The GSK group of companies

Division: Worldwide Development
Information Type: Clinical Study Report

Control: no-treatment

Protocol Title:	Master Protocol to Assess the Safety and Recommended Phase 2 Dose of Next Generations of Autologous Enhanced NY-ESO-1/ LAGE-1a TCR Engineered T cells, alone or in combination with other agents, in Participants with Advanced Tumors
Substudy 1 Title:	Assessment of Safety and Recommended Phase 2 Dose of Autologous T cells Engineered with an Affinity-enhanced TCR Targeting NY-ESO-1 and LAGE-1a, and co-expressing the CD8α (GSK3901961) in Participants with NY-ESO-1 and/or LAGE-1a Positive Previously Treated Advanced (Metastatic or Unresectable) Synovial Sarcoma / Myxoid/Round Cell Liposarcoma; or NY-ESO-1 and/or LAGE-1a Positive Previously Treated Metastatic Non-Small Cell Lung Cancer
Phase:	1
Compound Number:	GSK3901961
Document Date:	09 October 2023

Subject: Safety, Recommended Phase 2 Dose, Synovial Sarcoma, Myxoid/Round Cell Liposarcoma, Non-Small Cell Lung Cancer, NY-ESO-1, LAGE-1a, CD8α, Autologous T cells

Indication Studied: Previously treated advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma or metastatic non-small cell lung cancer

Initiation Date (Substudy 1): 09 March 2021

Completion Date: 26 May 2023

Sponsor Signatory: (and Medical Officer)
Nidale Tarek, MD
Senior Medical Director, Oncology Clinical Development
GSK

This study was performed in compliance with Good Clinical Practices and GSK Standard Operating Procedures for all processes involved, including the archiving of essential documents. This study complies with US 21 CFR 312.120.

Synopsis

Name of company: GSK Research & Development Limited

Name of finished product: Not available **Name of active substance:** GSK3901961

Study Number: 209012

Title: Master Protocol to Assess the Safety and Recommended Phase 2 Dose of Next Generations of Autologous Enhanced NY-ESO-1/ LAGE-1a TCR Engineered T cells, alone or in combination with other agents, in Participants with Advanced Tumors

Substudy 1 Title: Assessment of Safety and Recommended Phase 2 Dose of Autologous T cells Engineered with an Affinity-enhanced TCR Targeting NY-ESO-1 and LAGE-1a, and co-expressing the CD8α (GSK3901961) in Participants with NY-ESO-1 and/or LAGE-1a Positive Previously Treated Advanced (Metastatic or Unresectable) Synovial Sarcoma / Myxoid/Round Cell Liposarcoma; or NY-ESO-1 and/or LAGE-1a Positive Previously Treated Metastatic Non-Small Cell Lung Cancer

Investigators: Multicenter study

Study centers: Substudy 1 was opened to all 21 centers of the master protocol 209012 across 7 countries; 17 centers contributed to screening in 209012 study but only 2 sites in the US, 2 sites in Germany, 1 site in Australia, and 1 site in Sweden enrolled participants in Substudy 1.

Publication: None at the time of this report

Study Period: 09 March 2021 to 26 May 2023

Phase of Development: 1

Objectives and endpoints:

Below are the objectives and endpoints for Substudy 1. The substudy was stopped for further screening and enrolment in the master protocol 209012 due to a sponsor portfolio reprioritization decision to stop any further development of GSK3901961. The substudy was terminated early before further investigation on GSK3901961 could be performed. Therefore, only a subset of the exploratory endpoints was analyzed. The table below lists only those endpoints for which results are reported in this CSR. For the full list of objectives and endpoints, see Substudy 1 SAP Section 1.1.

Objectives	Endpoints
Primary	
To assess the safety, tolerability and determine the RP2D of GSK3901961 in HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 positive participants with:	• Frequency of DLTs • Frequency and severity of AEs, SAEs and AESI; as defined in the master protocol

Objectives	Endpoints
- NY-ESO-1 and/or LAGE-1a positive previously treated metastatic NSCLC (Cohort 1) - NY-ESO-1 and/or LAGE-1a positive, previously treated, advanced (metastatic or unresectable) SS/MRCLS (Cohort 2)	
Secondary - Efficacy	
To investigate the antitumor activity of GSK3901961 in HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 positive participants with: - NY-ESO-1 and/or LAGE-1a positive previously treated metastatic NSCLC (Cohort 1) - NY-ESO-1 and/or LAGE-1a positive, previously treated, advanced (metastatic or unresectable) SS/MRCLS (Cohort 2)	• ORR (investigator assessed according to RECIST v1.1) • DoR
Secondary – Pharmacokinetics	
To characterize in vivo cellular PK profile (levels, expansion, persistence) of GSK3901961 over time	• Cmax • Tmax • AUC(0-t), as data permit
Exploratory	
To further evaluate safety and tolerability of GSK3901961 in HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 positive participants with: - NY-ESO-1 and/or LAGE-1a positive previously treated metastatic NSCLC (Cohort 1) - NY-ESO-1 and/or LAGE-1a positive, previously treated, advanced (metastatic or unresectable) SS/MRCLS (Cohort 2)	• Changes in laboratory parameters; vital signs; ECOG PS; ECGs • RCL • Instances of insertional oncogenesis
To further evaluate the antitumor activity of GSK3901961 in HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 participants with: - NY-ESO-1 and/or LAGE-1a positive previously treated metastatic NSCLC (Cohort 1) - NY-ESO-1 and/or LAGE-1a positive, previously treated, advanced (metastatic or unresectable) SS/MRCLS (Cohort 2)	• OS
To evaluate potential immune response to GSK3901961	• Presence and titers of anti-GSK3901961 antibodies over time

Methodology:

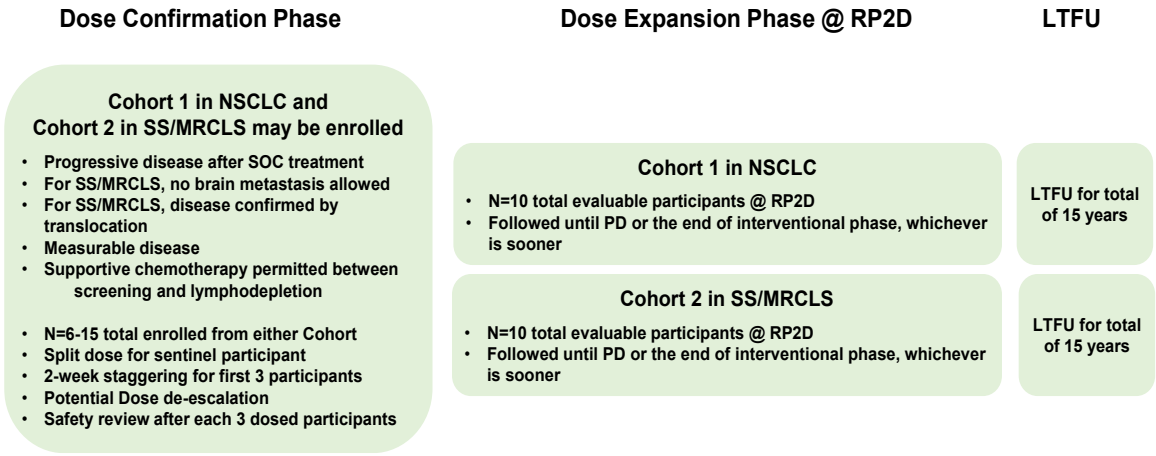
GSK3901961 belongs to the second generation of NY-ESO-1 TCR engineered T cells that incorporate additional sequences on the lentiviral vector construct to encode genes for molecules that would enhance T-cell function within the TME.

GSK3901961 consists of NY-ESO-1c259 TCR engineered autologous T cells that are modified by multi-component engineering transduction to co-express the α-chain of the CD8 co-receptor to:

- Enhance proliferation and persistence of the genetically engineered T cells;
- Increase helper functions including the Th1 antitumor response and recruitment of other immune cell types;
- Enhance activity of tumor-specific effector cells through stimulation by CD4+ T cells.

