1.14.4.1 INVESTIGATOR’S BROCHURE

This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided. An example is given in Appendix 1.

21 June 2019

Lineberger Comprehensive Cancer Center

University of North Carolina

450 West Drive, CB 7295

Chapel Hill, NC 27599

Edition:

Release Date:

|  |
| --- |
| CONFIDENTIALITY STATEMENT |
| The information contained in this document, particularly unpublished data, is the property or under control of Lineberger Comprehensive Cancer Center, and is provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an applicable Institutional Review Board or Independent Ethics Committee. The information is only to be used by you in connection with authorized clinical studies of the investigational drug described in the protocol. You will not disclose any of the information to others without written authorization from Lineberger Comprehensive Cancer Center, except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered. |

SYNOPSIS OF CHANGES TO THE INVESTIGATOR’S BROCHURE

Edition #: 21 June 2019

|  |  |
| --- | --- |
| Previous Edition | Date |
| # |  |

Overall Risk-Benefit

With the changes introduced in this edition of the IB, the risk/benefit assessment

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

Abs Antibodies

AE Adverse Event

ALC Absolute Lymphocyte Count

ALT Alanine Aminotransferase

AST Aspartate Aminotransferase

ATC Activated T-cells

AUC Area Under the Curve

bid Twice Daily

big-ET Proendothelin-1

BP Blood Pressure

BSA Body Surface Area

BUN Blood Urea Nitrogen

CAR Chimeric Antigen Receptor

cGMP Current Good Manufacturing Practice

cGTP Current Good Tissue Practice

Cmax Maximum Plasma Concentration

CNO Certificate of Non-Objection

CNS Central Nervous System

CONMED Concomitant Medication

CR Complete Remission

CRF Case Report Form

CRS Cytokine Release Syndrome

CTCAE Common Terminology Criteria for Adverse Events

DL Dose Level

DLT Dose Limiting Toxicity

DMSO Dimethyl Sulfoxide

DNA Deoxyribonucleic Acid

DSMC Data and Safety Monitoring Committee

EBV Epstein-Barr Virus

ECG Electrocardiogram

FACS Fluorescence-Activated Cell Sorting

FACT Foundation for the Accreditation of Cellular Therapy

FDA Food and Drug Administration

FEV1 Forced Expiratory Volume

GCP Good Clinical Practice

HAMA Human Anti-Mouse Antibody

HLA Human Leukocyte Antigen

HLH Hemophagocytic Lymphohistocytosis

HR Heart Rate

IATA International Air Transport Association

ICF Informed Consent Form

IB Investigator’s Brochure

ICH International Conference on Harmonization

IEC Independent Ethics Committee

IL Interleukin

INR International Normalized Ratio

IRB Institutional Review Board

IRB Institutional Review Board

iv Intravenous

kg Kilogram

L Liters

LCCC Lineberger Comprehensive Cancer Center

LDH Lactate Dehydrogenase

LPD Lymphoproliferative Disorders

m Meter

mAb Monoclonal Antibody

MAS Macrophage Activation Syndrome

mg Milligram

MHC Major Histocompatibility Complex

min Minute

mL Milliliter

mmHg Millimeters Mercury

ng Nanogram

NOEL No Observed Effect Level

NOAEL No Observed Adverse Event Level

NO Nitric Oxide

ORR Overall Response Rate

PAC Premature Atrial Contractions

PBMC Peripheral Blood Mononuclear Cell

PET Positron Emission Tomography

PFS Progression Free Survival

PK Pharmacokinetic

po By Mouth, Orally

qd Once Daily

qPCR Quantitative PCR

RCR Replication Competent Retrovirus

SAE Serious Adverse Event

RSI Reference Safety Information

scFV Single Chain Antibody

SD Stable Disease

SOP Standard Operating Procedure

TCR T-cell Receptor

TNF Tumor Necrosis Factor

TNF-R Tumor Necrosis Factor Receptor

Treg Regulatory T-cells

ULN Upper Limit of Normal

UNC University of North Carolina

VPF Vector Production Facility

WBC White Blood Cell

WHO World Health Organization

X-SCID X-Chromosomal Lined Severe Combined Immunodeficiency

# OVERVIEW

Instructional text extracted from <http://www.ich.org/cache/compo/276-254-1.html>. ICH Harmonised Tripartite Guideline, Guideline for Good Clinical Practice, E6 (R1). Step 5, May 1996.

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration: and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

This guideline delineates the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labeling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with Good Clinical Practice, relevant new information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and/or regulatory authorities before it is included in a revised IB.

Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible IRBs/IECs. In the case of an investigator sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor-investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in this guideline.

## Product Summary

A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product (s ) pharmacological class and its expected position within this class (e.g. advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

### Development Rationale

# PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION

A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.

To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.

Any structural similarities to other known compounds should be mentioned.

## Drug Product

### Description

is a directed, genetically modified autologous T-cell immunotherapy product that is composed of peripheral blood mononuclear cells (PBMC) that have undergone *ex vivo* T-cell activation, gene modification, expansion and formulation.

