STUDY PROTOCOL

Tile: Real-world Clinical effectiveness & Safety LV009, an *in vivo* CAR-T for the treatment of Hematologic cancers, Auto-immune diseases & HLA/ AAV sensitization.

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LIST OF ABBREVIATIONS

AE	Adverse event
ALL	acute lymphoblastic Leukemia
BMA/ BMP	Bone marrow aspirate/ Bone marrow puncture
BW	Body weight
CAR	Chimeric antigen receptor
CAR-T	Chimeric Antigen Receptor T Cells
CD	Cluster of differentiation
CI	Confidence interval
CNS	Central Nervous system
COA	Certificate of Analysis
CR	Complete response
CRF	Case Report Form
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CT	Computed tomography
DFS	Disease-free survival
DLBCL	B cell Lymphomas
EFS	Event-free survival
EMD	Extra medullary disease
FACS	Fluorescence-activated cell sorting, same as Flow-cytometry
FBC/ CBC	Full Blood Count/ Complete Blood Count

FCI	Flow-cyto-immuno-phenotyping
GMP	Good Manufacturing Practice
GVHD	graft versus host disease
Hb	Hemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency virus
HLA	Human leucocyte antigen
HLH-MAS	Haemophagocytic lymphohistiocytosis- macrophage activation syndrome
HSCT	haematopoietic stem-cell transplantation, aka bone marrow transplant
ICANS	Immune Effector Cell-Associated Neurotoxicity Syndrome
ICF	Informed Consent Form
IHC	Immunohistochemistry
IPT	Immuno-pheonotyping
IRB/IEC	Institutional Review Board/ Independent Ethics Committee
ISH	In situ hybridization
IV	Intravenous
LMIC	Low-middle Income countries
LNP	lipid nanoparticle
LP	Lumbar puncture
LV	Lentivirus
MG	Myasthenia Gravis,
MM	Multiple myeloma
MOH	Ministry of Health Malaysia
MRD	minimal residual disease
MRI	Magnetic resonance imaging
mRNA	messenger RNA
MS	Multiple sclerosis
NGS	Next Generation sequencing
NMOSD	Neuromyelitis optica spectrum disorder
OS	Overall survival
PBMC	peripheral blood mononuclear cells
PBMNC	Peripheral Blood Mononuclear cells
PCR	Polymerase chain reaction
PD	Progressive disease
PFS	Progression-free survival
Ph+	Philadelphia translocation with BCR–ABL1 fusion
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
PR	Partial response
PRN	Pro re nata; as circumstances may require
QC	Quality control
Rx	Treatment
SAE	Serious Adverse Event
SBP	Systolic blood pressure
SD	Stable disease
SLE	Systemic lupus erythematosus
SOC	Standard of care
sPO2	Arterial oxygen saturation
SS	Systemic sclerosis
TKI	Tyrosine kinase inhibitors
TLS	Tumour- lysis syndrome
TRM	Treatment related mortality
TU	Transducing Unit
TWC	Total white count