This was an FTIH, multi-cohort, non-randomized, open-label substudy (part of a Master Protocol) to investigate GSK3901961 in previously treated participants with advanced (metastatic or unresectable) SS/MRCLS or previously treated metastatic NSCLC, whose tumors express either NY-ESO-1 and/or LAGE-1a and are positive for either HLA-A*02:01, A*02:05, and/or A*02:06. The master protocol 209012 included 2 substudies. The first screening steps for target expression (HLA-typing and NY-ESO-1/Lage-1a tumor antigen expression) were common to all substudies in the core protocol and did not require allocation to a particular substudy until leukapheresis eligibility screening. Substudy allocation was conducted prior to leukapheresis, based on disease indication (NSCLC could only enroll in Substudy 1) and slot availabilities in Substudy 1 or 2 (for SS and MRCLS participants). Consequently, the target expression screening results are being reported for both Substudies 1 and 2 combined. This substudy consists of 2 phases: Dose Confirmation Phase and Dose Expansion Phase (Figure 1).

Figure 1 Substudy 1 Design



LTFU=long-term follow-up; MRCLS=myxoid/round cell liposarcoma; NSCLC=non-small cell lung cancer; PD=progressive disease; RP2D=recommended Phase 2 dose; SOC=standard of care; SS=synovial sarcoma.

Dose Confirmation Phase

Dose confirmation phase commenced first and within this phase, participants were assigned to 1 of 2 cohorts:

- Cohort 1: GSK3901961 in previously treated metastatic NSCLC

- Cohort 2: GSK3901961 in previously treated advanced (metastatic or unresectable) SS or MRCLS.

The primary objective of the dose confirmation phase was to identify the RP2D of GSK3901961. RP2D was to be determined as the MTD or lower that provides adequate biologic activity with superior tolerability. The MTD was defined as the dose that maximizes the probability of target toxicity of 30% while controlling the probability of excessive or unacceptable toxicity.

The DSC review was to occur after completion of the DLT period of 28 days after the last T-cell infusion in every 3 participants with either SS/MRCLS or NSCLC, to enable dose decision until the final dose selection was achieved (6 to 15 participants).

The starting dose was the RP2D of GSK3377794 (lete-cel); that is, the initial group of 3 participants were to receive a dose in the range of (1 to 8) × 10^9 transduced T cells. DLTs were assessed for each treated participant of the dose confirmation phase as per Core Protocol Section 8.2. If the number of participants with confirmed DLTs in the dosing group required a dose de-escalation according to the mTPI-2 model (see Substudy 1 Protocol Section 5.1.1.2), then a lower dose range of (0.1 to 0.8) × 10^9 transduced T cells was to be explored, with the possibility to re-escalate if the model supports such action.

Dose Expansion Phase

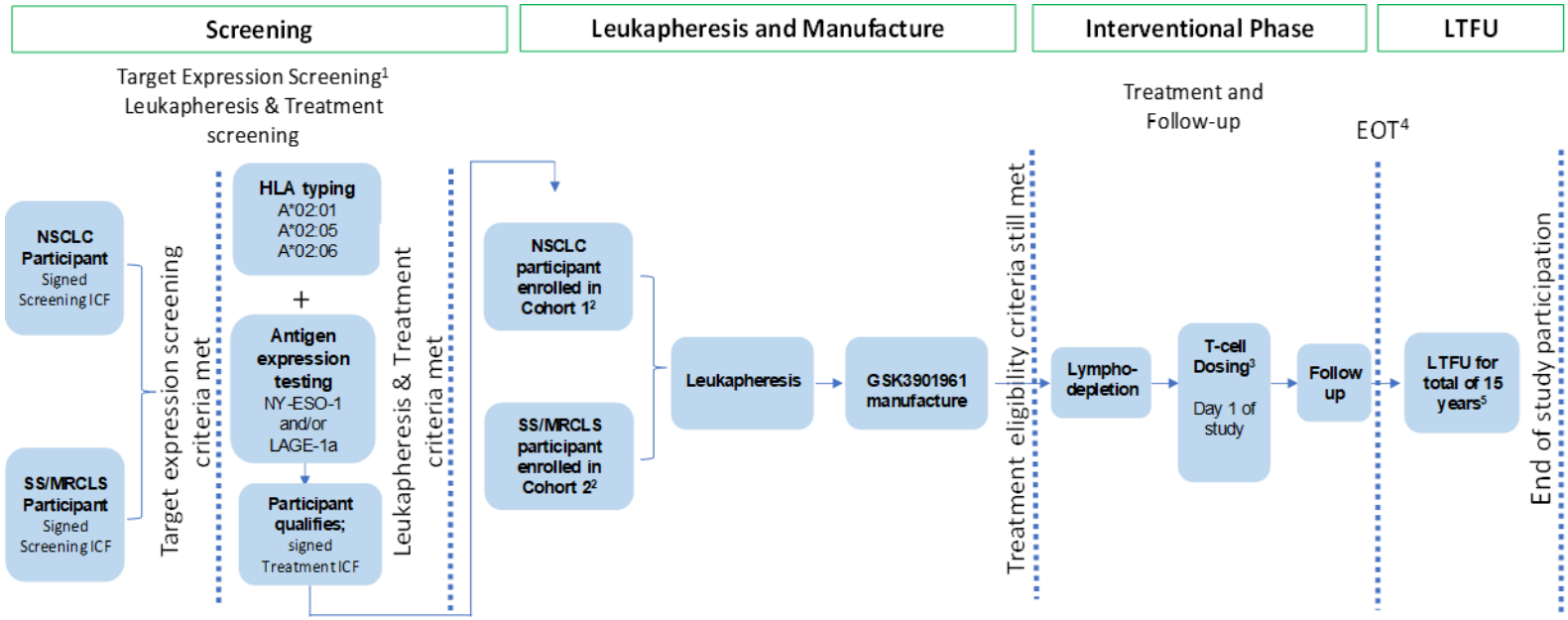
The dose expansion phase was to begin after determination of the RP2D. Each cohort was to enroll additional participants to ensure 10 participants become evaluable at the RP2D in each cohort. Evaluable participants were those who received T cell infusion and completed at least 2 post-baseline disease assessments since infusion or progressed or died or were withdrawn from the substudy.

Participant Journey

For each individual participant, the study consisted of the following (Figure 2): screening; leukapheresis and manufacture; interventional phase; and LTFU.

For more details, refer to Substudy 1 Protocol Section 5.1.3.

Figure 2 Participant Journey



DLT=dose-limiting toxicity; EOT=end of treatment (i.e., interventional) portion of the trial; HLA=human leukocyte antigen; ICF=informed consent form; LTFU=long-term follow-up; MRCLS=myxoid/round cell liposarcoma; NSCLC=non-small cell lung cancer; NY-ESO-1=New York esophageal antigen-1; SS=synovial sarcoma.

1. Screening, including HLA typing and antigen testing, could be done in this study or as part of a separate pre-screening protocol.
2. Sponsor was to inform Investigators of the participant assignments between substudies and indicate if the participant is a sentinel participant and the number of remaining slots.
3. The first participant to be dosed was to receive the total dose in 2 separate infusions as aliquots of ~30% and ~70% of the total manufactured dose, administered 7 days apart. The second infusion was to be administered only if no acute toxicities preventing full dosing were observed. If no DLTs were reported for the participants receiving split doses, then all subsequent participants administered the particular product were to receive the full dose as a single, i.e., one-time, infusion.
4. See Substudy 1 Protocol Section 5.3.1 for definition of the end of interventional phase for a participant.
5. The LTFU assessments and procedures could be done in this study or under a separate LTFU protocol.

Number of participants:

- Planned: 6 to 15 participants in the dose confirmation phase, and 10 participants in the dose expansion phase
- Recruited: 7 participants (5 participants were dosed with GSK3901961 in the dose confirmation phase and 2 participants underwent leukapheresis but did not receive lymphodepletion chemotherapy or T-cell infusion). All 7 participants had been previously treated for advanced SS and enrolled in Cohort 2. No participant with NSCLC (Cohort 1) or MRCLS (Cohort 2) was enrolled.
- Analyzed: 5 participants in the dose confirmation phase

Note: Substudy 1 was closed prior to the completion of the dose confirmation phase. Hence, RP2D was not determined, and the dose expansion phase was not started.