### Formulation

This is a biological product consisting of in freezing medium. The product has been generated from autologous PBMC, transduced with and expanded in the presence of cytokines.

 will be supplied in cryovials and cryobags containing cells at the concentration of of T-cells. Autologous T-cells (ATCs) will be frozen in a freezing medium containing:

* 10% dimethyl sulfoxide (DMSO)
* 50% Human Serum Albumin (25%) (or autologous serum, if available)
* 40% Hanks balanced salt solution

### Labeling, Storage, and Handling

#### Product Labeling

Due to being an autologous product, the intended recipient of the cellular product is known at the time of manufacturing. The product will be labeled with the recipient’s information.

As the dose is not known at the time that the cellular product is frozen, a coversheet with the volume and cell dose calculations based on the body surface area (BSA) and CAR transduction will be sent with the cells. These calculations should be rechecked at the center prior to infusion. It is acceptable to draw up to 20% more than the calculated dose to allow for wastage in the tubing. In some cases, there will be more cells than needed for the dose.

An example product label is included in Figure 1.

Figure 1 Example Product Label

#### Product Storage

The product will be stored in the vapor phase of liquid nitrogen in a continuously monitored cell bank. At the time of shipment to sites distant from the manufacturing facilities, the vials/bags will be removed from inventory following Standard Operating Procedures for product release. The vials will be placed in a validated charged liquid nitrogen dry shipper equipped with a continuous temperature monitor. The shipped will be labeled to comply with Foundation of the Accreditation of Cellular Therapy (FACT) an International Air Transport Association (IATA). Trained couriers will transport the shipper from the manufacturing site to the hospital for infusion. Upon receipt, the integrity of the vials/bags and the temperature of the shipper will be documented. The data form the temperature logger will be downloaded and printed. The shipping information will be retained at the storage facility.

#### Product Handling

At the time of administration, the cellular product will be thawed and infused per Standard Operating Procedures (SOPs) for infusion of hemopoietic cell products at the treating institution. All institutions participating in the study should be FACT accredited so they will have pertinent policies.

##### Thawing of the Cellular Product

The cellular product will be supplied in cryovial(s) or cryobag(s), which should be transported from the liquid nitrogen storage facility to the site of insuion in liquid nitrogen in a suitable container. In some centers, thawing may be performed in the cell processing laboaroty and then transported to the infusion site. Thawing of the cellular product should follow the following steps:

1. When the treating physician or his/her designee is ready, remove all vials/bags intended for infusion. Both the treating physician/designee and the processing technologist must check the identification on the vial against the patient’s name and number on the prescription. Any discrepancies must be investigated prior to thawing the product.
2. Thaw vials in a sterile beaker/water bath filled with sterile saline.
3. When the component has thawed, wipe the vial with an alcohol swab and place in the biological safety cabinet in an appropriate rack.
4. Remove the cap of a single vial and aspirate the dose required into a labeled syringe, and recap vial immediately. If using a bag, spike the bag with an appropriate adaptor and aspirate the required amount of volume in the syringe.
5. Recap the needle, using the one-handed technique or a recapping device. Remove the needle, attach the red cap, and hand the syringe to the treating physician or designee. This step is not applicable when using bags.
6. The treating physician or designee must compare the patient’s name and medical record number on the syringe with the information on the patient’s wristband bracelet. Any discrepancies must be investigated prior to infusion.
7. The processing technologist should save the thawed vial and either send it to the Microbiology laboratory for sterility and fungal culture or aspirate the residual fluid into a Bactec bottle, which will be sent to the Microbiology laboratory for sterility and fungal culture.

##### Infusion of the Cellular Product

Infusion of the cellular product should allow the following steps:

1. Nursing staff will ensure that the patient has IV access and that the line contains a stopcock for ATC infusion. Normal saline should be running through the IV line to be accessed.
2. Nursing staff will prepare for emergency procedures by ensuring that oxygen and suction equipment are available in the patient room.
3. Nursing staff should ensure that a Code Medication Sheet is available.
4. Nursing staff should ensure emergency drugs and equipment (epinephrine, Benadryl/diphenhydramine, hydrocortisone) are available.
5. Nursing staff will document baseline vital signs (body temperature, pulse rate, respiration rate, blood pressure, O2 saturation +/- breath sounds) on the frequent vital signs sheet.
6. A pre-medication of Benadryl 0.25 mg – 1 mg/kg (up to 50 mg) iv and, if applicable, Tylenol 650 mg (or per pediatric guideline) by mouth (PO) is administered 15-30 minutes prior to the infusion of the cellular product.
7. The cellular product will be infused as soon as possible after thawing.
8. Two licensed staff will identify the patient by verifying the information on the patient armband and component.
	1. They will check the identification bracelet on the recipient for correct name and hospital number.
	2. They will check the identification number on the bracelet against the number on the cellular product container.
9. The ATC infusion may be in a volume of up to 50 mL and may be given through the stopcock at the port closest to the patient. Following infusion, the syringe will be flushed with normal saline 2-3 times before it is removed and a luer lock placed on the stopcock.
10. A nurse must be at the bedside during the first 15 minutes of the infusion.
11. The nurse will monitor and record: vital signs (body temperature, pulse rate, respiration rate, blood pressure) and breath sounds at completion of infusion, at 30 and 60 minutes after completion of infusion.
12. Continuous pulse oximetry is monitored during infusion and for 30 minutes after completion of infusion.
13. Nursing staff will assess for immediate adverse effecting including:
	1. Allergic reaction (anaphylaxis)
	2. Decreased oxygenation (due to micro-emboli)
	3. Nausea/vomiting
	4. Arrhythmia (bradycardia, PAC)
	5. Hypertension
	6. Any other new symptom

##### Sterility Testing

In the case of a positive sterility result is received from the sample of the ATC product sent to Microbiology for culture, the patient’s attending physician must be notified immediately so the patient can be assessed and appropriate antibiotics started.