VSV-G	Vesicular stomatitis virus glycoprotein
WHO	World Health Organisation

PROTOCOL SUMMARY

Study title	Real-world Clinical effectiveness & Safety LV009, an in vivo CAR-T for the treatment of Hematologic cancers, Auto-immune diseases & HLA/ AAV sensitization.
Study objective	The study objective is to determine the real-world safety and effectiveness of LV009 therapy for 3 potential indications: (1) refractory or relapsed hematologic cancers (acute lymphoblastic Leukemia, B cell Lymphomas, multiple myeloma), (2) auto-immune diseases, (3) de-sensitization of patients awaiting organ transplant or AAV-based gene therapy who have pre-existing anti-HLA or anti-AAV antibodies.
Study design	This is an observational study designed to determine the real-world safety and effectiveness of LV009, an *in vivo* CAR-T therapy, among patients with hematologic cancers, auto-immune diseases, or HLA/AAV sensitization. Following the administration of LV009, patient will be monitored for toxicity and response to treatment. No subjects will be withdrawn from the study, and subjects could freely drop out from the study anytime, simply by not showing up.
Study Population	The study population consists of male or female patients with hematologic cancers, auto-immune diseases, or HLA/AAV sensitization who have exhausted all current standard of care (SOC) therapies and who will consent to receive LV009 therapy. *Inclusion criteria:* The participant may enter the study if ALL of the following apply: 1. Willing and able to give written informed consent for participation in the study. 2. Diagnosis by imaging or histologically or biomarker confirmed, 2.1 Refractory or relapsed hematologic cancers (acute lymphoblastic Leukemia, B cell Lymphomas, multiple myeloma) 2.2 Auto-immune diseases, including Systemic lupus erythematosus (SLE), Inflammatory Myositis, Systemic sclerosis, Myasthenia Gravis, Multiple sclerosis, Neuromyelitis optica, Stiff Person syndrome, Demyelinating radiculoneuropathy, Auto-immune Encephalitis, Thrombo-cytopenic purpura, Hemolytic anemia 2.3 Pre-existing anti-HLA or anti-AAV antibodies while on wait list for organ transplant or AAV-based gene therapy. 3. Adequate marrow, renal and hepatic functions. 4. Patients of reproductive potential (men and women) must agree to use medically accepted barrier methods of contraception (e.g., male or female condom) at the time of pregnancy test (women of childbearing potential only), during the course of the study and for 90 days after the last dose of study drug, even if oral contraceptives are also used. All subjects of reproductive potential must agree to use both a barrier

	method and a second method of birth control during the course of study and for 90 days after the last dose of study drug.
	Exclusion criteria 1. Known active central nervous system (CNS) metastases. 2. Known Hepatitis B or C or HIV infection 3. Active infection or fever ≥ 38°C within 3 days of the first scheduled dose of LV009
Estimated duration of the study	The study will require approximately 5 years from the time the first participant is enrolled until the last participant's cancer survival outcome.
Number of Participants	Approximately 100 subjects will be enrolled in the study
Duration of Participation	Each participant will participate in the study for 5 years or until death, whichever is earlier.

01 INTRODUCTION & RATIONALE

1.1 Chimeric antigen receptor T (CAR-T) therapy

Chimeric antigen receptor T (CAR-T) cells are genetically engineered to express Chimeric Antigen Receptor (CAR) which enable the T cells to recognize specific tumour antigen. Thus CAR-T are designed to redirect T-cell signaling to a target antigen of choice. CAR-T has been a remarkably effective cancer immunotherapy. Since 2017, the US FDA has approved seven CAR-T cell products indicated for a variety of refractory or relapsed hematologic cancers (acute lymphoblastic Leukemia, B cell Lymphomas, multiple myeloma) [1]. More recently, CAR T cell therapy has received first approval for the treatment of a solid cancer (claudin18.2-positive, HER2-negative advanced gastric/ gastroesophageal junction adenocarcinoma) [2]. Besides cancers, other emerging indications for CAR-T therapy include B cell–mediated autoimmune diseases [3] and de-sensitization of patients awaiting organ transplant or AAV-based gene therapy who have pre-existing anti-HLA or anti-AAV antibodies [4,5,6,7].

These conventional autologous CAR-T therapies rely on an *ex vivo* manufacturing process. The process starts with an apheresis procedure to harvest T cells from a patient, follows by isolation and activation of T cells, *in vitro* transduction of the CAR transgene via viral or non-viral vectors and expansion of the genetically modified cells, and subsequent reinfusion into the patient. This conventional *ex vivo* manufacturing process has several challenges:

- It is very costly. The commercially available products are listed at USD450,000 per infusion, severely limiting their accessibility in Low-middle Income countries (LMIC) [8].
- It is complex which can only be performed in specialized facilities [8].
- It is time-consuming, with up to 30% of patients who had undergone apheresis unable to receive subsequent CAR-T infusion because of disease progression or other comorbidities [9].
- And finally, the *in vitro* manipulation of T cells inevitably changes their phenotype, leading to differentiation and exhaustion phenotypes, which may impact on their efficacy [10].