Diagnosis and key eligibility criteria for inclusion:

Eligibility criteria were grouped into 3 parts and eligibility screening took place in the following 3 steps:

- Target expression screening: A set of criteria permitting participants' blood to be screened for HLA-type and an archival or fresh tumor sample to be screened for the expression of NY-ESO-1/LAGE-1a.
- Leukapheresis eligibility screening: To be fulfilled prior to performing leukapheresis procedure.
- Treatment eligibility screening: To be fulfilled prior to starting lymphodepleting chemotherapy and administration of GSK3901961.

Key inclusion criteria:

Refer to Substudy 1 Protocol Section 6.1 for the full list of inclusion criteria.

<u>Target expression screening:</u>

2. Participant was ≥18 years of age and weighed ≥40 kg on the day of signing informed consent form.

For participants with SS/MRCLS:

4. Participant had a diagnosis of SS or MRCLS as confirmed by local histopathology with evidence of disease-specific translocation. Note: Evidence of a relevant disease-specific translocation was required at latest prior to leukapheresis (Inclusion Criterion 12).
5. Participant had advanced (metastatic or unresectable) SS or MRCLS. Unresectable refers to a tumor lesion in which clear surgical excision margins cannot be obtained without leading to significant functional compromise.

For participants with NSCLC:

6. Participant had histologically or cytologically confirmed Stage IV NSCLC.

Leukapheresis eligibility screening:

8. Participant was positive for HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 alleles by a validated test in a designated central laboratory prior to leukapheresis.
9. Participant's tumor (either the most recent archival specimen or a fresh biopsy) tested positive for NY-ESO-1 and/or LAGE-1a expression (when LAGE-1a testing was available) by a GSK designated laboratory (and met the threshold criteria defined for the specific tumor type, i.e., ≥2+ in 30% of tumor cells).
10. Participant had measurable disease according to RECIST v1.1.
11. Participant had evidence of radiographic or clinical disease progression.
12. Participant with SS/MRCLS had confirmed evidence of a relevant disease-specific translocation.
    - For SS, presence of a translocation involving chromosome 18 (SYT gene) and/or chromosome X (SSX1, SSX2, or SSX4 genes);
    - For MRCLS, presence of a translocation involving chromosome 12 (DDIT3 gene) and/or chromosome 16 (FUS gene) and/or chromosome 22 (EWSR1 gene).
13. Prior therapies for SS/MRCLS participants: Participant had completed at least one standard of care treatment including anthracycline containing regimen unless intolerant to or ineligible to receive the therapy. Participants who were not candidates to receive anthracycline should have received ifosfamide unless also intolerant to or ineligible to receive ifosfamide. Participants who received neoadjuvant/adjuvant anthracycline or ifosfamide based therapy and progressed were eligible.
14. Prior therapies for NSCLC participants:
    a. For NSCLC lacking actionable genetic aberrations (i.e., wild type), per NCCN guidelines: participant had been previously treated with or is intolerant to PD-1/PD-L1 checkpoint blockade therapy and had been previously treated with or was intolerant to a platinum-based chemotherapy. Adjuvant therapy was counted as a regimen if completed within 6 months before relapse.

OR

    b. For NSCLC that harbors actionable genetic aberrations (e.g., BRAF, ALK/ROS1, etc.), per NCCN guidelines: participant had been previously treated with or is intolerant to standard of care therapy, including targeted therapy, as recommended by NCCN or equivalent country-level guidelines (e.g., ESMO, NICE).

OR

    c. Investigator decided that additional lines of standard of care therapy after the first line were not in the participant’s best interest. Participant could be considered eligible for the trial only in consultation with the medical monitor (or designee).

Treatment eligibility screening:

22. Participant had documented radiographic evidence of disease progression from prior line of therapy.

Treatment fitness (for safety):

Given potential changes in clinical status between screening/enrollment and the start of lymphodepleting chemotherapy, safety assessments done for target expression screening and leukapheresis eligibility screening were reassessed prior to lymphodepletion. If the results of any assessments or procedure were outside of the eligibility criteria, the investigator consulted with the GSK medical monitor prior to proceeding with lymphodepletion.

Key exclusion criteria:

Refer to Substudy 1 Protocol Section 6.2 for the full list of exclusion criteria.

Target expression screening:

3. Previous treatment with genetically engineered NY-ESO-1-specific T cells, NY-ESO-1 vaccine, or NY-ESO-1 targeting antibody.
4. Prior gene therapy using an integrating vector.

Leukapheresis eligibility screening:

6. Participant had CNS metastases (refer to Substudy 1 Protocol Section 6.2.2 Exclusion 6 for a list of exception criteria on CNS metastases for NSCLC participants).
7. Participant had a history of chronic or recurrent (within the last year prior to leukapheresis) severe autoimmune or immune mediated disease (e.g., Crohn's disease, systemic lupus) requiring steroids or other immunosuppressive treatments.

Treatment eligibility screening:

18. Participant had received cytotoxic therapy within 3 weeks prior to lymphodepleting chemotherapy.
19. Participant had received systemic corticosteroids or any other immunosuppressive therapy within 2 weeks prior to lymphodepleting chemotherapy.
20. Participant had received ≥50 Gy to a significant volume of the pelvis, long bones or spine, or a cumulative dose of radiation that, in the investigator's opinion would predispose patients to prolonged cytopenia after lymphodepletion.
21. All the participant's measurable lesions had been irradiated within 3 months prior to lymphodepletion. An irradiated measurable lesion with unequivocal progression following irradiation could be considered a target lesion regardless of time from the last radiotherapy dose.
22. Radiotherapy that involved the lung (V20 exceeding 30% lung volume or mean heart dose >20 Gy) within 3 months OR radiotherapy (including but not limited to

palliative radiotherapy) to lung/mediastinum with V20 less than 30% lung volume and with mean heart dose ≤20 Gy within 4 weeks (±3 days).

Treatment administration:

The study intervention in this study was GSK3901961. Participants underwent leukapheresis to obtain starting material for the manufacture of GSK3901961. Since HLA-typing and NY-ESO-1/Lage-1a expression testing were required prior to leukapheresis, bridging or standard of care systemic chemotherapy, experimental therapy, and/or local therapy (e.g., radiotherapy, cryoablation, surgical resection) may have been administered between target expression screening and leukapheresis. Additionally, systemic chemotherapy may have been administered between leukapheresis and the start of lymphodepletion, if a participant had PD and could not be treatment-free. Prior to administration of study intervention, participants received lymphodepleting chemotherapy consisting of fludarabine 120 mg/m^2 on Days -7 to -4, and cyclophosphamide 3600 mg/m^2 for the first participant on Days -5 and -4 and then 2700 mg/m^2 for other participants on Days -6 to -4 (note: the first participant was dosed per Protocol Amendment 1 and other participants were dosed per Protocol Clarification Letter or Protocol Amendments 3 or 4). G-CSF was started on Day -3. The intended dose of GSK3901961was within the range of (1 to 8) × 10^9 transduced T cells to be administered by IV infusion for the first 3 participants. If a dose de-escalation was decided by the DSC, the target dose range was lowered 10-fold to (0.1 to 0.8) × 10^9 transduced T cells for subsequent participants. The first study participant receiving GSK3901961 was a sentinel participant and was planned to receive the target dose of transduced T cells as 2 separate infusions of approximately 30% of the target dose on Day 1 and approximately 70% of the target dose on Day 8. If no DLT was reported all subsequent participants were to receive the target T-cell dose as a single infusion.