The result should also be reported to the Data Coordinating Center so the Sponsor can report the result to the appropriate organization e.g. the Institutional Review Board and FDA as described in current Good Tissue Practice/current Good Manufacturing Practice (cGTP/cGMP) regulations.

### Stability

At thaw of the cryopreserved cell product, a sample of the product will be assessed for post-thaw viability by Trypan Blue and whenever sufficient sample is available expression of the transgene.

# NONCLINICAL STUDIES

Introduction: The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavourable and unintended effects in humans.

The information provided may include the following, as appropriate, if known/available:

* Species tested
* Number and sex of animals in each group
* Unit dose (e.g., milligram/kilogram (mg/kg))
* Dose interval
* Route of administration
* Duration of dosing
* Information on systemic distribution
* Duration of post-exposure follow-up
* Results, including the following aspects:
* Nature and frequency of pharmacological or toxic effects
* Severity or intensity of pharmacological or toxic effects
* Time to onset of effects
* Reversibility of effects
* Duration of effects
* Dose response

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

There are no pertinent animal models for study the safety of CAR T-cells, so there are no formal preclinical studies of pharmacology or toxicology for this cellular product.

Some preclinical studies have been performed with in immune-incompetent mice models to assess antitumor activity as described in the below sections.

## Overview

There is a substantial body of literature delineates the use of CAR T-cells in rodent tumor models {Savoldo, 2007 #38}{Sadelain, 2003 #275}{Hombach, 2002 #276}{Di Stasi, 2009 #58}. Despite consistent and robust expression of CAR molecules in T cells, early clinical studies of the approach were disappointing. A major problem of CAR T-cells is their lack of expansion and persistence in vivo {Dotti, 2014 #18}{Dotti, 2009 #17}. A number of factors likely contributed to these differences but a major impact is related to the inability of CAR-engagement alone to recapitulate the co-stimulatory events that follow the physiologic engagement of the native αβTCR. Full activation and proliferation of T-cells requires not only TCR engagement (first signal), but also co-stimulation provided by antigen presenting cells (APCs, second signal) and cytokines (third signal) {Dotti, 2014 #18}{Dotti, 2009 #17}. A multiplicity of these costimulatory receptor-ligand and cytokine signals is required, in an optimal temporal and spatial sequence. CAR T-cells lack any such costimulatory molecule expression (e.g. CD80 and CD86) and do not release helper cytokine. CAR T-cells cannot receive activation through stimulation provided by professional APCs in secondary lymphoid organs since the native receptors on CAR T-cells are not specifically directed towards antigens on the hosts’ APCs. To compensate for the lack of costimulation following CAR engagement, costimulatory signaling domains (CD28, OX40, 41BB, etc.) have been incorporated as part of the CAR itself. These polyclonally activated T lymphocytes expressing these novel “second generation” CAR T-cells have been tested in rodent models and clinical studies testing these “second generation” CAR T-cells are currently open at several institutions {Brentjens, 2011 #19}{Kochenderfer, 2012 #20}{Porter, 2011 #21}{Savoldo B, 2011 #22}{Cruz, 2013 #23}{Lee, 2015 #24}{Kochenderfer, 2015 #25}{Maude, 2014 #27}{Kochenderfer, 2013 #26}{Savoldo, 2007 #38}.

Specifically for , published data supports the safety and efficacy of T-cells in immunodeficient mouse models. The below include pre-clinical data supporting the use of has been published.

## Pharmacology

Several *in vitro* and *in vivo* systems were evaluated to determine the therapeutic efficacy of . These systems involved the generation of from healthy donors cells or cells from patients with and using functional assays to determine the efficacy of when targeting cell lines….

Furthermore, the *in vivo* activity of in …

Additional ancillary assays were performed to further characterize the properties of including cross reactivity.

These pharmacology studies are further discussed in the below sections and detailed in . These studies are further summarized in Appendix 2.

## In Vitro Activity of

## Demonstrate In Vivo Efficacy

## Primary Pharmacodynamics

Refer to Section 3.4.

## Secondary Pharmacodynamics

The pharmacodynamic parameters for is cytokine response during *in vivo* T-cell activation and expansion, which is not applicable for the immunocompromised mouse model, which is devoid of normal B-cells. Human serum cytokine responses have been characterized in the clinical studies (Section 4.3.1).

## Safety Pharmacology

 is only expressed on and thus has limited tissue distribution. Additionally, this product is governed by the pharmacological principal of target-specific T cell-mediated cytotoxicity. As such, classical safety pharmacology studies that are required for low molecular weight drugs were not warranted nor were conducted for this product.

## Pharmacodynamic Drug Interactions

No pharmacodynamics drug interactions studies have been conducted.

## Non-Clinical Pharmacokinetics and Metabolism

### Cellular Engraftment and Persistence of

#### Absorption

Not applicable as is administered via intravenous infusion.

#### Distribution

#### Metabolism and Excretion/Elimination

The fate of is expected to be similar to that of other lymphocytes.

### Toxicokinetics

No toxicokinetic data were collected.

