TITLE PAGE

Protocol Title: A Screening Protocol to Support Preliminary Eligibility for Clinical Trials Evaluating Safety and Efficacy of Adoptive Cell Therapies in Participants with Solid Tumors and Hematologic Malignancies.

Protocol Number: 213033

Compound Number: None

Study Phase: Phase 1/Phase 2

Short Title: Screening Protocol for Preliminary Eligibility Determination for Adoptive Cell Therapy Trials

Sponsor Name and Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Regulatory Agency Identifying Number(s):

IND: N/A

EudraCT: N/A

NCT:

WHO:

Other:

Approval Date: 22-JUN-2021

SPONSOR SIGNATORY:

Protocol Title: A Screening Protocol to Support Preliminary Eligibility for Clinical Trials Evaluating Safety and Efficacy of Adoptive Cell Therapies in Participants with Solid Tumors and Hematologic Malignancies.

Protocol Number: 213033

Compound Number: None

Gregg Fine, MD Vice President, Clinical Development Cell and Gene Therapies Oncology R&D	**Date**

The signed page is a separate document

Medical Monitor Name and Contact Information
May be found in the Study Reference Manual

TABLE OF CONTENTS

PAGE

1. PROTOCOL SUMMARY 4
1.1. Synopsis 4
1.2. Schema 8
1.3. Schedule of Activities (SoA) for Study 213033 9

2. INTRODUCTION 10
2.1. Study Rationale 10
2.2. Background 11
2.3. Benefit/Risk Assessment 12
2.3.1. Risk Assessment 12
2.3.2. Benefit Assessment 13
2.3.3. Overall Benefit: Risk Conclusion 13

3. OBJECTIVES AND ENDPOINTS 13

4. STUDY DESIGN 14
4.1. Overall Design 14
4.1.1. Protocol Flow 14
4.2. Scientific Rationale for Study Design 14
4.3. Justification for Dose 14
4.4. End of Study Definition 15
4.4.1. Study completion for participants 15
4.4.2. End of study 15

5. STUDY POPULATION 15
5.1. Inclusion Criteria 15
5.2. Exclusion Criteria 15
5.3. Lifestyle Considerations 16
5.4. Screen Failures 16

6. STUDY INTERVENTION 17

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 17
7.1. Discontinuation of Study Intervention 17
7.2. Participant Discontinuation/Withdrawal from the Study 17
7.3. Lost to Follow-Up 17

8. STUDY ASSESSMENTS AND PROCEDURES 18
8.1. HLA Compatibility Testing 19
8.2. Efficacy Assessments 19
8.3. Safety Assessments 19
8.4. Serious Adverse Events 19
8.4.1. Time Period and Frequency for Collecting SAE Information 19
8.4.2. Method of Detecting SAEs 20
8.4.3. Follow-up of SAEs 20
8.4.4. Regulatory Reporting Requirements for SAEs 20
8.5. Pharmacokinetics 20

8.6. Genetics 20
8.7. Biomarkers 20
8.8. Immunogenicity Assessments 20
8.9. Health Economics OR Medical Resource Utilization and Health Economics 21

9. STATISTICAL CONSIDERATIONS 21
9.1. Statistical Hypotheses 21
9.2. Sample Size Determination 21
9.3. Populations for Analyses 21
9.4. Statistical Analyses 21
9.4.1. Safety Analyses 21
9.4.2. Other Analyses 21
9.5. Interim Analyses 22

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 23
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 23
10.1.1. Regulatory and Ethical Considerations 23
10.1.2. Financial Disclosure 23
10.1.3. Informed Consent Process 24
10.1.4. Data Protection 25
10.1.5. Dissemination of Clinical Study Data 25
10.1.6. Data Quality Assurance 25
10.1.7. Source Documents 26
10.1.8. Study and Site Closure 26
10.1.9. Publication Policy 27
10.2. Appendix 2: AE and SAE: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 28
10.2.1. Definition of AE 28
10.2.2. Definition of SAE 29
10.2.3. Recording and Follow-Up of AE and SAE 30
10.2.4. Reporting of SAE to GSK 32
10.3. Appendix 3: Abbreviations and Trademarks 33

11. REFERENCES 35

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Screening Protocol to Support Preliminary Eligibility for Clinical Trials Evaluating Safety and Efficacy of Adoptive Cell Therapies in Participants with Solid Tumors and Hematologic Malignancies.

Short Title: Screening Protocol for Preliminary Eligibility Determination for Adoptive Cell Therapy Trials

Rationale:

Adoptive T-cell therapy (ACT) is a therapeutic approach that uses autologous (patient's own) or allogeneic (donor) T lymphocytes, that are subsequently genetically engineered to express a tumor-targeting receptor, expanded in vitro and reinfused into the participant, with the aim of generating and propagating an anti-tumor T-cell immune response. T cells can be engineered through a variety of approaches. Two that are currently under intensive evaluation include: chimeric antigen receptors (CARs) and engineered T-cell receptors (TCRs). T cells are obtained from the participant by leukapheresis and then engineered to express either CARs or TCRs. CARs bind to cell surface expressed proteins, whereas TCRs bind to epitopes of internal tumor-associated antigens (TAAs) presented in complex with HLA molecules on the cell surface.