Batch numbers of the study intervention for the 5 dosed participants are listed in the table below:

Participant ID	Batch number	Manufacturer
110804	G0038	Miltenyi Biotec
110028	G0064	Miltenyi Biotec
110456	G0086	Miltenyi Biotec
110916	G0090	Miltenyi Biotec
110251	G0089	Miltenyi Biotec

Study assessments:

Safety assessments included the rate of AEs, SAEs, AESIs, DLTs, as well as physical exams, ECOG PS, vital signs, cardiac assessments (ECHO, MUGA, ECG), pulmonary assessments, clinical laboratory assessments, T-cell persistence, and RCL.

All participants were to be followed for survival and for 15 years after GSK3901961 infusion for observation of delayed AEs in accordance with FDA requirements for gene therapy clinical trials.

A DSC was established for making dose recommendations for GSK3901961 based on a review of all relevant data. The committee was tasked to determine whether the same dose can be given to additional participants; or decide to move to a lower dose level. DSC meetings were to take place after each consecutive group of 3 participants had been dosed in the substudy and followed for the DLT period of 28 days.

DSC meetings took place after 2 participants were dosed at the DL1 dose range. As the first 2 participants treated at DL1 experienced DLTs, formal DSC endorsement of GSK's recommendation not to treat a third participant at the DL1 dose level and to de-escalate the dose to the DL-1 was obtained via email. Following dosing of the next 3 participants at the planned DL-1 range $(0.1 \text{ to } 0.8)\times10^9$ transduced T cells, it was agreed that no further DSC meetings were required as no further participants were to be dosed due to study termination.

To evaluate potential immune response to GSK3901961, presence and titers of anti-GSK3901961 antibodies over time were determined.

Efficacy endpoints relied on tumor assessments for response and progression that were evaluated according to RECIST v1.1 (see Master Protocol Section 12.6). RECIST v1.1 was used in the assessment of disease burden (target and non-target lesions determination) at baseline and as the primary measure of tumor response endpoints.

T-cell vector copies (expansion/persistence) in the peripheral blood were measured in participants by quantitation of transduced cells by PCR of transgene from DNA extracted from PBMC. Persistence was measured to establish the relationships with response to the study intervention as well as a long-term safety measure. For all PK analyses, expansion/persistence of the engineered T cells was applied in lieu of "concentration" to derive PK parameters.

Statistical Methods:

The final analysis was to be performed after the completion of the following sequential steps:

1. Enrolment was complete and all enrolled participants had received T-cell infusion, and
2. All participants had completed the substudy.
    - Completed the substudy was defined as when all enrolled participants had transferred to the separate LTFU protocol, declined consenting to the LTFU protocol, completed LTFU requirement in the applicable study, had been lost to follow-up, or withdrawn or died.
3. All required database cleaning activities had been completed and database release and database lock had been declared by Data Management.

No inferential statistical hypothesis testing was conducted, i.e., no p-values were calculated. Unless otherwise specified, continuous data were summarized using descriptive statistics: number of subjects (n), mean, standard deviation, median, minimum, and maximum. Categorical data were summarized as the number and

percentage of participants in each category. CIs used 95% confidence levels unless otherwise specified.

The primary endpoints were frequency of DLTs, frequency and severity of AEs and SAEs, and frequency and severity of the AESIs. Toxicities meeting the DLT criteria are listed in Core Protocol Section 8.2 and must have been considered to be at least possibly related to transduced T cells and occurred within the DLT assessment period of 28 days after last dosing of T cells.

The secondary efficacy endpoint was ORR, which was defined as the percentage of participants with a confirmed CR or a confirmed PR as the BOR relative to the total number of participants within the relevant cohort and analysis population per RECIST v1.1 as determined by the local investigators. Participants with either no valid post-baseline assessments, or non-measurable disease at baseline, or experienced death prior to the first disease assessment were treated as non-responders i.e., these participants were included in the denominator when calculating the ORR, and BOR was summarized as NE. The ORR was reported along with the Clopper-Pearson exact 95% CI based on the mITT analysis set. Another secondary efficacy endpoint was DoR, which was defined as the interval of time (in months) from first documented evidence of the confirmed response (PR or CR) to the date of disease progression per RECIST v1.1 criteria or death due to any cause, among participants with a confirmed response of PR or CR as the BOR. DoR was summarized based on the mITT analysis set using the Kaplan-Meier method, or by standard summary statistics if there were no more than 5 confirmed responders within a cohort. See Core SAP Section 4.3.1 for more details on efficacy analyses.

Secondary PK endpoints included Cmax, Tmax, and AUC(0-t) based on the PK analysis set. PK parameters were calculated using standard noncompartmental analyses according to current working practices and using appropriate software. All calculations of noncompartmental parameters were based on actual sampling times. See Core SAP Section 4.3.2 for more details on PK analyses.

Sample size determination

Participants were to be recruited in blocks of 3 in the dose confirmation phase (up to 6-15 participants) until the RP2D could be determined based on the mTPI-2 recommended dose. Once the RP2D was established, the substudy was to expand to up to 10 participants treated at that dose. See Substudy 1 SAP Section 5 for more details.

Analysis sets

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	All participants who signed an ICF to participate in the study.	• Screen Failures
Enrolled[a]	All participants who started leukapheresis procedure. Note: this analysis set included patients that did not meet the treatment eligibility criteria prior to lymphodepletion or patients that withdrew or died prior to lymphodepletion or T-cell infusion.	• Specific required Study Population displays
ITT	All participants who started leukapheresis procedure.	• Study Population • Safety (where appropriate)

Analysis Set	Definition / Criteria	Analyses Evaluated
	Note: this analysis set included patients that did not meet the treatment eligibility criteria prior to lymphodepletion or patients that withdrew or died prior to lymphodepletion or T-cell infusion.	• Sensitivity for Secondary Efficacy Endpoint (ORR)[b]
Lymphodepletion	All ITT participants who started lymphodepletion chemotherapy.	• Safety – including AEs and Exposure
Modified ITT (mITT)	All ITT participants who received any dose of NY-ESO-1 specific T cells.	• Safety (where appropriate) • Efficacy
DLT Evaluable	Participants in the mITT analysis set who were part of the dose confirmation phase that either had a DLT (meeting the definition of a DLT as defined in Core Protocol Section 8.2) or had completed the DLT assessment period of 28 days since last T-cell infusion. Note: For participants who received a single dose, the DLT assessment period was up to and including Day 28, and for participants who received split dose, the DLT assessment period was up to and including 28 days after the second split-dose.	• Safety – summary of DLTs for dose confirmation phase
Modified ITT 90 (mITT 90)[c]	Participants in the mITT analysis set who had been followed-up for at least 90 days since the last T-cell infusion.	• Safety – summary of delayed AEs
Evaluable[d]	Participants in the mITT analysis set who received the RP2D and had completed at least 2 disease assessments after infusion or progressed or died or were withdrawn or lost to follow-up from the substudy.	• Interim Analysis (for dose expansion participants and dose confirmation participants who received RP2D)
Pharmacokinetic (PK)	Participants in the mITT analysis set from whom at least one persistence sample was obtained, analyzed, and was measurable.	• PK

AE=adverse event; DLT=dose limiting toxicity; ICF=informed consent form; ITT=intent-to-treat; ORR=overall response rate; PK=pharmacokinetics; RP2D=recommended phase 2 dose.

a. Enrolled and ITT analysis sets are identical. The enrolled analysis set is required for disclosure reporting by EudraCT.
b. Efficacy sensitivity analysis was not performed due to study closure based on protocol stopping provisions.
c. The mITT 90 analysis set was not used since summary of delayed AEs was not produced following closure of substudies based on protocol stopping provisions.
d. Note that all substudies were closed prior to achieving RP2D based on protocol stopping provisions and therefore the Evaluable Analysis Set was not required for analysis purposes.

Changes in conduct of the study or planned analyses

Only a subset of the previously planned analyses per protocol was performed as the study was closed for further screening and enrolment in the master protocol 209012 due to a sponsor decision to stop any further development of GSK3901961.