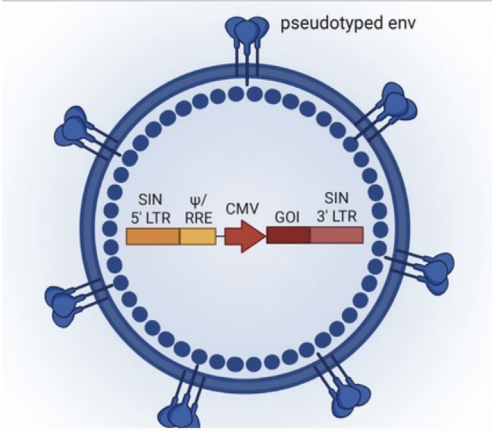
1.2 In vivo CAR-T

To overcome the above-mentioned barriers, a transformative alternative has recently emerged: in vivo generation of CAR-T cells through direct infusion of a CAR-encoding vector. This approach enables endogenous T cell reprogramming without apheresis and ex vivo manipulation. Proof of concept has been demonstrated using both viral (lentiviral and adenoviral) and non-viral (lipid nanoparticle) platforms [11,12]. Clinical translations have also begun demonstrating early safety and efficacy for the treatment of cancer and autoimmune disease [13,14]. Eliminating the costly and complex ex vivo manufacturing process will have huge potential to lower the cost, increase treatment quality and enable more timely delivery of treatment to severely ill patients.

The availability of lower cost *in vivo* CAR-T will significantly improve accessibility to this important advanced therapy Low-middle Income countries (LMIC).
One promising candidate is LV009 (manufacturer PersonGen BioTherapeutics, Suzhou China), an improved third-generation Lentiviral vector (LV) intended for intravenous administration to generate a fully human anti-CD19 / anti-BCMA CAR T cell in vivo.

The LV is an enveloped spherical RNA virus 80-150 nm in size belonging to the Retroviridae family, Lentivirus genus. Projections of envelope make the surface appear rough with tiny spikes (see figure).
Its envelope (env) is pseudotyped with an engineered vesicular stomatitis virus glycoprotein (VSV-G) fusogen, and is further engineered to display a CD7-targeting camelid single-domain antibody (VHH nanobody) together with a CD3-targeting monoclonal antibody.
Binding to these receptors redirects the LV to selectively target and transduce CD7 and CD3 positive T cells and natural killer (NK) cells, enabling precise *in vivo* delivery of CAR19 transgene and cellular reprogramming.

LV009 viral vector construct



Abbreviations: env envelope; GOI gene of interest (CD19 CAR); RRE rev response element; CMV, cytomegalovirus; LTR long terminal repeat; SIN self-inactivating;

Preclinical data from mouse models indicate LV009 generated in vivo both CAR T cells and CAR NK cells with subsequent depletion of CD19+ B cells, potent
antitumor efficacy and favorable safety, following a single intravenous administration [15].
LV009 will be undergoing clinical trial in China (ClinicalTrials.gov number, to be registered). The treatment is also being made available under early or expanded access use for selected patients outside China unable to enrol in clinical trials.

All patients to be treated with LV009 provided through this early or expanded access program shall be enrolled under this protocol to evaluate its safety and clinical effectiveness.

02 STUDY OBJECTIVES

The study objective is to determine the real-world safety and effectiveness of LV009 therapy for 3 potential indications: (1) refractory or relapsed hematologic cancers (acute lymphoblastic Leukemia, B cell Lymphomas, multiple myeloma), (2) auto-immune diseases, (3) de-sensitization of patients awaiting organ transplant or AAV-based gene therapy who have pre-existing anti-HLA or anti-AAV antibodies.

2.1 Specific objectives

The specific objectives are:

- To determine clinical effectiveness of LV009, an *in vivo* CAR-T therapy, for the above-mentioned indications.
- To describe the safety profile of LV009 as evaluated by adverse events reporting and laboratory tests.

03 STUDY DESIGN

This is an observational study designed to determine the real-world safety and effectiveness of LV009, an *in vivo* CAR-T therapy, among patients with hematologic cancers, auto-immune diseases, or HLA/AAV sensitization.

Following the administration of LV009, patient will be monitored for toxicity and response to treatment.

No subjects will be withdrawn from the study, and subjects could freely drop out from the study anytime, simply by not showing up.