### Drug-Drug Interactions

No formal drug-interaction studies have been completed. It is not expected that will have pharmacokinetic drug interactions.

## Toxicology

Available preclinical models do not allow for the investigation of *in vivo* side effects as animal models do not have the target antigen and immunocompromised mouse models must be used. Frequent side effects identified with other CAR T cell products such as cytokine release syndrome, neurotoxicity and tumor lysis syndrome may not be identified or investigated in the preclinical models.

### In Vitro Expansion Profile of

### In Vivo Safety Assessment of

### Genotoxicity/Mutagenicity Studies

Genotoxicity assays and mutagenicity studies were not performed. There was no evidence of transformation and/or immortalization of T-cells in the in vivo expansion studies of healthy donor and patient-derived T-cells transduced with . Additionally, the in vivo studies of immunocompromised mice did not show signs of abnormal cell growth or clonal cell expansion for after the infusion.

Genetic analysis of integration locations in X products determined that there was no evidence for preferential integration near genes of concern or preferential outgrowth of cells with integration sites near genes of concern.

Fertility studies have not been performed.

### Carcinogenicity Studies

Classical carcinogenicity studies are not appropriate for this genetically modified CAR T cell product and thus the potential for carcinogenicity has not been addressed.

There has been concern that even a single retroviral integration can contribute to oncogenesis. Insertional upregulation of cellular proto-oncogenes was the main cause of 5 serious adverse event in two different X-chromosomal linked severe combined immunodeficiency (X-SCID) gene therapy trials. The French study reported 4 cases. Fischer’s group replaced the missing common gamma chain (γc) in X-SCID patients with ex vivo retroviral transduction of autologous stem cells. Four of 11 treated patients developed T-ALL associated with a single retroviral integrant [1, 2]. The integration site of the retrovirus was similar. More recently, a case of leukemia has also been reported in a second study in SCID patients conducted in the United Kingdom. It is likely that correction of γc deficiency and related immunodeficiency syndrome represent special cases. The γc is a shared component of the IL-2, IL-4, IL-7, IL-9 and IL-15 receptors. Hence it is a crucial component of T-cell proliferation and thymogenesis. A proliferative advantage is expected for the progeny of stem cells with functional γc. In females carriers of X-SCID, there is a pattern of non-random X-inactivation in T, B and NK-cells. Moreover, a patient with X-SCID developed substantial numbers of T-cells following spontaneous reversion of the mutant allele in a single hematopoietic stem cell. High efficiency retroviral transduction of human stem cells is difficult to achieve, even with GALV pseudotyping. It is likely that in X-SCID few truly pluripotent stem cells were transduced and that the stem cell pool expressing the highest level of transgene (due to integration at a transcriptionally active site) then underwent numerous doublings to restore the entire T-cell compartment. Random mutations caused by this supra-physiological proliferation, combined with retroviral integration in a transcriptionally active region, might then have led to leukemogenesis.

More recently, 1 of 10 children treated on a gene therapy trial for Wiskott-Aldrich Syndrome developed acute lymphocytic leukemia [3]. In this study, ex vivo retroviral transduction of autologous hematopoietic stem cells with the gene for the defective product (Wiskott-Aldrich Syndrome protein) was performed. Similar to X-SCID patients, the child had a leukemic clone with a retroviral insertion site near the LMO2 gene (communicated at the 2010 ASH annual meeting plenary session). In Wiskott-Aldrich Syndrome, a in X-SCID, a proliferative advantage is expected in the presence of the transgene and thus mechanisms similar to those above described may have been the basis for leukemic transformation. Additionally, 2 subjects treated in a gene therapy trial for chronic granulomatous disease developed myelodysplastic syndrome. One subject died from overwhelming sepsis 27 months after gene therapy, whereas the second subject underwent successful allogenic hematopoietic stem cell transplantation. These patients received autologous hematopoietic stem cells retrovirally transduced to express the missing or defective NADPH oxidase gene. Genetic analysis showed insertional activation at another proto-oncogene in both patients, ecotropic viral integration site 1, which is thought to have accounted for genetic instability and indirectly led to monosomy 7 and MDS. Although in contrast to X-SCID and Wiskott-Aldrich Syndrome, no selective advantage for the transgene-expressing cells was expected because the transgene is not required for survival, the finding of transgene silencing in most abnormal clones suggests some selective pressure against high level oxidase expression, which then may have driven expansion of the pre-leukemic cells.

CAR T-cell products has a very different risk profile than the above previously reported studies. Large doses of transduced T-cells (in the order of 1010 cells) have been administered to subjects that received prior lymphodepletion and no leukemogensis occurred. Although the inclusion of endodomains (such as CD28) in the CAR may enhance proliferation of transgenic T-cells in response to the targeted antigen, there is no reason to believe this effect will lead to uncontrolled T-cell expansion. Ex vivo and published in vivo data using several artificial T-cell receptors show that CD28 sustains limited and temporary expansion over approximately 3 weeks {Maher, 2002 #78}. A clinical trial using one of our CAR T-cell products, CD19-CAR-specific T-cells including the CD28 endodomain, indicated that the T-cells expand significantly for only 2-3 weeks and then they decline without evidence of further expansion {Savoldo B, 2011 #22}. Thereafter, the cells maintain the expression of the transgene, but proliferate further only in the presence of both antigen and exogenous cytokines.