The following are the key changes to previously planned analyses per protocol:

1. Since the substudy was closed prior to the establishment of the RP2D, no related analyses were provided (e.g., analyses based on the Evaluable analysis set).
2. The Interim and Primary analyses described in Substudy 1 Protocol Section 10.5 were not conducted; only the Final Analysis was undertaken.
3. Most exploratory endpoints were not analyzed (see SAP for details).
4. As appropriate, listings were produced in lieu of tables and figures given the low sample size (see SAP for details).

5. No subgroup analyses were undertaken because of recruiting fewer participants than the planned target sample size.

There were no changes in the conduct of the study or planned analyses after the finalization of the core SAP dated 10 May 2023 and post-database lock.

Summary:

Participant Disposition:

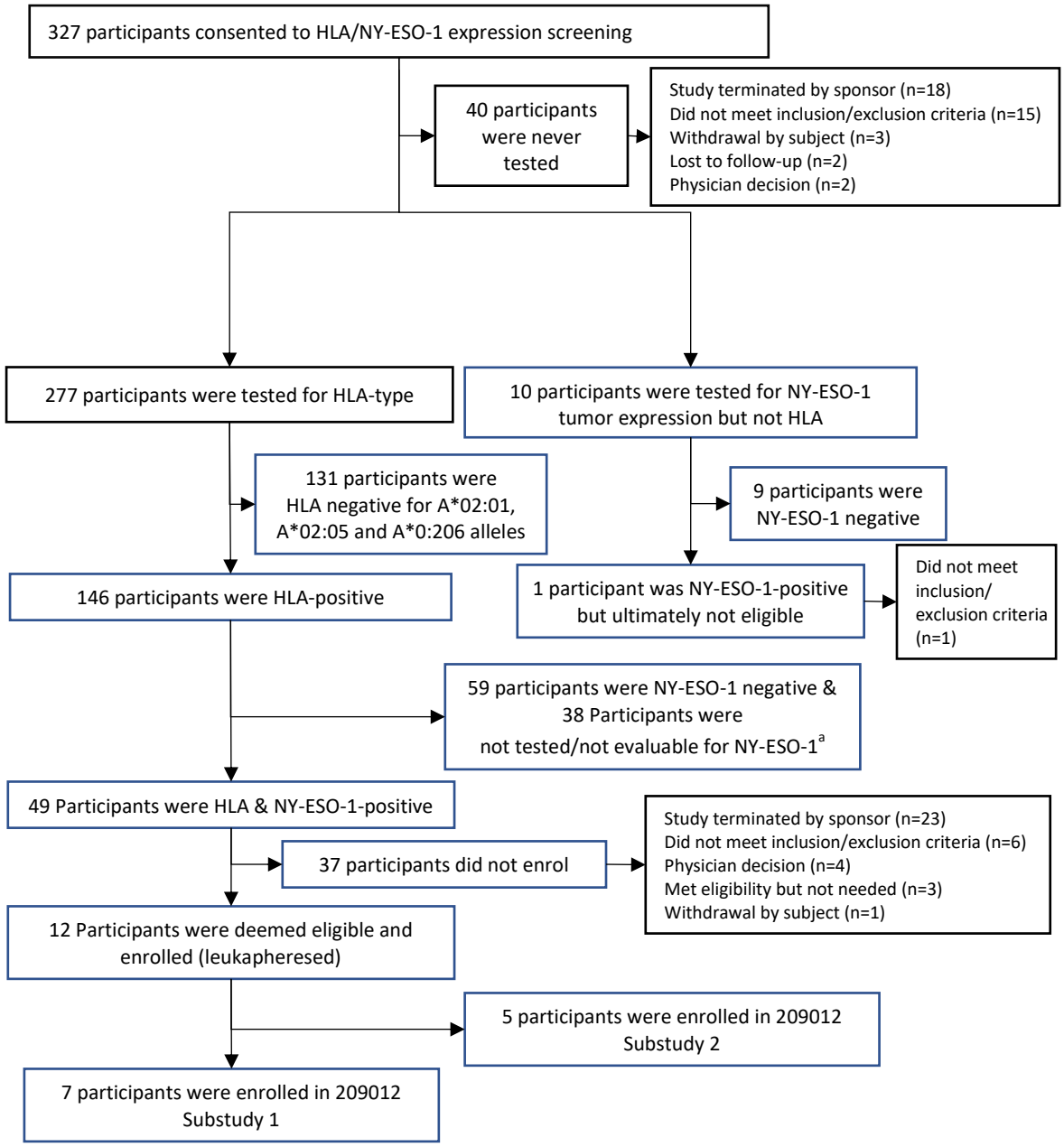
Participants in Substudy 1 were enrolled from 1 center in Australia (N=1), 2 centers in Germany (N=3), 1 center in Sweden (N=1), and 2 centers in the US (N=2) (Source: Table 1.0180).

A total of 327 participants were screened across all substudies; of whom, 12 participants (4%) were enrolled and 315 (96%) were screen failures. Of the 315 screen failures, 40 participants consented but never initiated HLA/NY-ESO-1 testing, 237 participants were either HLA negative or NY-ESO-1 negative/not evaluable, and 38 participants had other reasons for screen failure (see Figure 3 for details). Of 277 participants tested for HLA type, 146 participants (53%) were found positive for HLA-A*02:01, A*02:05, or A*02:06.

Of 61 participants with SS/MRCLS eligible for NY-ESO-1 tumor expression test, 42 participants (69%) met criterion of 2+ or 3+ in ≥30% of tumor cells. Of 63 participants with NSCLC eligible for NY-ESO-1 tumor expression test, 8 participants (13%) met criterion of 1+, 2+, or 3+ in ≥10% of tumor cells.

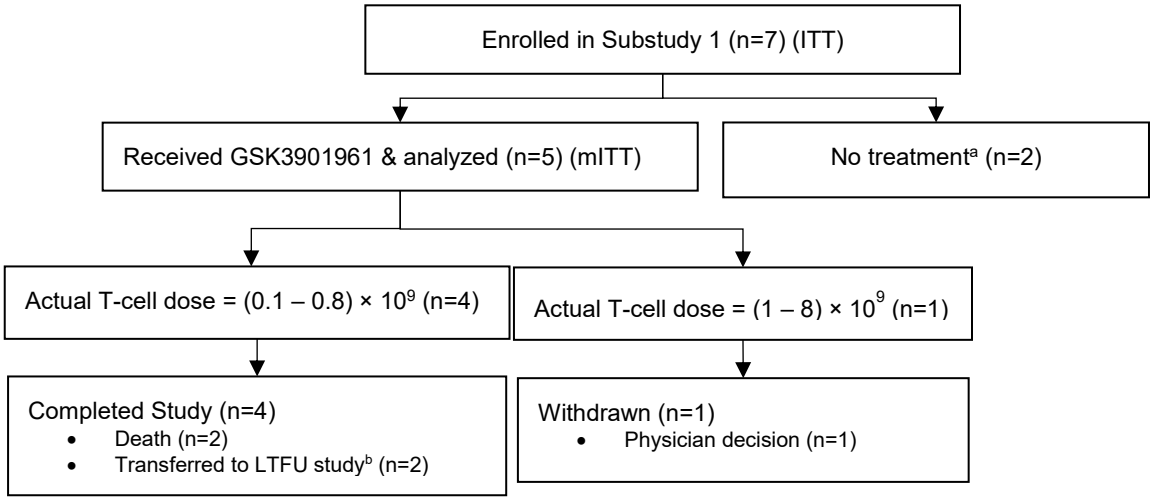
Of 12 participants enrolled in the study, 7 participants entered Substudy 1 (Figure 4). Of these 7 participants, 5 participants were treated with GSK3901961 and therefore included in the mITT population; 2 participants underwent leukapheresis but did not initiate treatment: 1 participant did not meet eligibility criteria prior to lymphodepletion, and 1 participant died prior to lymphodepletion. Two of the 5 participants treated with GSK3901961 died during the study from disease progression, 2 participants were transferred to the LTFU study 208750 after confirmed disease progression, and 1 participant was withdrawn from the study due to poor compliance. Of note, no participant with NSCLC was enrolled.