04 STUDY POPULATION

The study population consists of male or female patients with hematologic cancers, auto-immune diseases, or HLA/AAV sensitization who have exhausted all current standard of care (SOC) therapies and who will consent to receive LV009 therapy.

4.1 Inclusion criteria

The participant may enter the study if ALL of the following apply:

1. Willing and able to give written informed consent for participation in the study.
2. Diagnosis by imaging or histologically or biomarker confirmed,
   - 2.1 Refractory or relapsed hematologic cancers (acute lymphoblastic Leukemia, B cell Lymphomas, multiple myeloma)
   - 2.2 Auto-immune diseases, including Systemic lupus erythematosus (SLE), Inflammatory Myositis, Systemic sclerosis, Myasthenia Gravis, Multiple sclerosis, Neuromyelitis optica, Stiff Person syndrome, Demyelinating radiculoneuropathy, Auto-immune Encephalitis, Thrombo-cytopenic purpura, Hemolytic anemia
   - 2.3 Pre-existing anti-HLA or anti-AAV antibodies while on wait list for organ transplant or AAV-based gene therapy.
3. Adequate marrow, renal and hepatic functions.
4. Patients of reproductive potential (men and women) must agree to use medically accepted barrier methods of contraception (e.g., male or female condom) at the time of pregnancy test (women of childbearing potential only), during the course of the study and for 90 days after the last dose of study drug, even if oral contraceptives are also used. All subjects of reproductive potential must agree to use both a barrier method and a second method of birth control during the course of study and for 90 days after the last dose of study drug.

4.1 Exclusion criteria

1. Known active central nervous system (CNS) metastases.
2. Known Hepatitis B or C or HIV infection
3. Active infection or fever ≥ 38°C within 3 days of the first scheduled dose of LV009

05 STUDY CONDUCT & DATA MANAGEMENT

5.1 Study data

Data management will be conducted by a data manager who is responsible for the documentation, management and reporting of the study data.

Collection of study data is the joint responsibility of the designated Data Manager and investigators participating in this study.

Each subject shall have the following data collected:

5.1.1 Baseline data

Variables	Data
Demographic	Age, sex, nationality
Co-morbidity	Other diseases under treatment
Treatment indication	• Refractory or relapsed hematologic cancers (acute lymphoblastic Leukemia, B cell Lymphomas, multiple myeloma) • Auto-immune diseases, including Systemic lupus erythematosus (SLE), Inflammatory Myositis, Systemic sclerosis, Myasthenia Gravis, Multiple sclerosis, Neuromyelitis optica, Stiff Person syndrome, Demyelinating radiculoneuropathy, Auto-immune Encephalitis, Thrombo-cytopenic purpura, Hemolytic anemia • Pre-existing anti-HLA or anti-AAV antibodies while on wait list for organ transplant or AAV-based gene therapy
LV009	Dose & dosing schedule
Concomitant therapy	Any Concomitant therapy such as surgery, chemo-radiation and Immune checkpoint inhibitors (ICI)

5.1.2 Outcome data

Variables	Data
Post treatment adverse events	Safety will be evaluated by using adverse events reporting and laboratory tests. Toxicity shall be graded according to the NCI's protocol "Common Terminology Criteria for Adverse Events v4.02".
Post treatment clinical effectiveness	***Survival outcome after treatment for Hematologic cancers:*** (a) Overall survival (OS): Death as a result of any cause (b) Progression-free survival (PFS): Disease progression or death as a result of any cause (c) Event-free survival (EFS): Failure of treatment or death as a result of any cause (d) Disease-free survival (DFS): Time to relapse or death as a result of disease or acute toxicity of treatment
	Tumour response for acute lymphoblastic Leukemia (ALL) • Complete response (CR) is defined as 5% marrow blasts, absence of circulating blasts, and no extramedullary sites of disease with absolute neutrophil count (ANC) 1000 per μL or more and platelets 100 000 per μL or more • Complete response with incomplete count recovery (CRi) is a complete response as defined above but with cytopenia (ANC<1000/ μL or platelets<100 000 per μL • Complete MRD response (CMR) is defined as CR with less than 0.01% marrow blasts by flow cytometry • Stable disease (SD) is disease that does not meet criteria for complete response, complete response with incomplete count recovery, or progressive disease (see below) • Progressive disease (PD) is defined as worse marrow blasts (M) status or no change in M status but greater than 50% increase in absolute peripheral blast count. M status is defined as follows: M1 (best) <5% marrow blasts; M2 5-25% and M3 (worst) >25% marrow blasts present.
	Tumour response for B cell Lymphomas • Complete response (CR) is defined as disappearance of all evidence of disease in nodal masses, spleen and liver as determined by CT (or PET), and in the marrow as determined by morphologic and immunohistochemistry (IHC) assessments.