GlaxoSmithKline (GSK) is developing both CAR and TCR T-cell therapies (TCR-T) for the investigational treatment of patients with various malignancies. New-York Esophageal Antigen-1 (NY-ESO-1) and Tumor antigen, cancer testis antigen (LAGE-1a) are members of the cancer-testis family of tumor antigens (CTAs). NY-ESO-1 is a cytoplasmic protein that is detectable in multiple cancer types including, but not limited to non-small cell lung cancer (NSCLC), bladder cancer, melanoma, liver cancer, synovial sarcoma, myxoid/round cell liposarcoma (MRCLS), and multiple myeloma. Specific peptide epitopes of the NY-ESO-1 or LAGE-1a protein are processed and presented on the surface of the tumor cell in complex with an human leukocyte antigen (HLA) molecule, which can be recognized by T cells. Therefore, targeting these CTAs through TCR T-cell therapies require participants to have HLA histocompatibility. The SLLMWITQCaa 157-165 peptide has been identified that is common to both NY-ESO-1 and LAGE-1a antigens presented on the surface of HLA-A*02. T cells have been genetically engineered to express an affinity-enhanced TCR toward this SLLMWITQC peptide. The retained optimized TCR clone was called NY-ESO-1 c259 or c259. The T-cell product (GSK3377794, lete-cel) consists of autologous T cells transduced with a self-inactivating lentiviral vector encoding the affinity enhanced NY-ESO-1 specific TCR (c259).

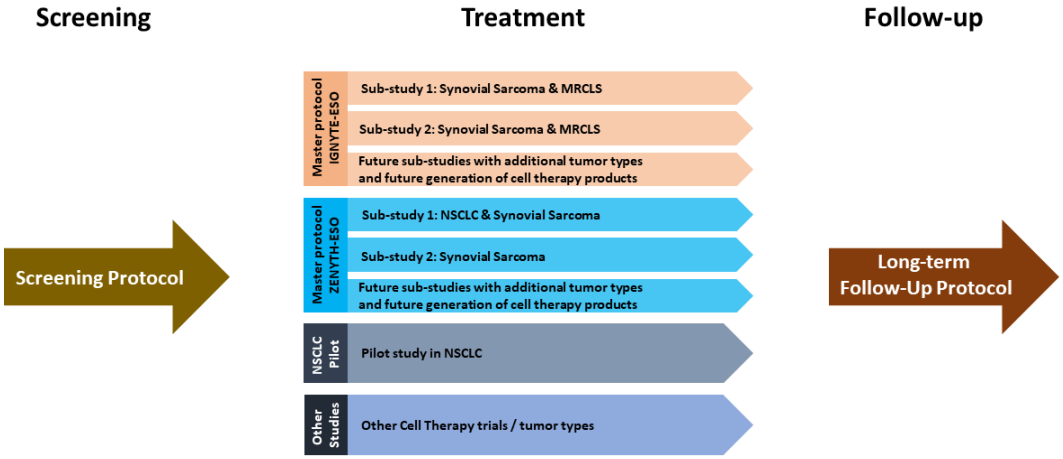
GSK is developing lete-cel and several next generation products that contain this NY-ESO-1 TCR for the investigational treatment of patients with various malignancies. The engineered T-cell receptor is compatible with HLA alleles (HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06), which are carried by roughly 45% of the world's population and targets the presentation of TAAs, NY-ESO-1 and/or LAGE-1a.

This screening study is designed to determine preliminary eligibility of participants who may be potential candidates for GSKs ACT studies by screening for appropriate biomarkers.

The study will include collection of blood samples at local referral centers for facilitating HLA compatibility screening and referral of HLA-histocompatible patients to GSK TCR-T cell investigational treatment trials. GSK-sponsored TCR-T trials are set up at a limited number of specialist centers due to the complex nature and requirements of ACT investigational treatment trials. Therefore, this screening study will facilitate testing for HLA-histocompatible patients over a wider geographic area at centers that do not have the ACT investigational treatment trials available. In the future, the screening study may be expanded to other centers including investigational treatment trial sites as well as include screening for additional biomarkers such as tumor antigen screening as defined by current and future investigational treatment studies.

HLA compatibility testing within this protocol will facilitate closer-to-home testing for patients and reduce the burden of travelling to a trial site.. Additionally, due to the high screen fail rate associated with finding patients who are HLA compatible, there is a need to improve overall access to trials beyond the investigational treatment sites.

In addition to ongoing studies, GSK has developed two master protocols (see below schema) for first time in human and for further development of a series of cell therapies. The master protocols are designed to facilitate the addition of new substudies investigating new tumor types and/or new cell therapy agents or combinations of agents. Future additional investigational treatment trials may exist as individual studies outside of the two master protocols described above. Through a simple and generally applicable design, this screening protocol is intended to broaden access to these and other current and future clinical trials by supporting screening outside the investigational treatment protocols.



MRCLS – Myxoid/Round Cell Liposarcoma; NSCLC – Non-small cell lung cancer

Objectives and Endpoints

Below are current objectives and endpoints.

Objectives	Endpoints
Primary (Operational)	
• Determine germline HLA genotype of all enrolled participants.	• Prevalence of HLA-A*02:01, HLA-A*02:05, or HLA-A*02:06 allele subtypes
CCI [redacted]	

Overall Design:

This is a multicenter protocol that will involve initial biomarker screening to determine potential eligibility for GSK's ACT investigational treatment trials.