Figure 3 Participant Disposition up to Enrolment



Source: Table 1.0130.
HLA=human leukocyte antigen; NY-ESO-1=New York esophageal antigen-1.
a After the database lock, the NY-ESO-1 expression assay vendor informed the study team that Participant 110017 was erroneously considered NY-ESO-1 negative when the participant's sample should have been reported as not evaluable due to lack of available tumor cells. A new corrected result report was issued. This figure presents the corrected data.
Data as of 10 July 2023.

Figure 4 Participant Disposition Post Enrolment



Source: Table 1.0100, Table 1.0170.
LTFU=long-term follow-up; mITT=Modified Intent-to-Treat.
a One participant did not meet eligibility criteria and 1 participant died prior to lymphodepletion.
b Two participants had disease progression.
Data as of 10 July 2023.

Protocol deviations:

A listing of important protocol deviations by actual dose for the mITT Population is presented in Table 1. Important protocol deviations were reported for 4 participants ("missed assessment" in 4 participants, "biological sample specimen procedures" in 2 participants, "assessment not properly performed" in 1 participant, "adverse event of special interest" in 1 participant, and "study treatment not administered per protocol" in 1 participant).

Table 1 Important Protocol Deviations by Actual Dose

Participant ID	Protocol Deviation	Impact on Participant Eligibility	Impact on Primary Endpoint
110456	Missed assessments: • The site forgot to repeat triple ECG assessment 7 days prior to leukapheresis after it was already performed during leukapheresis eligibility screening 15 days prior to leukapheresis. • ICE assessment was not done on Day 6. • No viral hepatitis serology was performed for the event - monitoring criteria level 2 (ALT absolute). • No local lab assessments were done at Week 3 visit (hematology, clinical chemistry, coagulation, CRP).	None	None
	Study treatment not administered per protocol: The site adjusted the dose of fludarabine to 20 mg/m^2 for renal impairment instead of 30 mg/m^2 based on EGFR values, not based on CrCl, as required per protocol. The medical monitor was informed about the reduced	None	None

Participant ID	Protocol Deviation	Impact on Participant Eligibility	Impact on Primary Endpoint
	dose shortly before the start of lymphodepletion, but the reason for this reduction (incorrect reference) did not become clear until after the start of lymphodepletion; it was therefore no longer possible to adjust the dose correctly according to protocol.		
	Assessment not properly performed: As per the site sample "transgene for persistence" was collected at Day 4 visit, but was broken in the centrifuge, therefore could not be sent to the vendor for analysis.	None	None
110251	Missed assessment: • At Day 8 visit, single EKG, ECOG, and ICANS were not performed. • At Day 15, Day 22, and Day 29 visits, vital signs, temperature, respiration rate, and pulse oximetry were not done.	None	None
110804	Missed assessment: • The site did not perform 24-hour CrCl assessment prior to treatment (baseline): only 24-hour creatinine urine collection was performed but clearance was not assessed. (Participant was over 65 years of age). CrCl is an eligibility lab assessment. However retrospective estimation of CrCl based on serum creatinine found the participant eligible but requiring fludarabine dose reduction (CrCl = 66.6 mL/min) • On Day 1, ICE assessment was not done due to staff error.	None	None
	Biological sample specimen procedures: The site did not perform local tests for CMV IgM and PCR at baseline. Only IgG was assessed.	None	None
110916	Biological sample specimen procedures: • Direct bilirubin, glucose, LDH, and reticulocytes were not assessed within the 7 days before leukapheresis. • Coagulation test not done at Day 8 visit. • At Week 3 visit, the site collected a liquid biopsy sample, which was not indicated at that timepoint in the SOA.	None	None
	Missed assessment: • CMV seropositive - no PCR done at baseline and Day 15. • No CMV testing with PCR done on Day 1.	None	None
	Adverse event of special interest: The participant experienced a Grade 1 CRS with tachycardia and fever. The event was entered in the eCRF after the diagnosis was clarified by the subinvestigator (within 24 hours after becoming aware of the event). However, the medical monitor was not made aware via email of the event.	None	None

Source: Listing 3.
ALT=alanine aminotransferase; CMV=cytomegalovirus; CrCl=creatinine clearance; CRP=C-reactive protein; CRS=cytokine release syndrome; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EGFR=estimated glomerular filtration rate; EKG=echocardiography; ICANS=immune effector cell-associated neurotoxicity syndrome; ICE=immune effector cell-associated encephalopathy; IgG=immunoglobulin G; IgM=immunoglobulin M; LDH=lactate dehydrogenase; PCR, polymerase chain reaction; SOA=schedule of assessments.
Data as of 10 July 2023.

One participant (110028) had a non-important protocol deviation of out-of-window assessment due to the COVID-19 pandemic (Source: Listing 4). There was no impact of COVID-19 on the integrity of the study and reliability of the conclusions.

Demographics and baseline characteristics:

A summary of demographics characteristics by actual dose for the mITT Population is presented inTable 2. The mean age of the 5 participants was 46.6 years (range: 27, 76). Two participants (40%) were female, and 3 participants (60%) were male. All 5 participants were White and Not Hispanic or Latino.

Table 2 Summary of Demographic Characteristics by Actual Dose (mITT Population)

	Dose Confirmation Phase		
	GSK3901961 $(1\text{-}8) \times 10^9$ (N=1)	GSK3901961 $(0.1\text{-}0.8) \times 10^9$ (N=4)	Total (N=5)
Sex, n (%)			
Female	1 (100)	1 (25)	2 (40)
Male	0	3 (75)	3 (60)
Age (Years)[a]			
Mean (SD)	27.0	51.5 (17.79)	46.6 (18.90)
Median (Min, Max)	27.0 (27, 27)	48.0 (34, 76)	45.0 (27, 76)
Ethnicity, n (%)			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	1 (100)	4 (100)	5 (100)
Race Detail, n (%)			
White - Arabic/North African Heritage	1 (100)	0	1 (20)
White - White/Caucasian/European Heritage	0	4 (100)	4 (80)
BMI (kg/m^2) at Leukapheresis Eligibility Screening			
Mean (SD)	21.981	21.498 (3.4722)	21.595 (3.0147)
BSA (m^2) at Leukapheresis Eligibility Screening[b]			
Mean (SD)	1.625	1.798 (0.1887)	1.764 (0.1808)

Source: Table 1.0220.
BMI=body mass index; BSA=body surface area; Max=maximum; Min=minimum; mITT=Modified Intent-to-Treat; SD=standard deviation.
a. Only year of birth was collected: day and month of birth were imputed to 30 June.
b. BSA was derived using DuBois & Dubois formula.
Note: The reference date for age was GSK3901961 infusion date.
Data as of 10 July 2023.

A summary of disease characteristics at screening by actual dose for the mITT Population is provided in Table 3. All 5 participants had SS and were positive for HLA-A*02:01 (heterozygous). Three participants had 100% tumor cells positive, 1 participant had 90% tumor cells positive, and 1 participant had 30% tumor cells positive for NY ESO-1 (2+/3+ per immunohistochemistry) (Source: Listing 49). All 5 participants had metastatic Stage IV disease at screening. Four participants (80%) received 1 or more prior

radiotherapy before leukapheresis. Two participants (40%) received radiotherapy between leukapheresis and lymphodepletion (this was palliative radiotherapy for both participants). All 5 participants received prior systemic therapy in the advanced (metastatic/unresectable) setting before the start of lymphodepletion (1 participant received 1 prior regimen, 1 participant received 2 prior regimens, 2 participants received 3 prior regimens, and 1 participant received 4 prior regimens). Best response to the most recent prior systemic therapy in the metastatic/advanced setting was SD in 4 participants (80%) and PD in 1 participant (20%). Four participants had bridging therapy between leukapheresis and lymphodepletion.

