 2 mg/kg IV daily (4 doses) or with alemtuzumab 3 mg IV for the first day followed by 10 mg IV per day for 5 days. Strategies to minimize the risks for opportunistic infection should be taken if subjects are treated with either horse/rabbit ATG or alemtuzumab per institutional guidelines. Treatment options for patients who are refractory to steroids, ATG, and alemtuzumab are the following: sirolimus, mycophenolate, mofetil, infliximab, etanercept, and extracorporeal photopheresis.

Chronic GvHD

Treatment of moderate or severe cGvHD: Prednisolone 1 mg/kg per day for 2 weeks with subsequent tapering if improvements. Tapering consists of prednisolone 1 mg/kg on alternate days over 4 weeks.

Topical steroids may be used in conjunction with systemic steroids in patients with cGvHD limited to the skin or with concomitant involvement of other organs. Second-line treatment of cGvHD is not standardized and specific organ involvement could determine the choice of therapy administered. The following treatment options should be considered for steroid refractory cGvHD patients:

- Ibrutinib or ruxolitinib or belumosudil
- Sirolimus, pentostatin, or rituximab (if primarily skin and musculoskeletal)
- Imatinib (if primarily sclerodermoid skin and lung)
- Extracorporeal photopheresis (if primarily skin, mouth, and liver)

APPENDIX 6. COCKCROFT-GAULT AND MDRD FORMULA

Table 23: Cockcroft-Gault Formula

Serum creatinine units	Gender	Estimated Creatinine Clearance (mL/min)
mg/dL	Male	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)}}{72 \times \text{subject serum creatinine (mg/dL)}}$
	Female	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)} \times 0.85}{72 \times \text{subject serum creatinine (mg/dL)}}$
µM/dL	Male	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)} \times 1.23}{\text{Subject serum creatinine (µM/dL)}}$
	Female	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)} \times 1.04}{\text{Subject serum creatinine (µM/dL)}}$

Table 24: MDRD Formula

$eGFR = 175 \times (S_{Cr})^{-1.154} \times (age)^{-0.203} \times 0.742$ [if female] $\times 1.212$ [if Black]

Abbreviations: eGFR=estimated glomerular filtration rate; MDRD=modification of diet in renal disease.

APPENDIX 7. CRITERIA FOR MACROPHAGE ACTIVATION SYNDROME

Macrophage activation syndrome will be defined as subjects meeting the criteria detailed in Table 25.

Table 25 Macrophage Activation Syndrome Criteria

Meets ALL of the following:	
Characteristic	**Value**
Fever	38.3°C
Ferritin	>684 ng/mL
Meets 2 of the following:	
Platelet count	<181,000/µL
AST	>48 IU/L
Triglycerides	>156 mg/dL
Fibrinogen	≤360 mg/dL

Abbreviations: AST=aspartate aminotransferase.

Source: 2016 Classification Criteria for Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis: A European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. (Ravelli 2016)

APPENDIX 8. BAYESIAN TOXICITY STOPPING BOUNDARIES

Table 26 Treatment Groups A + B (AEs)

Maximum planned sample size=42 in Phase 1 (Treatment Groups A + B) **Minimum number of patients before stopping rules apply=6** **Treatment group size=1** **Maximum toxicity rate of AEs allowed=33%[a]** **Posterior probability of excessive toxicity threshold ≥80%** **Prior distribution (1,1)**												
Number of subjects dosed, n	1	2	3	4	5	6	7	8	9	10	11	12
Boundary, b_n [b]	-	-	-	-	-	*3*	*4*	*4*	*5*	*5*	*5*	*6*
Number of subjects dosed, n	13	14	15	16	17	18	19	20	21	22	23	24
Boundary, b_n [b]	*6*	*6*	*7*	*7*	*8*	*8*	*8*	*9*	*9*	*9*	*10*	*10*
Number of subjects dosed, n	25	*26*	*27*	*28*	*29*	*30*	*31*	*32*	*33*	*34*	*35*	*36*
Boundary, b_n [b]	*11*	*11*	*11*	*12*	*12*	*12*	*13*	*13*	*14*	*14*	*14*	*15*
Number of subjects dosed, n	*37*	*38*	*39*	*40*	*41*	*42*						
Boundary, b_n [b]	*15*	*15*	*16*	*16*	*16*	*17*						

Abbreviations: AE=adverse event; b_n= =number of subjects in treatment group.

a. Refer to protocol Section 10.3.5.3 for a description of AEs to be evaluated for stopping bounds which will be used to assess stopping boundaries

b. If the number of patients experiencing an AE exceeds the stopping boundary, the study will be paused and the SRC will review all available data.

Table 27 Treatment Groups A + B (Deaths)

Maximum planned sample size=42 in Phase 1 (Treatment Groups A + B) **Minimum number of patients before stopping rules apply=3** **Treatment group size=1** **Maximum toxicity rate of death allowed=10%** [a] **Posterior probability of excessive toxicity threshold ≥80%** **Prior distribution (1,1)**												
Number of subjects dosed, n	1	2	3	4	5	6	7	8	9	10	11	12
Boundary, b_n [b]	-	-	*1*	*1*	*1*	*1*	*1*	*2*	*2*	*2*	*2*	*2*
Number of subjects dosed, n	13	14	15	16	17	18	19	20	21	22	23	24
Boundary, b_n [b]	*2*	*2*	*3*	*3*	*3*	*3*	*3*	*3*	*3*	*3*	*4*	*4*
Number of subjects dosed, n	25	*26*	*27*	*28*	*29*	*30*	*31*	*32*	*33*	*34*	*35*	*36*
Boundary, b_n [b]	*4*	*4*	*4*	*4*	*4*	*4*	*5*	*5*	*5*	*5*	*5*	*5*
Number of subjects dosed, n	*37*	*38*	*39*	*40*	*41*	*42*						
Boundary, b_n [b]	*5*	*5*	*6*	*6*	*6*	*6*						

Abbreviations: AE=adverse event; b_n= =number of subjects in treatment group.

a. Deaths associated with disease progression

b. If the number of patients dying exceeds the stopping boundary, the study will be paused and the SRC will review all available data.