This protocol is designed to facilitate screening for HLA histocompatibility testing by blood sample analysis in participants diagnosed with various malignancies. This will support participant identification for referral into an appropriate GSK cell therapy investigational treatment trial. It is anticipated that this screening protocol will support clinical trials of lete-cel, next generation NY-ESO-1 TCR T-cell products (e.g. GSK3901961, GSK3845097, etc) and other GSK engineered T-cell assets, as these assets become available for clinical development, and additional tumor types as the investigational treatment master protocols expand and/or as other investigational treatment protocols are initiated.

Number of Participants:

Approximately 1000 participants will be enrolled in this screening study. The overall number of participants screened under this protocol will depend upon the recruitment progress on investigational treatment trials.

Procedures and Duration:

During study Visit 1, all participants who consent to the screening study and are determined to meet the eligibility criteria for Study 213033 will provide the mandatory screening samples. Participants who consent to the screening study are considered screened in the study. A blood sample for HLA compatibility testing will be collected.

Details of HLA compatibility testing and of sample management are provide in the SRM. Participants who provide blood sample for HLA compatibility testing are considered enrolled in the study.

If the participant is determined to have qualifying results for an intended investigational treatment protocol, then the participant may be considered for referral to GSK trial site to complete the rest of the eligibility assessments for the investigational treatment trial.

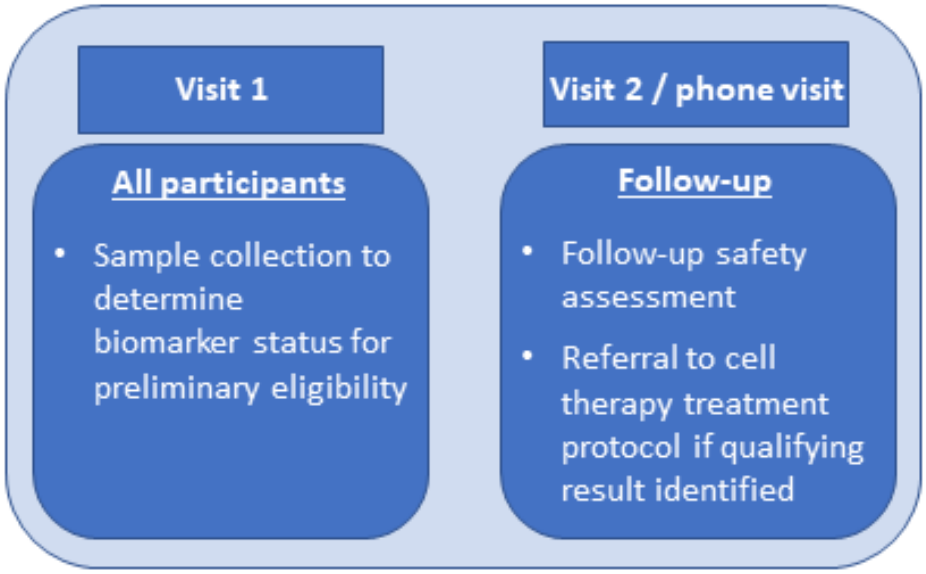
If a participant is referred to a GSK investigational treatment study, depending on the specific requirements of the investigational treatment protocol, the test result from this screening study may be used. Compatibility testing may however need to be repeated, either with the sample that was already provided as part of this screening study, or in rare cases a fresh sample may need to be collected under the investigational treatment study. All participants who have provided a sample for testing will undergo a safety assessment for any serious adverse events (SAEs) assessed as related to protocol-mandated study procedures or adverse events (AEs) leading to study withdrawal.

Active study involvement should typically be complete in ≤2 weeks for all participants.

The screening protocol will remain open until all designated GSK-sponsored investigational ACT treatment clinical trials are closed to enrollment or at the discretion of GSK.

Data Monitoring Committee: There is no Data Monitoring Committee for this study.

1.2. Schema


Visit 1
All participants
• Sample collection to determine biomarker status for preliminary eligibility
Visit 2 / phone visit
Follow-up
• Follow-up safety assessment
• Referral to cell therapy treatment protocol if qualifying result identified