Table 3 Summary of Disease Characteristics at Screening by Actual Dose (mITT Population)

	Dose Confirmation Phase		
	GSK3901961 (1-8) × 10^9 (N=1)	GSK3901961 (0.1-0.8) × 10^9 (N=4)	Total (N=5)
Primary Tumor Type, n (%)			
Synovial Sarcoma	1 (100)	4 (100)	5 (100)
HLA Status, n (%)			
Positive	1 (100)	4 (100)	5 (100)
One HLA Allele positive			
A*02:01 - other	1 (100)	4 (100)	5 (100)
Two HLA Alleles positive	0	0	0
NY-ESO-1 Status, n (%)			
Positive	1 (100)	4 (100)	5 (100)
NY-ESO-1 Expression Score (2+/3+) (%)			
Min.	90	30	30
1st Quartile	90.0	65.0	90.0
Median	90.0	100.0	100.0
3rd Quartile	90.0	100.0	100.0
Max.	90	100	100
Extent of Disease at Screening, n (%)			
Metastatic	1 (100)	4 (100)	5 (100)
Disease Stage at Screening, n (%)			
IV	1 (100)	4 (100)	5 (100)
TNM Staging: Primary Tumor, n (%)			
TX	0	3 (75)	3 (60)
T2	1 (100)	1 (25)	2 (40)

	Dose Confirmation Phase		
	GSK3901961 (1-8) × 10^9 (N=1)	**GSK3901961 (0.1-0.8) × 10^9 (N=4)**	**Total (N=5)**
TNM Staging: Regional Lymph Nodes, n (%)			
NX	0	2 (50)	2 (40)
N0	0	1 (25)	1 (20)
N1	0	1 (25)	1 (20)
N2	1 (100)	0	1 (20)
TNM Staging: Distant Metastasis, n (%)			
MX	0	1 (25)	1 (20)
M1	1 (100)	3 (75)	4 (80)
Grade at Screening, n (%)			
n	1	2	3
2	1 (100)	1 (50)	2 (67)
3	0	1 (50)	1 (33)
Status of Measurable Disease at Screening, n (%)			
Yes	1 (100)	4 (100)	5 (100)
Non-target Lesions, n (%)			
Yes	1 (100)	4 (100)	5 (100)
NY-ESO-1 Tumor Biopsy Site, n (%)			
Primary	1 (100)	2 (50)	3 (60)
Metastatic	0	2 (50)	2 (40)
Anatomical Location of Biopsy Site, n (%)			
Chest	0	1 (25)	1 (20)
Foot	0	1 (25)	1 (20)
Lung	1 (100)	1 (25)	2 (40)
Other	0	1 (25)	1 (20)
Number of Prior Radiotherapy Regimens Before Start of Leukapheresis, n (%)			
0	0	1 (25)	1 (20)
1	1 (100)	1 (25)	2 (40)
>1	0	2 (50)	2 (40)
Radiotherapy Between Leukapheresis and Lymphodepletion, n (%)			
Yes	0	2 (50)	2 (40)
No	1 (100)	2 (50)	3 (60)

	Dose Confirmation Phase		
	GSK3901961 (1-8) × 10^9 (N=1)	GSK3901961 (0.1-0.8) × 10^9 (N=4)	Total (N=5)
Number of Prior Systemic Therapy Regimens in the Metastatic/Advanced Setting Before Start of Lymphodepletion, n (%)			
1	1 (100)	0	1 (20)
2	0	1 (25)	1 (20)
3	0	2 (50)	2 (40)
4	0	1 (25)	1 (20)
Best Response to Most Recent Prior Systemic Therapy in the Metastatic/Advanced Setting, n (%)			
Complete Response	0	0	0
Partial Response	0	0	0
Stable Disease	1 (100)	3 (75)	4 (80)
Progressive Disease	0	1 (25)	1 (20)
Not Evaluable	0	0	0
Neo-Adjuvant Therapy, n (%)			
Yes	0	2 (50)	2 (40)
No	1 (100)	2 (50)	3 (60)
Adjuvant Therapy, n (%)			
Yes	0	1 (25)	1 (20)
No	1 (100)	3 (75)	4 (80)

Source: Table 1.0240.
HLA=human leukocyte antigen; Max=maximum; Min=minimum; mITT=Modified Intent-to-Treat; NY-ESO-1=New York esophageal antigen-1; TNM=tumor, node, and metastasis.
Note: For Participants 110804 and 110916, "Grade at Screening" was unknown.
Data as of 10 July 2023.

Exposure:

Table 6 shows planned versus actual doses of GSK3901961 for the 5 mITT participants. Per protocol, the first 3 participants were to receive DL1 planned dose of (1 to 8) × 10^9 transduced T cells. As the first 2 participants treated at DL1 experienced DLTs, the DSC endorsed GSK's recommendation not to treat a third participant at the DL1 dose level and to de-escalate the dose for the next set of 3 participants to the DL-1 planned dose of (0.1 to 0.8) × 10^9 transduced T cells.

A summary of exposure to study treatment by planned dose for the mITT Population is presented in Table 4. Four of the 5 participants received lymphodepletion chemotherapy doses according to the protocol (including dose reduction provisions). One of the 5 participants received a reduced lymphodepleting regimen outside of the protocol reduction provisions:

- For Participant 110456, the site based the fludarabine dose adjustment on eGFR and not on CrCl resulting in dose reduction of fludarabine to 20 mg/m^2/day × 4 days. In addition, the participant had transfemoral amputation resulting in 15% decrease in the BSA; thus, the cyclophosphamide dose was reduced by 15% to 765 mg/m^2/day × 3days. Since the fludarabine dose had already been reduced due to eGFR, no further adjustments were made based on the reduced BSA.

The median cumulative dose of cyclophosphamide was 1800 mg/m^2 (range: 1800, 2700), and the median cumulative dose of fludarabine was 90 mg/m^2 (range: 60, 120).

Table 4 Summary of Exposure to Study Treatment by Planned Dose (mITT Population)

	Dose Confirmation Phase		
Dose	**GSK3901961 DL1 (N=2)**	**GSK3901961 DL-1 (N=3)**	**Total (N=5)**
Cyclophosphamide Cumulative Dose (mg/m^2)			
Median (Min, Max)	2250 (1800, 2700)	1800 (1800, 2295)	1800 (1800, 2700)
Fludarabine Cumulative Dose (mg/m^2)			
Median (Min, Max)	90 (60, 120)	90 (80, 90)	90 (60, 120)
Actual Transduced Cell Dose Received			
<0.1 (× 10^9 cells), n (%)	0	0	0
≥0.1 to ≤0.8 (× 10^9 cells), n (%)	1 (50)	3 (100)	4 (80)
>0.8 to <1 (× 10^9 cells), n (%)	0	0	0
≥1 to ≤8 (× 10^9 cells), n (%)	1 (50)	0	1 (20)
>8 (× 10^9 cells), n (%)	0	0	0
Median (Min, Max)	2.95 (0.80, 5.10)	0.80 (0.60, 0.80)	0.80 (0.60, 5.10)

Source: Table 3.0340.
Max=maximum; Min=minimum; mITT=Modified Intent-to-Treat.
DL1 planned dose range is (1 to 8) × 10^9 transduced cells;
DL-1 planned dose range is (0.1 to 0.8) × 10^9 transduced cells.
Data as of 10 July 2023.

The first participant (110804) to receive GSK3901961 was a sentinel participant and planned to receive the target dose under DL1 dose level to be infused in 2 aliquots (at Day 1 [~30%] and Day 8 [~70%]). However, the participant experienced toxicities, including a DLT, that precluded the participant from receiving the second aliquot. The dose received was 0.8 × 10^9 transduced cells.

Because of the DLT reported for the first sentinel participant, the second participant (110028) was also dosed as a sentinel participant and received the planned dose of 5.1 × 10^9 cells in 2 aliquots: 1.7 × 10^9 transduced cells on Day 1 and 3.4 × 10^9 transduced Table 5 cells on Day 8 ().

As the first 2 participants received a transduced T cell dose ≥0.8×10^9 as a first infusion, the DSC endorsed GSK's recommendation to administer the full planned transduced T-cell dose at DL-1 as a single infusion for all subsequent participants treated with GSK3901961.