	• Partial response regression of measurable disease and no new sites in nodal masses, spleen and liver as determined by CT (>50% reduction in SPD) and/or PET. • Stable disease is disease that does not meet criteria for complete or partial response (above), or progressive disease (see below) • Progressive disease or relapsed is defined as any new lesion or increase by > 50% of previously involved sites from nadir
	Tumour response for multiple myeloma • Complete Response (CR): No detectable M-protein in blood or urine via immunofixation, any soft-tissue plasmacytomas disappear, and bone marrow plasma cells drop to < 5%. • Partial Response (PR): A ≥ 50% reduction in serum M-protein, along with a ≥ 90% reduction or normalization in urine M-protein or measurable plasmacytoma size. • Stable disease is disease that does not meet criteria for complete or partial response (above), or progressive disease (see below) • Progressive disease or relapsed is defined as a 25% increase in M-protein or free light chain levels, or the return of clinical symptoms (CRAB criteria)— Calcium elevation, Renal failure, Anemia, or Bone lesions.
	Treatment response for Auto-immune diseases: Per commonly used response criteria for individual diseases below: • Systemic lupus erythematosus (SLE): Definition of Remission in SLE (DORIS) and Lupus Low Disease Activity State (LLDAS) remission [16] • Inflammatory Myositis: International Myositis Assessment and Clinical Studies Group (IMACS) Core Set Measures [17] • Systemic sclerosis: broader Scleroderma Clinical Trials Consortium Activity Index (SCTC-AI) [18] • Myasthenia Gravis: Quantitative Myasthenia Gravis (QMG) score [19] • Multiple sclerosis: No Evidence of Disease Activity (NEDA-3) [20] • Neuromyelitis optica: Annualized Relapse Rate (ARR), the average number of confirmed attacks per patient-year. • Immune Thrombo-cytopenic purpura (ITP): International Working Group (IWG) Response criteria [21] • Immune Hemolytic anemia: Hb concentration and Transfusion avoidance
	Treatment response for HLA/AAV sensitization • Elimination of circulating anti-HLA or anti-AAV antibodies • Depletion of circulating B cells • Successful engraftment without antibody-mediated rejection or Successful AAV vector mediated transgene transduction

5.2 Quality Assurance of Data

Quality assurance (QA) of all data capturing and handling procedures is essential in the conduct of health research. QA is the joint responsibility of the designated Data Manager and investigators participating in this study.

06 STATISTICAL ANALYSIS

6.1 Sample size considerations

Sample size is estimated based on the overall survival between the treatment group (LV009) and the historical control group (not treated with LV009).
For the reference disease relapsed paediatric ALL in LMICs [22,23,24], we expect a hazard ratio of 0.5 (ratio of survival probability of treated group versus untreated group). For alpha 0.05 (two-sided) and power of 0.9, the required total sample size is 84 (42 each group) [25]. Allowing for 20% drop out rate, the sample size required is therefore 100 (50 each group). In the event drop-out rate were to approach 20%, concerted effort will be initiated to recall subjects and/or collect missing data remotely.

6.2 Descriptive statistics

Categorical variables (nominal or ordinal) will be summarized using frequency and percentage of subjects at each level of the variable, and will be compared using the χ^2 test or Fisher's exact test for variables with low expected counts
Continuous variable summaries will include n, mean, median, standard deviation, minimum and maximum values, and analyzed using two sample t-test or Wilcoxon rank-sum test. All subjects without missing data will be included in the analysis.