1.3. Schedule of Activities (SoA) for Study 213033

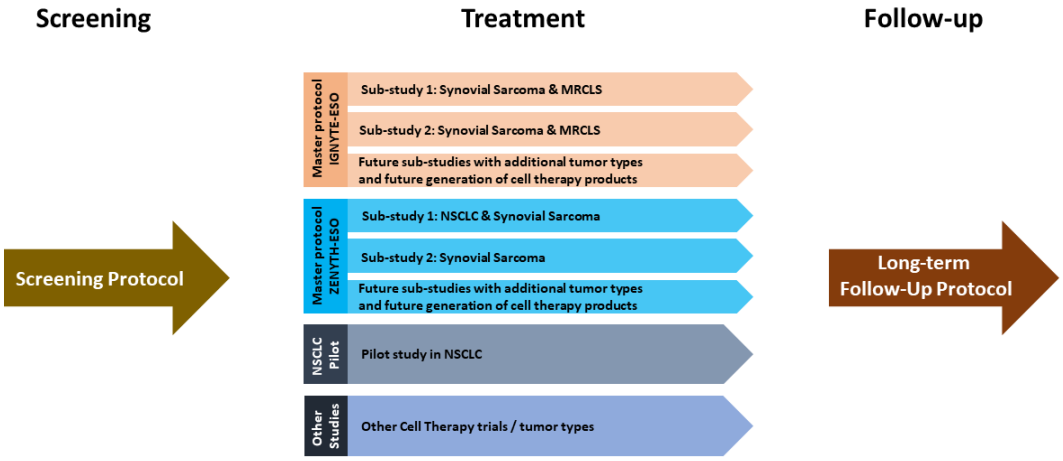
Procedures	Visit 1	Visit 2[4]	
Informed consent	X		**Footnotes:**
Inclusion and exclusion criteria	X		1 CCI [redacted] including chemotherapy, radiotherapy and surgeries will be collected for all enrolled Synovial Sarcoma / myxoid/round cell liposarcoma (MRCLS) participants; and will be recorded in the Screening eCRF.
CCI [redacted]			
Eatern Cooperative Oncology Group (ECOG) status	X		2.Human Leukocyte Antigen (HLA) sample – one blood sample (see Section 8.1).
CCI [redacted]			3.If prior molecular HLA Class I typing HLA A results are available, record in the electronic case report form (eCRF). Prior HLA result will not replace the HLA genotyping that is a mandatory part of this screening study. If patient is known to be positive for HLA 02:01, HLA A02:05 and/or HLA A02:06 then patient can be referred to an investigational site.
HLA genotyping [2,3]	X		4.Visit 2 is Completion / Withdrawal and may occur remotely via tele health / phone visit
Review of serious adverse events (SAEs) that are related to study procedure(s) or adverse events (AEs) and SAEs that lead to study withdrawal	X	X	
Consider referral to an appropriate investigational treatment trial		X	

2. INTRODUCTION

2.1. Study Rationale

This screening study is designed to facilitate the identification of potential participants for GlaxoSmithKline (GSK) sponsored trials investigating engineered Adoptive Cell Therapy (ACT), via assessment of target biomarkers for preliminary eligibility for the investigational treatment trials. Given the complexity of the engineered ACT preparation and administration, the ACT investigational treatment trials will be open at a limited number of tertiary medical centers in limited geographic areas. In the initial rollout, the screening study will be open at local referral sites and therefore will support identification of patients over a wider geographic area at centers that do not have the ACT investigational treatment trials available allowing closer-to-home testing and thereby reducing the burden for patients to travel to distant sites for initial screening. During this initial phase of study implementation, the screening study will include HLA compatibility testing to determine preliminary eligibility for GSK's T-cell Receptor-targeting (TCR T) investigational treatment trials.

Currently enrolling trials for GSK T-cell therapy require participants to have the histocompatible HLA genotypes (HLA-A*02:01, HLA-A*02:05, or HLA-A*02:06), which are carried by roughly 45% of the world's population [Gonzalez-Galarza, 2015]. More than 50% of screened participants will not carry a compatible HLA genotype. The screening protocol serves as a simple study to facilitate screening for HLA histocompatible participants. The screening protocol reduces the burden of travel to a distant T-cell investigational treatment site for participants who are HLA-incompatible for a GSK T-cell investigational treatment protocol. In addition to ongoing studies, GSK has developed two master protocols (see below schema) for first time in human and for further development of a series of cell therapies. The master protocols are designed to facilitate the addition of new substudies investigating new tumor types and/or new cell therapy agents or combinations of agents. Future additional investigational treatment trials may exist as individual studies outside of the two master protocols described above. Through a simple and generally applicable design, this screening protocol is expected to support participant enrollment into a range of ACT studies investigating an array of tumor types and evaluating a collection of agents available now (such as lete-cel, GSK3901961 and GSK3845097) and in the future.



In the future, the screening study may be expanded to other centers including investigational treatment trial sites. Additionally, the study may include screening for additional biomarkers such as tumor antigen as defined by current and future investigational treatment studies; as well as use of local and decentralized laboratory testing options.

2.2. Background

Background for ACT

ACT is a personalized therapeutic approach involving the infusion of a cancer patient's own (autologous) or donor (allogenic) tumour-specific cytotoxic T cells with the goal of recognizing, binding, activating, proliferating and destroying tumor cells. T cells can be engineered using two approaches that are currently under intensive evaluation: chimeric antigen receptors (CARs) and engineered TCRs. T cells are obtained from the participant by leukapheresis and then engineered to express either CARs or TCRs. CARs bind to cell surface expressed proteins, whereas TCRs bind to epitopes of internal tumor-associated antigens (TAAs) presented in complex with HLA molecules on the cell surface.

Background for Current GSK TCR T cells

GSK is developing a number of different TCR T-cell therapies that target the cancer testis antigens (CTAs) New-York Esophageal Antigen-1 (NY-ESO-1) and Tumor antigen, cancer-testis antigen family (LAGE-1a), tumor-associated proteins found in several tumor types. NY-ESO-1 and LAGE-1a are members of the cancer-testis family of tumor antigens (CTAs). Specific peptide epitopes of the NY-ESO-1 or LAGE-1a protein are processed and presented on the surface of the tumor cell in complex with an HLA molecule, which can be recognized by T cells. Therefore, targeting these CTAs require compatible HLA alleles in patients participating in the investigational treatment trials. The SLLMWITQCaa 157-165 peptide has been identified to be common to both NY-ESO-1 and LAGE-1a antigens presented on the surface of HLA-A*02 molecules. The T cells for therapy have been genetically engineered to express an affinity-enhanced TCR toward the SLLMWITQC peptide. The retained optimized TCR clone was called NY-ESO-1 c259 or c259. The T-cell product consists of autologous T cells transduced with a self-inactivating lentiviral vector encoding the affinity enhanced NY-ESO-1 specific TCR (c259).