To date, more than 200 subjects have received genetically modified cells in clinical trial including subjects we have treated on one of our protocols using retrovirally marked autologous marrow or retrovirally marked EBV-CTLs {Brenner, 1993 #79}{Heslop, 1996 #80}{Heslop, 2010 #81}{Rooney, 1998 #60}. In none of these studies has malignancy caused by retroviral transduction been reported. Furthermore, a review of CAR T-cell products written by Bonifant et. al. relays that to date there are no cases of malignant transformation and no evidence of vector-induced immortalization, clonal expansion, or enrichment for integration sites near genes implicated in growth control or transformation {Bonifant, 2016 #277}. Given the previous experience with retroviral gene therapy, the risk of retroviral inducted leukemogenesis are low.

### Reproductive Toxicity Studies

Reproductive toxicity studies have not been conducted for .

### Juvenile Toxicity Studies

Juvenile toxicity studies have not been conducted for .

### Other Toxicity Studies

#### Tissue Cross Reactivity

## Overall Assessment of Non-Clinical Studies

The above described preclinical studies have demonstrated that is able to specifically target . The in vitro and in vivo studies have further provided strong evidence for the efficacy of for targeting .

Preclinical models do not allow for the identification of specific potential product-related risks such as cytokine release syndrome, neurotoxicity and tumor lysis syndrome that have been seen in human clinical trials of other CAR T-cell products. However, clinical protocols associated with this product have strict guidelines for the monitoring of potential severe side effects such as CRS in order to provide a comprehensive clinical management plan to reduce the risk to enrolled subjects. Preclinical studies showed that there was no uncontrolled proliferation of and its derived T-cell generations were see in in vitro and in vivo assays. The carcinogenic potential could not be identified in the preclinical studies. The possibility of oncogenicity was deemed to be low based on aggregate data from other similar CAR T-cells products. Long term gene therapy related side effects will be monitored for a total of 15 years in the associated clinical protocols utilizing this product.

# EFFECTS IN HUMANS

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational product(s) other than from in clinical trials, such as from experience during marketing.

## Overview

### Clinical Studies

 are ongoing clinical studies. In addition, completed clinical studies include . A summary of ongoing and complete clinical studies is included in Appendix 3.

## Cellular Kinetics of

### Introduction

The in vivo kinetics of are referred to throughout this section as “cellular kinetics.”

There are several key unique characteristics of CAR T cells that may affect their long term (spanning years) and short term (spanning up to a year) cellular kinetics. These characteristics include 1) their ability to expand after interaction with the target antigen 2) their ability to exit the peripheral blood and lymphoid tissues 3) their ability to interact exit the central blood stream and initiate leukocyte and endothelial cell interactions (margination) and 4) their ability to initiate apoptosis.

### Clinical Cellular Kinetics of

As opposed to the more classical concepts of absorption, distribution, metabolism and excretion, the cellular kinetics of are better described in terms of the products *in vivo* persistence and expansion.

Persistence is defined as the duration of time during which detected *in vivo.*

Expansion is defined as the initial rate of proliferation and the maximum number of CAR T-cells detected in vivo.

Expansion can be compared to the Cmax or the maximal concentration in vivo following administration.

Expansion and persistence of are measured using two methodologies: 1) Flow cytometry to measure the CAR T-cell populations and functional persistence 2) qPCR to measure transgene copy number.

##### Peripheral Blood

##### Humoral Immunogenicity

##### Dose Response, Dose Exposure and Exposure Response

##### Intrinsic and Extrinsic Parameters

##### Bone Marrow

##### Peripheral Blood

##### Humoral Immunogenicity

##### Dose Response, Dose Exposure and Exposure Response

##### Intrinsic and Extrinsic Parameters

##### Bone Marrow

### Bioanalytical Methods

### Absorption and Distribution

### Metabolism and Excretion

The fate of is expected to be similar to that of other lymphocytes.

### Drug-Drug Interactions

No formal drug-interaction studies have been completed. It is not expected that will have pharmacokinetic drug interactions.

The effect of on metabolizing enzyme or transporters is unknown.

### Cellular Kinetics in Different Patient Populations

## Efficacy in Subjects

A total of X infusions of were given prior to the initial efficacy assessment. An additional X infusions may have additionally be given to patients dependent on the disease response to the initial infusion and whether they experienced toxicity related to . The below data represents responses from the initial infusion.

### Exploratory Biomarker Analysis

### Efficacy in

#### Demographics and Baseline Characteristics

#### Efficacy

### Efficacy in

#### Demographics and Baseline Characteristics

#### Efficacy

### Time to Clinical Worsening

#### Supportive Phase 2 Studies

#### Phase 3 Placebo-Controlled Studies

#### Long-Term Studies

### Survival

## Safety

A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

### Safety Evaluations ‑ Methodology and Definitions

### Adverse Events

Table 1 Adverse Events Regardless of Study Drug Attribution

|  |  |  |
| --- | --- | --- |
| Toxicity Category | Toxicity | SubjectsN=?n (%) |
|  |  |  |

Table 2 Grade 3-5 Adverse Events Regardless of Study Drug Attribution

|  |  |  |
| --- | --- | --- |
| Toxicity Category | Toxicity | SubjectsN=?n (%) |
|  |  |  |