6.3 Estimation of treatment effectiveness

Covariate balance will be evaluated using a plot of the mean differences between variable values (standardized for continuous variables) for the treated and untreated groups, with a difference of 0.1 or less considered to be acceptable.

Survival curves for the treated and untreated groups will be estimated with the Kaplan–Meier estimator. We will use the Kaplan–Meier estimator with outcome and censoring events to compute the probability ("risk") of the outcome. We then calculate risk ratios for treated as compared with untreated and estimate the treatment effectiveness as one minus the risk ratio.
The 95% confidence intervals will be estimated using the percentile bootstrap method with 500 repetitions. All subjects without missing data will be included in the analysis.

STATA statistical software will be used to conduct the analysis.

07 ETHICS AND REGULATORY CONSIDERATIONS

7.1 Independent Ethics Committee

The study shall be conducted according to the protocol, and will comply with applicable research guidelines [26] and other regulatory requirements. Study data will be archived for 1 year only after completion of the study.
The protocol and any other required documents will be submitted to an Independent Ethics Committee (IEC) for approval. Any amendments to the protocol, other than administrative ones, must also be approved by this committee.

7.2 Subject Information and Consent

Written consent will be obtained from each subject to be involved in the study by the investigator. Every subject will be informed in detail about the nature of the study, its purpose, the requirement to collect blood samples for testing, which may entail discomfort.

The process, place and timing for obtaining informed consent are as follows:

The investigator or his/her representative will explain the nature of this observational study to the subject, and answer all questions regarding this study. Prior to any sample collection and data collection, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. Subjects will be given sufficient time to consider their participation in this study

As per international guidelines [26], if the subject or participant is illiterate or otherwise unable to read the consent form but gives oral consent, a witness or a translator fluent in both English and the subject's spoken language must sign. Therefore, if he/she is illiterate, a literate witness must sign (if possible, this person should be selected by the subject and should have no connection to the research team). Hence, both the subject (or the subject's representative) and witness must sign the consent form

A translator must orally present the entire ethic's approved English version of the consent form to the subject or the subject's legally authorized representative in a language understandable to him/her. The entire consent process must be witnessed by an individual who is fluent in both English and the language understandable to the subject or the subject's legally authorized representative. The translator may serve as the witness.

The governing principles of human subject research: respect for persons, beneficence, and justice, require that researchers not exclude subjects based solely on their inability to read, speak or understand English. Hence it is the Investigator's responsibility to communicate directly with subjects, or to provide a reliable alternative to ensure that:

- Study participation is voluntary, as indicated by free and truly informed consent (respect for persons); and
- Study schedules, procedures, and risks are accurately communicated, and subjects have ongoing opportunities to express concerns and ask questions, in order to minimize risks to subjects (beneficence); and
- There are fair procedures and outcomes in the selection of research subjects so that risks and benefits of research are shared in society (justice).

The subject must have been given a copy of the informed consent form (ICF) prior to being asked to sign. The decision to participate in the study that is made by the subject must be entirely voluntary. The investigator or his/her designee must emphasize to the subject that consent for study participation may be withdrawn at any time without penalty or loss of benefits to which the subject is otherwise entitled

7.3 Study documentation and Record keeping

The investigators must maintain adequate and accurate records to document the conduct of the study and substantiate the study data. The investigator shall arrange for the retention of all study documents and records for at least 1 year after completion or discontinuation of the study. The study data will be destroyed upon approval from Investigators after study closure. For the purposes of ensuring compliance with the protocol and applicable regulatory requirements, the investigator will permit auditing by the designee / inspection by applicable regulatory authorities.

The investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The confidentiality of the data verified and the anonymity of the subjects should be respected during these inspections

7.4 Confidentiality

Subject confidentiality and privacy are strictly held in trust by the investigators, study team and affiliates. Investigators maintains the confidentiality of records and that confidentiality extends to cover test results of biological samples in addition to the clinical information (if available) relating to the subject. Therefore, the study data will be stored in secure electronic format and will not be disclosed without the express permission of the subject, however authorized representatives of Investigator(s) and representatives of the IEC/IRB, as well as regulatory agencies may inspect records in certain circumstances without prior approval.