Previous clinical trials with GSK3377794 (lete-cel) have shown very encouraging responses in participants with synovial sarcoma: ORR=61% (n=18) [Robbins, 2015] and ORR=50% (n=12) [D'Angelo, 2018]; metastatic melanoma: overall response rate (ORR) = 55% (n=20) [Robbins, 2015]; and multiple myeloma: ORR = 60% (n=20) [Rapoport, 2015]. Lete-cel is currently under clinical investigation in multiple indications including multiple myeloma, synovial sarcoma, myxoid/round cell liposarcoma, non-small cell lung cancer (NSCLC).

Despite this encouraging clinical activity, not all patients receiving lete-cel or other ACTs have experienced a clinical benefit. Additionally, some patients who achieved responses have eventually relapsed with their disease [D'Angelo, 2018]. The likely mechanisms for the limited efficacy observed in some patients are multifold. To address this, GSK is

currently developing the next generations of TCR T-cell therapies such as GSK3901961, GSK3845097, etc. which comprise of efficacy-enhancing technologies embedded into lete-cel; as well as an array of other ACT products.

One requirement of all TCR-directed therapies is that the engineered TCR must recognize a peptide epitope of the TAA that is processed and presented on the tumor cell surface, and forms the major histocompatibility complex (MHC). The lentiviral vectors used for manufacturing of TCR T cells express NY-ESO-1/LAGE-1a that is optimized to recognize the SLLMWITQC peptide fragment presented by HLA-A*02 on the cell surface. The final T-cell product is comprised of autologous CD4 and CD8 T cells that have been transduced with this lentiviral vector. GSK TCR T-cell therapies are engineered to enhance the recognition of presented peptides by HLA, and therefore those participants who have HLA histocompatibility may potentiallyrespond to this TCR T cell therapy. Future versions of the GSK TCR T cells may target additional tumor antigens as presented by different HLA molecules.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

No investigational product is used in this screening study; consequently, there are no risks due to exposure to study drug. The primary risk to patients in this protocol is the risk associated with specimen collection.

This screening protocol will include facilitation of HLA histocompatibility testing. To enable this, each patient is asked to provide a single sample of whole blood for HLA testing at the first visit following institutional standard procedure. The risks associated with this procedure are due to possible complications related to a blood draw, such as pain, bleeding and/or bruising and possible infection although serious complications are likely to be very rare. In majority of cases, this blood sample is expected to be collected with participants' routine laboratory collections that are done as part of standard of care. Therefore, the HLA blood draw may not pose additional risk.

There is a low likelihood for an additional blood draw for HLA histocompatibility testing under an investigational treatment protocol depending on how the test result was generated in the screening protocol and the requirements of the investigational treatment protocol. HLA histocompatibility genotyping test carries a low risk of false positive or false negative test results. A false positive test result will mean that the participant may be eligible to enter the screening phase of a GSK TCR T-cell investigational treatment protocol and would proceed with additional screening in the master protocol. A false negative test result would mean that the participant would not be eligible to enter the screening phase of a GSK TCR T-cell investigational treatment protocol.

The sites are directed to take all appropriate safety measures to protect the well-being of the participant and to follow-up on any SAE that would be related to the study procedure.

2.3.2. Benefit Assessment

The most direct potential benefit to participants in this screening study is to determine if they have qualifying screening test results, and therefore, may be eligible to enter the screening phase of a GSK TCR T-cell investigational treatment protocol or potentially other TCR studies that require HLA compatibility testing. However, there is no guarantee of further eligibility for or benefit from treatment under investigational treatment protocol.

Participants who are determined not to have the compatible HLA genotype may obtain this information at their local clinic rather than by traveling to a possibly distant investigational treatment trial site for the HLA compatibility assessment; thereby decreasing the overall burden on the patient.

2.3.3. Overall Benefit: Risk Conclusion

A key benefit to participants is the opportunity to be assessed for their preliminary eligibility for a GSK TCR T-cell investigational treatment protocol with minimal logistical issues. This benefit would be of particular value to participants who are determined to be ineligible on initial screening for a GSK TCR T-cell investigational treatment protocol. The primary risks in this screening protocol are those associated with blood draw for HLA compatibility testing and the described risks of false positive and/or false negative test results. However, the blood sample for HLA compatibility testing may be collected at the same time as other routine laboratory collections and therefore does not pose additional risk. Balancing the benefits of early identification of key eligibility criteria, locally to reduce burden of travel and the low risks associated with a blood draw, the benefits appear to outweigh the risks.