Table 3 Adverse Events Determined by the Sponsor to be at least Possibly Related to Study Drug

|  |  |  |
| --- | --- | --- |
| Toxicity Category | Toxicity | SubjectsN=?n (%) |
|  |  |  |

Table 4 Grade 3-5 Adverse Events Determined by the Sponsor to be at least Possibly Related to Study Drug

|  |  |  |
| --- | --- | --- |
| Toxicity Category | Toxicity | SubjectsN=?n (%) |
|  |  |  |

#### Adverse Events in Study Subjects

#### Supportive Phase 2 Studies

#### Phase 3 Placebo-Controlled Studies

#### Long-Term Studies

### Deaths, Serious Adverse Events, and Discontinuations Due to Adverse Events

Table 5 Serious Adverse Events and Deaths Regardless of Study Drug Attribution

|  |  |  |
| --- | --- | --- |
| Toxicity Category | Toxicity | SubjectsN=?n (%) |
|  |  |  |

Table 6 Serious Adverse Events and Deaths Determined by the Sponsor to be at least Possibly Related to Study Drug

|  |  |  |
| --- | --- | --- |
| Toxicity Category | Toxicity | SubjectsN=?n (%) |
|  |  |  |

#### Supportive Phase 2 Studies

#### Phase 3 Placebo-Controlled Studies

#### Long-Term Studies

### Cytokine Release Syndrome

Table 7 Cytokine Release Syndrome Post CAR T-cell Infusion

|  |  |
| --- | --- |
|  | SubjectsN=?n (%) |
| Number of Subjects with CRS |  |
| Of Subjects with CRS (% of subject with CRS) |  |
|  Admitted to the ICU |  |
|  Duration of time in ICU |  |
|  Range of time in ICU |  |
|  Incubated  |  |
|  Duration of incubation |  |
|  Range of time incubated |  |
|  Disseminated intravascular coagulation observed |  |
|  Bleeding observed |  |
|  Blood product given in support of bleeding |  |
|  Received Tociluzumab |  |
|  1 dose |  |
|  2 doses |  |
|  Received Steroids |  |
| The Highest Grade CRS episode is summarized for each subject. |

### Safety of Subsequent Infusions

## Conclusions on Safety and Efficacy in Humans

## Investigator Notifications

Table 8 IND Safety Reports

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study | Indication | Manufacturer No. | Suspected Adverse Reaction | Date of Report |
|  |  |  |  |  |

# MARKETING EXPERIENCE

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarised (e.g., formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

 has not been marked in any country and no marketing applications have been submitted.

# GUIDANCE FOR THE INVESTIGATORS

This section should provide an overall discussion of the nonclinical and clinical data, and should summarise the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that is based on previous human experience and on the pharmacology of the investigational product.

Indication

 will be evaluated in patients with . The cellular product will be assessed for safety and persistence. Information will be collected about the antitumor activity.

Product

The product has been generated from the recipient by transduction with gamma retroviral vector encoding CAR.

 will be supplied in cryovials or bags in a validated charged liquid nitrogen dry shipper. Upon receipt the vials should be transferred to liquid nitrogen storage at the facility.

The cellular product will be frozen in a freezing medium containing:

* 10% dimethyl sulfoxide (DMSO)
* 50% Human Serum Albumin (25%) (or autologous serum, if available)
* 40% Hanks balanced salt solution

Safety

 cells will primarily targeted cells. Potential toxicities may be categorized as those related to infusion of T-cells, transduction, cross-reactivity with normal tissues, cytokine release syndrome (CRS), macrophage activation syndrome (MAS) and tumor lysis syndrome.

Infusion of T-cells

This cellular product is manufactured using autologous peripheral blood, so there is no risk of alloreactivity. Many previous studies have infused much larger numbers of autologous T-cells that have been activated ex vivo with no adverse effects {Laport, 2003 #33}{Rapoport, 2005 #34}.

Transduction

Retroviral transduction results in new, random integration in host cell DNA, which rarely may cause abnormal or uncontrolled proliferation. This effect is much more common with replication-competent retrovirus, where each cell receives multiple integrants. The producer line and all batches of supernatant were tested with biological assays for RCR to exclude this possibility.