Research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in a research study database which is a secure, cloud-based system that is HIPAA, GDPR, Annex 11, and 21 CFR 11 compliance system for the collection and storage of clinical research and survey information. Research Data will identify participants only by a unique study identification number. The decode list for this information will be maintained securely and not disclosed to recipients of the Research Data. Non-identifiable Research Data may be disclosed outside of Investigators and affiliates for the purposes of research and education, public health

08 ADMINISTRATIVE MATTERS

8.1 Notification of regulatory authority(ies)

All necessary arrangements for the registration and approval of this study with the responsible authorities and the deposition of the required data and document will be undertaken by the Principal Investigator.

8.2 Study Termination

PI reserves the right to terminate this study and remove all study materials from the study site at any time. Reasons that may require termination of the study include:

- It becomes apparent that sample collection is unsatisfactory with respect to quality or quantity
- Data recording is inaccurate and/or incomplete
- Deliberate violation of the signed protocol.

8.3 Publication policy

Authorship of any publication arising out of this research will be determined by mutual agreement. Any proposed publications may also require prior approval of a relevant local authority.

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Appendix OUTCOME Tables

PRIMARY OUTCOME MEASURE

Outcome 1	
Measure	Incidence and Severity of Post-Treatment Adverse Events
Description	Safety will be evaluated by the incidence, type, severity, seriousness, and relationship to LV009 of adverse events occurring after LV009 administration. Adverse events will be assessed through clinical evaluation, laboratory tests, and other relevant clinical investigations. Toxicities will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.02, as specified in the study protocol.
Time Frame	From LV009 administration through 5 years after administration or death, whichever occurs first.

SECONDARY OUTCOME MEASURE

Outcome 2	
Measure	Overall Survival (OS) in Participants With Hematologic Cancers
Description	Overall survival is defined as the time from the date of LV009 administration to death from any cause among participants with hematologic cancers. Participants who are alive at the time of analysis will be censored at the date they were last known to be alive.
Time Frame	From LV009 administration through 5 years after administration or death, whichever occurs first.

The study has three different populations. OS is relevant to the hematologic cancer population, but not necessarily to the autoimmune or HLA/AAV sensitization populations.

SECONDARY OUTCOME MEASURE

Outcome 3	
Measure	Progression-Free Survival (PFS) in Participants With Hematologic Cancers
Description	Progression-free survival is defined as the time from the date of LV009 administration to the first documented disease progression or death from any cause, whichever occurs first, among participants with hematologic cancers. Disease progression will be assessed using the disease-specific response and progression criteria specified in the study protocol. For acute lymphoblastic leukemia (ALL), progression will be assessed based on worsening bone marrow or peripheral blood disease, including an increase in blast burden. For B-cell lymphomas, progression will be assessed based on the appearance of new lesions or an increase in previously involved lesions according to clinical and imaging assessments. For multiple myeloma, progression will be assessed based on disease-specific changes in monoclonal protein, free light chains, plasmacytomas, or other clinical manifestations of disease. Participants who have not experienced disease progression or death will be censored at the date of their last disease assessment.
Time Frame	From LV009 administration through 5 years after administration or death, whichever occurs first.

SECONDARY OUTCOME MEASURE

Outcome 4	
Measure	Event-Free Survival (EFS) in Participants With Hematologic Cancers

Description	Event-free survival is defined as the time from the date of LV009 administration to the first occurrence of treatment failure, disease progression, disease relapse, or death from any cause, whichever occurs first, among participants with hematologic cancers. Treatment failure, disease progression, and relapse will be assessed using the disease-specific response and progression criteria specified in the study protocol. Participants who have not experienced an event at the time of analysis will be censored at the date of their last disease assessment or last known survival status, as applicable.
Time Frame	From LV009 administration through 5 years after administration or death, whichever occurs first.

SECONDARY OUTCOME MEASURE

Outcome 5	
Measure	Disease-Free Survival (DFS) in Participants With Hematologic Cancers
Description	Disease-free survival is defined as the time from the date of LV009 administration to the first documented disease relapse or death from disease or treatment-related toxicity, whichever occurs first, among participants with hematologic cancers who achieve a disease-free state following LV009 administration. Disease relapse will be assessed using the disease-specific response and progression criteria specified in the study protocol. Participants who remain disease-free at the time of analysis will be censored at the date of their last disease assessment.
Time Frame	From LV009 administration through 5 years after administration or death, whichever occurs first.