3. OBJECTIVES AND ENDPOINTS

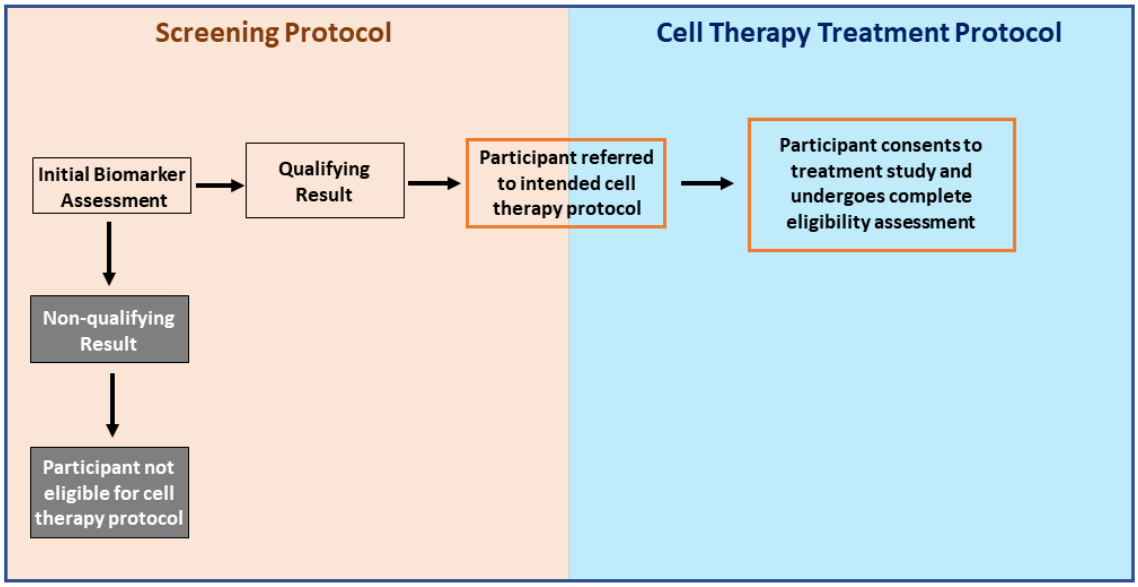
Objectives	Endpoints
Primary (Operational)	
• Determine germline HLA genotype of all enrolled participants.	• Prevalence of HLA-A*02:01, HLA-A*02:05, or HLA-A*02:06 allele subtypes
CCI [redacted]	

4. STUDY DESIGN

4.1. Overall Design

This multicenter screening study will assess initial biomarker status to facilitate referral of eligible patients for further evaluation to a GSK cell therapy trial site enrolling participants with various malignancies. This screening protocol will support clinical trials of lete-cel, GSK3901961 & GSK3845097, in tumor types currently under investigation as well as additional indications and other GSK cell therapy assets in the future. Recruitment to these studies can be challenging due to the high screen fail rate on key eligibility criteria, such as compatible HLA genotype, investigation of rare tumor types and / or wide distribution of care of the potential patient population compared to a relatively small number of sites where ACT investigational treatment trials may be conducted.

4.1.1. Protocol Flow



4.2. Scientific Rationale for Study Design

This screening study will prospectively assess biomarkers to determine preliminary eligibility for GSK's ACT investigational treatment trials. Initially, the screening study will facilitate screening for participants for compatible HLA genotype. In the future, additional biomarkers (e.g. tumor antigens) may be assessed and will be introduced by protocol amendment.

This screening study facilitates the identification and referral of patients who are positive for expression of target biomarkers into appropriate GSK ACT investigational treatment trials, especially trials in rare tumor types such as synovial sarcoma, or of projected high screen fail rates such as NSCLC.

4.3. Justification for Dose

Not applicable.

4.4. End of Study Definition

4.4.1. Study completion for participants

Participants are considered to have completed the study once all specified sample collection and/or study procedures have been completed, or they die, or withdraw from the study, or the study ends (whichever occurs first).

4.4.2. End of study

End of study is defined once all follow-up assessments are complete and all participants are referred to the eligible investigational treatment protocol, or died or are lost to follow-up (Section 7.3). The screening protocol will remain open until all designated GSK-sponsored adoptive cell therapy clinical trials are closed to enrollment and the last participant in the screening study has completed their last visit or until a date otherwise determined at the discretion of GSK.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. The inclusion and exclusion criteria are only applicable for the purposes of this screening protocol. Each TCR T-cell investigational treatment protocol will have additional criteria that are specific to that investigational treatment and the tumor type(s) under investigation.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

1. Able to provide written informed consent.
2. Histologically or cytologically confirmed diagnosis of locally advanced high-risk (metastatic or unresectable) solid tumor or hematological malignancy. Refer to SRM for additional disease characteristics and eligible tumor types.
3. Male or female ≥18 years of age (or ≥10 years of age with synovial sarcoma or MRCLS).
4. Life expectancy of >6 months.
5. Performance status: ECOG 0-1

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions that could interfere with the subject's safety, obtaining informed consent or compliance to the screening study procedures.

2. Any prior treatment with oncology cell and/or gene therapy (including TCR-T therapy or chimeric antigen receptor- T cells [CAR-T] therapy) unless agreed in advance with Sponsor.
3. Prior gene therapy using an integrating vector unless agreed in advance with Sponsor.
4. Any other prior malignancy that is not in complete remission. Exceptions include:

   a. completely resected non-melanoma skin cancer, or successfully treated in situ carcinoma (melanoma in situ, basal cell carcinoma, prostate ca in-situ, periosteal osteosarcoma)

   b. previous malignancies that have been definitively treated, and have been in remission for 5 years may be enrolled upon consultation with sponsor Medical Monitor or designee
5. Clinically significant systemic illness:

   a. serious active infections or significant cardiac, pulmonary, hepatic or other organ dysfunction, that in the judgment of the Investigator would compromise the participant's ability to tolerate procedures in a investigational treatment study such as leukapheresis or lymphodepletion, or significantly increase the risk of complications OR

   b. prior or active demyelinating disease
6. Previous treatment with genetically engineered NY-ESO-1-specific T cells, NY-ESO1 vaccine, or NY-ESO-1 targeting antibody.
7. Previous allogeneic hematopoietic stem cell transplant within the last 5 years or solid organ transplant.