Recently, there has been concern that even a single retroviral integration can contribute to oncogenesis. Insertional upregulation of cellular proto-oncogene was the main cause of 5 serious adverse events to two different X-chromosomal linked severe combined immunodeficiency (X-SCID) gene therapy trials. The France study reported 4 cases. Fischer’s group replaced the missing common gamma chain (γc) in X-SCID patients with ex vivo retroviral transduction of autologous stem cells. Four of 11 treated patients developed T-ALL associated with a single retroviral integrant [1, 2]. The integration site of the retrovirus was similar. More recently, a case of leukemia has also been reported in a second study in SCID patients conducted in the United Kingdom. It is likely that correction of γc deficiency and related immunodeficiency syndrome represent special cases. The γc is a shared component of the IL-2, IL-4, IL-7, IL-9 and IL-15 receptors. Hence it is a crucial component of T-cell proliferation and thymogenesis. A proliferative advantage is expected for the progeny of stem cells with functional γc. In females carriers of X-SCID, there is a pattern of non-random X-inactivation in T, B and NK-cells. Moreover, a patient with X-SCID developed substantial numbers of T-cells following spontaneous reversion of the mutant allele in a single hematopoietic stem cell. High efficiency retroviral transduction of human stem cells is difficult to achieve, even with GALV pseudotyping. It is likely that in X-SCID few truly pluripotent stem cells were transduced and that the stem cell pool expressing the highest level of transgene (due to integration at a transcriptionally active site) then underwent numerous doublings to restore the entire T-cell compartment. Random mutations caused by this supra-physiological proliferation, combined with retroviral integration in a transcriptionally active region, might then have led to leukemogenesis. More recently, 1 of 10 children treated on a gene therapy trial for Wiskott-Aldrich Syndrome developed acute lymphocytic leukemia [3]. In this study, ex vivo retroviral transduction of autologous hematopoietic stem cells with the gene for the defective product (Wiskott-Aldrich Syndrome protein) was performed. Similar to X-SCID patients, the child had a leukemic clone with a retroviral insertion site near the LMO2 gene (communicated at the 2010 ASH annual meeting plenary session). In Wiskott-Aldrich Syndrome, a in X-SCID, a proliferative advantage is expected in the presence of the transgene and thus mechanisms similar to those above described may have been the basis for leukemic transformation. Additionally, 2 subjects treated in a gene therapy trial for chronic granulomatous disease developed myelodysplastic syndrome. One subject died from overwhelming sepsis 27 months after gene therapy, whereas the second subject underwent successful allogenic hematopoietic stem cell transplantation. These patients received autologous hematopoietic stem cells retrovirally transduced to express the missing or defective NADPH oxidase gene. Genetic analysis showed insertional activation at another proto-oncogene in both patients, ecotropic viral integration site 1, which is thought to have accounted for genetic instability and indirectly led to monosomy 7 and MDS. Although in contrast to X-SCID and Wiskott-Aldrich Syndrome, no selective advantage for the transgene-expressing cells was expected because the transgene is not required for survival, the finding of transgene silencing in most abnormal clones suggests some selective pressure against high level oxidase expression, which then may have driven expansion of the pre-leukemic cells.

This product should have a very different risk profile. The transduced cells will have no particular proliferative advantage over non-transduced T-cells. To date, more than 500 patients have received genetically modified cells in clinical trials. In none of these has malignancy caused by retroviral transduction been reported. There are over 250 clinical trials incorporating CAR T-cells registered as being open on clinicaltrials.gov, across all malignancies. There have been no reported incidences of retroviral transduction related side effects as a result of CAR T-cell therapy.

Cross-Reactivity with Normal Tissues

CRS

Cytokine release syndrome is a potential major side effect of CAR T-cell therapy and results from the release of inflammatory cytokines secondary to T-cell activation. The severity of CRS may be related to tumor burden, particularly for therapy involving CAR T-cells {Maus, 2014 #32}. CRS may correlate with anticancer activity (although whether the severity correlates, as well, is an outstanding question. CRS is often accompanied by high levels of IL-6 {Maus, 2014 #32}.

Symptoms of CRS vary greatly and may include (but are not limited not) fever, rash, hypoxemia, delirium, hypotension, nausea and diarrhea. When associated with CAR T-cell therapy, symptom onset can occur days to weeks after the infusion, perhaps associated with maximal in vivo expansion of T-cells. Very high doses of T-cells may result in early more severe reactions, although a clear dose response relationship has not yet been defined. Strategies to minimize this syndrome including lowing the dose of CAR T-cells and treatment with an anti-IL-6 receptor antibody, or in severe cases, corticosteroids.

MAS

Macrophage activation syndrome has been found previously in patients with acute lymphoblastic leukemia receiving CAR T-cell therapy. Macrophage activation syndrome is characterized by pancytopenia, liver insufficiency, coagulopathy and neurological sympotoms. MAS is thought to be mediated by uncontrolled prolideration and activation of T-cells leading to macrophage activation and differentiation and cytokine production with hemophagocytic lymphohistocytosis (HLH).

Diagnosis of macrophage activation syndrome includes pancytopenia, fever, elevated AST, elevated ALT, elevated triglycerides, elevated LDH, increased PT, and increased aPTT associated with fibrin split products and decreased fibrinogen. Additionally, splenomegaly, hepatomegaly and CNS dysfunction characterized by lethargy, irritability, disorientation, headache, seizures and coma can be found.

Tumor Lysis Syndrome

Neurotoxicity from CAR T-cell therapy can occur as part of cytokine release syndrome or as an independent process. The underlying pathophysiology for neurologic toxicity from CAR T-cell therapy is not fully understood. CAR T-cells in the CNS may play a role. However, the heightened systemic inflammatory and cytokine state resulting from CAR T-cell therapy may also be a factor, as other therapies associated with increased cytokine levels have also been associated with neurologic toxicities, such as high-dose interleukin-2 (IL-2) and blinatumomab.

The symptoms and manifestations of neurotoxicity are broad and range from confusion/altered mental status to seizure to cerebral edema. Routine monitoring is critical in patients receiving CAR T-cell therapy to identify neurologic symptoms early and neurology should be consulted for any patients that exhibit early signs/symptoms of neurotoxicity. Early interventions should be employed to prevent worsening, especially if therapies are already indicated such as corticosteroids.