PRE-SPECIFIED OUTCOME MEASURE

Outcome 6	
Measure	Treatment Response in Participants With Hematologic Cancers
Description	Treatment response to LV009 will be assessed in participants with refractory or relapsed hematologic cancers using disease-specific response criteria specified in the study protocol. For acute lymphoblastic leukemia (ALL), treatment response will be categorized as complete response (CR), complete response with incomplete count recovery (CRi), complete molecular response (CMR), stable disease (SD), or progressive disease (PD), based on bone marrow blast percentage, peripheral blood findings, blood count recovery, and measurable residual disease (MRD), as applicable. For B-cell lymphomas, treatment response will be categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease/relapse, based on clinical and imaging assessment of disease involvement. Complete response requires disappearance of evidence of disease, while partial response requires regression of measurable disease without new sites of disease. Progressive disease/relapse is defined according to the disease-specific progression criteria specified in the study protocol. For multiple myeloma, treatment response will be categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease/relapse, based on monoclonal protein, free light chain, bone marrow, plasmacytoma, and clinical assessments, as applicable. The best treatment response category achieved following LV009 administration will be recorded for each participant.

Time Frame	From LV009 administration through 5 years after administration or death, whichever occurs first.

PRE-SPECIFIED OUTCOME MEASURE

Outcome 7	
Measure	Treatment Response in Participants With Autoimmune Diseases
Description	Treatment response to LV009 will be assessed in participants with autoimmune diseases using disease-specific clinical response criteria specified in the study protocol. The applicable disease-specific assessment will depend on the participant's underlying autoimmune disease. For **systemic lupus erythematosus (SLE)**, treatment response will be assessed using the Definition of Remission in SLE (DORIS) criteria and Lupus Low Disease Activity State (LLDAS) criteria. For **inflammatory myositis**, treatment response will be assessed using the International Myositis Assessment and Clinical Studies Group (IMACS) Core Set Measures. For systemic sclerosis, treatment response will be assessed using the Scleroderma Clinical Trials Consortium Activity Index (SCTC-AI). For myasthenia gravis, treatment response will be assessed using the Quantitative Myasthenia Gravis (QMG) score. For multiple sclerosis, treatment response will be assessed using No Evidence of Disease Activity-3 (NEDA-3), based on the absence of clinical relapse, disability progression, and new or enlarging magnetic resonance imaging (MRI) lesions, as applicable. For neuromyelitis optica, treatment response will be assessed using annualized relapse rate (ARR), calculated as the number of confirmed disease attacks divided by the participant's duration of follow-up in years. For immune thrombocytopenia (ITP), treatment response will be assessed using the International Working Group (IWG) response criteria. For immune hemolytic anemia, treatment response will be assessed using hemoglobin concentration and transfusion avoidance. The applicable disease-specific response category or clinical measure will be recorded for each participant.
Time Frame	From LV009 administration through 5 years after administration or death, whichever occurs first.

PRE-SPECIFIED OUTCOME MEASURE

Outcome 8	
Measure	Change in Anti-HLA or Anti-AAV Antibody Levels in Sensitized Participants
Description	Change in circulating anti-HLA or anti-AAV antibody levels from baseline will be assessed in participants with pre-existing HLA or AAV sensitization following LV009 administration. Anti-HLA or anti-AAV antibody levels will be measured using the applicable clinically accepted laboratory assay. The antibody response will be characterized by the change in antibody level from baseline and whether the antibody

	level reaches a clinically acceptable level for the participant's intended organ transplantation or AAV-based gene therapy, as applicable. For participants awaiting organ transplantation, transplantation-related clinical outcomes, including successful engraftment and occurrence of antibody-mediated rejection, may be recorded as clinical follow-up information. For participants awaiting AAV-based gene therapy, successful AAV vector-mediated transgene transduction may be recorded as clinical follow-up information when applicable.
Time Frame	From LV009 administration through 5 years after administration or death, whichever occurs first.