5.3. Lifestyle Considerations

No restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but who are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes participant identifier, demography, screen failure details, eligibility criteria, protocol deviations, and any SAEs related to protocol-mandated study procedures and, for certain tumor types, medical history, disease characteristics including sites of metastasis and prior lines of anti-cancer treatments.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under this screening protocol or directly under the investigational treatment protocol.

Consent to another GSK TCR T-cell investigational treatment protocol is allowed.

6. STUDY INTERVENTION

No investigational drug will be used in Study 213033. Consequently, the following sections are not applicable to this protocol:

- Section 6.1: Study Intervention(s) Administered
- Section 6.2: Preparation/Handling/Storage/Accountability
- Section 6.3: Measures to Minimize Bias: Randomization and Blinding
- Section 6.4: Study Intervention Compliance
- Section 6.5: Treatment Overdose
- Section 6.6: Concomitant Therapy
- Section 6.7: Dose Modification
- Section 6.8: Continued Access to Study Intervention after the End of the Study

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Not applicable.

7.2. Participant Discontinuation/Withdrawal from the Study

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

The participant will be permanently discontinued from the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

A participant will be determined to have withdrawn from study early for any of the following reasons:

- The participant is able to but did not provide the required sample(s).
- The participant withdraws consent
- Death of any cause
- Any other reasons

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she is unable to be contacted by the study site.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- The maximum amount of blood collected from each participant over the duration of the study will not exceed 10 mL. If for any reason there is a need for additional sample, additional blood draw may be required.
- Data collection: Patients diagnosed with certain cancers who undergo HLA compatibility testing in the screening protocol may be targeted for a registrational or registration intent cell therapy investigational treatment study. Therefore, in support of the investigational ACT treatment trials the additional data below will be collected for such indications. At this time, this applies to synovial sarcoma and MRCLS but may apply to other indications in future.

8.1. HLA Compatibility Testing

HLA compatibility testing at the allelic level (4-digit) will be carried out on a mandatory whole blood sample as described in the SRM.

Participants who have previously been determined to have the compatible HLA genotype (HLA-A*02:01, HLA-A*02:05, or HLA-A*02:06) using a high-resolution test may be referred to the GSK investigational treatment study without repeating the HLA compatibility testing under this screening study. Such participants will undergo repeat HLA compatibility testing as specified in the GSK investigational treatment study.

8.2. Efficacy Assessments

Not applicable.

8.3. Safety Assessments

All participants will be followed for all SAEs related to protocol-mandated procedure(s), and AEs or SAEs leading to withdrawal from the study.

8.4. Serious Adverse Events

The definition of an AE and SAE can be found in Appendix 2.

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an SAE and remain responsible for following up SAEs that are considered related to the study procedure(s), or that caused the participant to withdraw early whether or not related to study procedures (see Section 7). AEs (SAE for this case) will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

8.4.1. Time Period and Frequency for Collecting SAE Information

- All SAEs assessed as related to protocol-mandated procedure(s) or both AEs and SAEs leading to early study withdrawal (whether or not related to study procedures) will be collected from the signing of the informed consent form (ICF) until conclusion of study participation (completes study, withdraws early, or screen fails), at the time points specified in the SoA (Section 1.3).
- All SAEs assessed as related to protocol-mandated procedure(s) or leading to early study withdrawal (whether or not related to study procedures) will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 2. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to a study procedure, the investigator must promptly notify the sponsor.

8.4.2. Method of Detecting SAEs

- The method of recording, evaluating, and assessing causality of SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.
- Care will be taken not to introduce bias when detecting SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about SAE occurrence.

8.4.3. Follow-up of SAEs

After the initial SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs assessed as related to protocol-mandated procedure(s), or leading to early study withdrawal (whether or not related to study procedures), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 2.

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAE from the sponsor will review and then file it along with the Investigator's Brochure (IB) and will notify the IRB/IEC, if appropriate according to local requirements.

8.5. Pharmacokinetics

Not applicable.

8.6. Genetics

Not applicable.

8.7. Biomarkers

Not applicable.

8.8. Immunogenicity Assessments

Not applicable

8.9. Health Economics OR Medical Resource Utilization and Health Economics

Not applicable

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

This is a screening protocol. No hypothesis will be tested under this protocol.

9.2. Sample Size Determination

Approximately 1000 participants will be enrolled in this screening study. The overall number of participants screened under this protocol will depend upon the recruitment progress on investigational treatment trials. Enrolment will continue until minimum sample size defined for investigational treatment protocols have been reached or until decided by GSK.

9.3. Populations for Analyses

For purposes of data summarization and reporting, the following populations are defined:

Population	Description
Screened	All participants who sign the ICF
Enrolled	All participants who provide sample for biomarker assessment

9.4. Statistical Analyses

9.4.1. Safety Analyses

All safety analyses will be performed on all patients who provided informed consent.