Development of Human Anti-Mouse Antibody (HAMA)

Like the majority of available CAR T-cell therapies, this cellular product was generated using a single chain antibody variable fragment (scFv) of murine origin. Although there are several reports were CAR T-cells containing an scFv with murine sequences have been given to cancer patients, and antibodies (IgG’s) to the CAR have been detected, to date adverse effects of these antibodies have not been reported in human studies. [4, 5]. Similarly, human subjects given infusion of T-cells engineered to express murine T-cell receptors have developed antibodies to the T-cell receptors without adverse effects [6].

There is, however, a possibility that an acquired immune response to a component of the cell product, related to the CAR itself. The clinical scenario of such reaction consists of an IgE-mediated anaphylaxis event triggered by systemic degranulation of mast cells and basophils {Castells, 1987 #123}. To confirm a clinically suspected anaphylaxis event, tryptase levels can be measured in sera samples. Serum tryptase is the best clinically measurable indicator of recent mast cell degranulation, with levels typically peaking 15-60 minutes after symptom onset and declining with a half-life of 2 hours {Schwartz, 1989 #124}.

It is therefore required that IgG HAMA are tested prior to subsequent infusions, if applicable. The absence of HAMA must be confirmed prior to re-infusion.

Clinical Studies

|  |  |
| --- | --- |
| Dosage/Administration: |  will be administered at doses ranging from to . After thawing, the product will be drawn up in a syringe in a biological safety cabinet and infused intravenously. |
| Contraindications: |  should not be infused in patients who do not meet the eligibility criteria. |
| Interactions: |  should be infused in a line with normal saline running and be flushed with normal saline. |
| Pregnancy/Lactation: | It is not known how could affect an unborn child. |
| Early Reactions: | Adverse events attributable to T-cell administration occur in a small percentage of the treated population and include a mild increase in blood pressure, not requiring intervention, and mild headache. Early reactions are usually related to the cryopreserved components and include mild flushing, slight slowing of heart rate, and a “bad taste” in the mouth. Severe immediate reactions are rare after T-cell infusions and include pulmonary edema and dyspnea, persistent nausea and vomiting, increased blood pressure, fever, anaphylactic shock, bradycardia and/or cardiac arrest. |
| Management of Early Reaction: | Early reactions generally do not require intervention. If a severe reaction occurs, the patient should be immediately transferred to the ICU for intensive monitoring and intervention with blood pressure support, steroids and management of anaphylaxis. |
| Late Reaction: | Late adverse events attributable to T-cell administration include cross reactivity with normal tissues, CRS, MAS, neurotoxicity, and tumor lysis syndrome. CRS may present with systemic fever, skin rash and a general feeling of unwellness, blood pressure changes, acute pulmonary edema and dyspnea, hypoxia, pulmonary infiltrates, capillary leak syndrome, weight gain, renal impairment and electrolytic changes. |
| Management of Late Reaction: | Depending on severity, the patient may need to be transferred to the ICU for intensive monitoring and intervention with blood pressure and respiratory support, steroids, and management of anaphylaxis. Initiation of broad-spectrum antibiotics should be considered. In the case of severe or life-threatening CRS, the IL-6 receptor antibody (tocilizumab) should be given. |
| Dependence/Abuse Potential: | None |

APPENDICES

Company Core Data Sheet

Tabular Summary of Nonclinical Studies

Tabular Summary of Clinical Studies

1. REFERNCE SAFETY INFORMATION (RSI)

The RSI for constitutes the sponsor’s list of expected SARs which is used for regulatory reporting purposes.

The following RSI for is used for safety reporting purposes in clinical studies conducted within the United States.

1. TABULAR SUMMARY OF NONCLINICAL STUDIES

| Study Name | Key Findings | Reference (Figure #) |
| --- | --- | --- |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |

1. TABULAR SUMMARY OF CLINICAL STUDIES

| Protocol No.Report No. (References)StatusStart‑completion dates | Design/Objectives | Study population and demographics | Dose (No. exposed each treatment), Route and Dosage Form | Results/Conclusions |
| --- | --- | --- | --- | --- |
| Phase 1 Studies |
|  |  |  |  |  |  |
| Phase 2 Studies |
|  |  |  |  |  |  |
| Phase 3 Studies |
|  |  |  |  |  |  |

References

1. Hacein-Bey-Abina, S., et al., *A serious adverse event after successful gene therapy for X-linked severe combined immunodeficiency.* N Engl J Med, 2003. **348**(3): p. 255-6.

2. Hacein-Bey-Abina, S., et al., *LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1.* Science, 2003. **302**(5644): p. 415-9.

3. Ott, M.G., et al., *Correction of X-linked chronic granulomatous disease by gene therapy, augmented by insertional activation of MDS1-EVI1, PRDM16 or SETBP1.* Nat Med, 2006. **12**(4): p. 401-9.

4. Kershaw, M.H., et al., *A phase I study on adoptive immunotherapy using gene-modified T cells for ovarian cancer.* Clin Cancer Res, 2006. **12**(20 Pt 1): p. 6106-15.

5. Till, B.G., et al., *Adoptive immunotherapy for indolent non-Hodgkin lymphoma and mantle cell lymphoma using genetically modified autologous CD20-specific T cells.* Blood, 2008. **112**(6): p. 2261-71.

6. Davis, J.L., et al., *Development of human anti-murine T-cell receptor antibodies in both responding and nonresponding patients enrolled in TCR gene therapy trials.* Clin Cancer Res, 2010. **16**(23): p. 5852-61.