Data will be listed and summarized according to the GSK reporting standards, where applicable. Complete details will be documented in the Reporting and Analysis Plan (RAP). Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report.

SAE data will be summarized overall; by tumor type; and by HLA subtype. These summaries will be categorized by frequency and proportion of total subjects. All SAEs will be coded using the standard Medical Dictionary for Regulatory Activities (MeDRA). Summary of AEs leading to study withdrawal will also be provided.

9.4.2. Other Analyses

Primary Objective:

Compatible HLA genotypes for HLA-A locus will be listed and summarized by tumor type. Separate summaries of HLA-A may be given by ethnicity. The patient data and HLA result obtained for the purposed of eligibility determination into the GSK 208467 study may be used for the future regulatory registrations.

CCI

[redacted]

9.5. Interim Analyses

No interim analysis is planned for this study. The data from this study may be used anytime to support data analysis on the cell therapy investigational treatment studies that the participants will be referred to.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council of Harmonization (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulation (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Where country and/or local regulations allow, electronic consenting may be permitted. For such participants, blood sample collection must be performed at the next feasible scheduled visit to the site. Where applicable country and local regulations; and infrastructure for home healthcare allow, upon approval by the sponsor, home healthcare visit may take place at a location other than the clinical trial site to perform study assessments including but not limited to blood sample collection.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF. Such participants will be assigned a unique subject identifier at the time of rescreening.
- GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about the study intervention or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have the study intervention approved for medical use or approved for payment coverage.

The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research in accordance with standard operating procedure (SOP)-GSKF-410. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate will not provide this separate signature.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to summary tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic case report form (eCRF) unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the case report form (CRF).
- Guidance on completion of CRFs will be provided in eCRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling

of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Detailed information about study data collection and management process including systems used can be found in the study Data Management Plan.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in eCRF completion guidelines.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.8. Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study activity development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate participant follow-up

10.1.9. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: AE and SAE: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., electrocardiogram (ECG), radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• Any abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death

- Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a existing condition that did not worsen from baseline is not considered an AE.

Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect
Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

All participants will be followed for all SAEs related to study procedures and for all SAEs leading to withdrawal from the study.

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an SAE and remain responsible for following up SAEs that are considered related to the study procedure(s) or that caused the participant to withdraw early, whether or not related to study procedures (see Section 7).

10.2.3. Recording and Follow-Up of AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
• The Investigator will make an assessment of intensity for each AE and SAE reported during the study according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v 5.0).

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention [defined as investigational intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.2.4. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to study participation (causality) within 72 hours of SAE entry into the eCRF. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor/SAE coordinator by telephone. • Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF could be an alternative method to transmit this information to the **medical monitor or the SAE coordinator** if eCRF is not available. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the SRM.

10.3. Appendix 3: Abbreviations and Trademarks

ACT	Adoptive Cell Therapy
AE	Adverse event
CAR	Chimeric Antigen Receptor
CAR-T	Chimeric Antigen Receptor -T cell
CFR	Code of Federal Regulation
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSR	Clinical study report
CTA	Cancer testis antigens
ctDNA	Circulating tumor DNA
CV	Cardiovascular
DLBCL	Diffuse Large B-cell Lymphoma
DNA	Deoxyribonucleic acid
DOR	Duration of response
eCRF	Electronic case report form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HIPAA	Health Insurance Portability and Accountability Act
HLA	Human Leukocyte Antigen
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council of Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LAGE-1a	Tumour antigen, cancer-testis antigen family
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major histocompatibility complex
mL	Milliliter
MRCLS	Myxoid/round cell liposarcoma
NSCLC	Non-small cell lung cancer
NY-ESO-1	New-York Esophageal Antigen-1
ORR	Overall Response rate
RAP	Reporting and Analysis Plan
SAE	Serious adverse event
SOA	Schedule of Activities
SOP	Standard Operating Procedure
SRM	Study reference manual
SUSAR	Suspected unexpected serious adverse reaction
TAA	Tumor-associated antigen
TCR T	T-cell Receptor-targeting

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
None

Trademarks not owned by the GlaxoSmithKline group of companies
MeDRA

11. REFERENCES

D'Angelo SP, Melchiori L, Merchant MS, Bernstein D, Glod J, Kaplan R, et al. Antitumor Activity Associated with Prolonged Persistence of Adoptively Transferred NY-ESO-1c259T Cells in Synovial Sarcoma. Cancer Discov. 2018 Aug; 8(8):944-957.

Gonzalez-Galarza FF, Takeshita LY, Santos EJ, Kempson F, Maia MH, Silva AL, et al. Allele frequency net 2015 update: new features for HLA epitopes, KIR and disease and HLA adverse drug reaction associations. Nucleic Acid Research 2015; 28:D784-8. Website: www.allelefrequencies.net

Rapoport AP, Stadtmauer EA, Binder-Scholl GK, Goloubeva O, Vogl DT, Lacey SF, et al. NY-ESO-1-specific TCR-engineered T cells mediate sustained antigen-specific antitumor effects in myeloma. Nat. Med. 2015; 21:914–921.

Robbins PF, Kassim SH, Tran TL, Crystal JS, Morgan RA, Feldman SA, et al. A pilot trial using lymphocytes genetically engineered with an NY-ESO-1- reactive T-cell receptor: long-term follow-up and correlates with response. Clin. Cancer Res. 2015; 21:1019–1027.