Ultimately, 1 participant received GSK3901961 at the dose of (1 to 8) × 10^9 cells, and the other 4 participants at the dose of (0.1 to 0.8) × 10^9 cells. Overall, the median number of transduced T cells was 0.8×10^9 cells (range: 0.6×10^9, 5.1×10^9).

Table 5 Individual Exposure to Study Treatment by Actual Dose (mITT Population)

Participant ID	Transduced T cells (× 10^9)		
	1st Infusion (Day 1)	2nd infusion (Day 8)	Total
110804	0.8	0	0.8
110028	1.7	3.4	5.1
110456	0.8	NA	0.8
110916	0.6	NA	0.6
110251	0.8	NA	0.8

Source: Listing 15.
mITT=Modified Intent-to-Treat; NA=not applicable.
Note: Participants 110804 and 110028 were sentinel participants to receive split doses.
Data as of 10 July 2023.

Concomitant medications

A summary of concomitant medications by actual dose for the mITT Population is presented in Table 1.0270. All 5 participants received concomitant medications during the study. Overall, the most common concomitant medications (received by >50% of participants) were paracetamol (100%); and G-CSF, ibuprofen, Mesna, metoclopramide, ondansetron, piperacillin, and tazobactam (60% each).

Safety results:

Dose-limiting toxicities:

Two out of 5 (40%) participants had reported T-cell-related AEs that met the protocol defined DLT criteria and were endorsed by the DSC (Table 6). The following DLTs were reported (Source: Listing 19):

- Participant 110804 had ALT increased (onset 2 days, duration 37 days, nonserious, Grade 3, related to T-cell infusion, resolved); and
- Participant 110028 had rash maculopapular (onset 22 days, duration 32 days, serious, Grade 3, related to T-cell infusion, resolved) and ALT increased (onset 23 days, duration 16 days, nonserious, Grade 3, related to T-cell infusion, resolved).

One participant had reported T-cell-related event of Grade 3 ALT increased, that met protocol defined exceptions from the DLT criteria.

- Participant 110456 had ALT increase (onset 5 days, duration 26 days, nonserious, Grade 3, related to T-cell infusion, resolved). The Grade 3 ALT increase for this participant was considered possibly related to T-cell infusion and did not return to Grade ≤1 (or Baseline) within 7 days from the onset but did not require any intervention nor was considered to be clinically significant by the investigator. The investigator considered ALT elevation for the participant to meet protocol defined exceptions from the DLT criteria and the investigator's assessment was endorsed by the DSC.

Table 6 Summary of Dose-Limiting Toxicities by Actual Dose and Planned Dose (DLT Evaluable Population)

GSK3901961		Planned Dose		
	Actual Dose	DL1 (N=2)	DL-1 (N=3)	Total (N=5)
n [No. of Participants with DLT]	(1-8) × 10^9 (N=1)	1[a] [1]	0 [0]	1 [1]
	(0.1-0.8) × 10^9 (N=4)	1[b] [1]	3 [0]	4 [1]

Source: Table 3.0105.
AE=adverse event; DL1=(1-8) × 10^9 T cells; DL-1=(0.1-0.8) × 10^9 T cells; DLT=dose-limiting toxicity; eCRF=electronic case report form.
a. The sentinel participant 110028 in DL1 (planned dose level 1-8 × 10^9) received both T cell doses.
b. The sentinel participant 110804 in DL1 (planned dose level 1-8 × 10^9) did not receive the second dose of T cells on Day 8; and is summarized under actual dose level (0.1-0.8) × 10^9.
Data as of 10 July 2023.

Adverse events (pretreatment, before T-cell infusion):

During eligibility assessment, 1 participant (110903) experienced a Grade 3 SAE of pneumothorax that was considered related to the study procedure. This participant does not belong to the ITT Population as he was not deemed eligible because of his worsening disease.

The pre-lymphodepletion phase (ITT Population) includes AEs that started before the first day of lymphodepletion chemotherapy. During the pre-lymphodepletion phase, 5 of 7 enrolled participants (71%) had at least 1 AE (Source: Table 3.0120); none of these AEs were related to the study procedure. Four out of 7 participants had at least 1 SAE in the pre-lymphodepletion phase; the same group of 4 were also those enrolled participants reported with Grade ≥3 AEs (Source: Listings 20, 22, and 23) (Narratives of these participants are provided in the CASE NARRATIVES section).

The lymphodepletion phase includes AEs that started or worsened on or after the start of lymphodepletion and before T-cell infusion. During the lymphodepletion phase (Lymphodepletion Population), 3 of 5 treated participants (60%) had at least 1 AE

(Source: Table 3.0130). One participant had a Grade 4 AE; no SAE was reported (Source: Listing 20).

Treatment-emergent adverse events:

AEs that started or worsened on or after T-cell infusion were classified as TEAEs. A summary of TEAEs by actual dose is presented in Table 7. All 5 participants had TEAEs. Overall, the most common TEAEs, occurring in >50% of participants, were CRS, leukopenia/WBC decreased, neutropenia/neutrophil count decreased, and thrombocytopenia/platelet count decreased (80% each); and ALT increased, anemia/RBC count decreased, AST increased, COVID-19, nausea, pyrexia, and rash/rash maculopapular (60% each).

Table 7 Summary of TEAEs by Actual Dose (mITT Population)

	Dose Confirmation		
Preferred Term, n (%)	**GSK3901961 (1-8) × 10^9 (N=1)**	**GSK3901961 (0.1-0.8) × 10^9 (N=4)**	**Total (N=5)**
Any TEAE	**1 (100%)**	**4 (100%)**	**5 (100%)**
Cytokine release syndrome	1 (100%)	3 (75%)	4 (80%)
Leukopenia/White blood cell count decreased	1 (100%)	3 (75%)	4 (80%)
Neutropenia/Neutrophil count decreased	1 (100%)	3 (75%)	4 (80%)
Thrombocytopenia/Platelet count decreased	1 (100%)	3 (75%)	4 (80%)
Alanine aminotransferase increased	1 (100%)	2 (50%)	3 (60%)
Anaemia/Red blood cell count decreased	1 (100%)	2 (50%)	3 (60%)
Aspartate aminotransferase increased	1 (100%)	2 (50%)	3 (60%)
COVID-19	1 (100%)	2 (50%)	3 (60%)
Nausea	1 (100%)	2 (50%)	3 (60%)
Pyrexia	1 (100%)	2 (50%)	3 (60%)
Rash/Rash maculo-papular	1 (100%)	2 (50%)	3 (60%)
Blood lactate dehydrogenase increased	1 (100%)	1 (25%)	2 (40%)
C-reactive protein increased	0	2 (50%)	2 (40%)
Procalcitonin increased	0	2 (50%)	2 (40%)
Fatigue	1 (100%)	1 (25%)	2 (40%)
Non-cardiac chest pain	1 (100%)	1 (25%)	2 (40%)
Hypoalbuminaemia	1 (100%)	1 (25%)	2 (40%)
Hypokalaemia	1 (100%)	1 (25%)	2 (40%)
Rhinovirus infection	0	1 (25%)	1 (20%)
Staphylococcal skin infection	1 (100%)	0	1 (20%)

	Dose Confirmation		
Preferred Term, n (%)	**GSK3901961 (1-8) × 10^9 (N=1)**	**GSK3901961 (0.1-0.8) × 10^9 (N=4)**	**Total (N=5)**
Urinary tract infection	0	1 (25%)	1 (20%)
Blood alkaline phosphatase increased	1 (100%)	0	1 (20%)
Blood phosphorus decreased	0	1 (25%)	1 (20%)
Blood potassium increased	0	1 (25%)	1 (20%)
Interleukin level increased	0	1 (25%)	1 (20%)
Lymphocyte count decreased	1 (100%)	0	1 (20%)
Serum ferritin increased	0	1 (25%)	1 (20%)
Troponin increased	1 (100%)	0	1 (20%)
Leukocytosis	0	1 (25%)	1 (20%)
Abdominal pain	1 (100%)	0	1 (20%)
Anal incontinence	0	1 (25%)	1 (20%)
Constipation	0	1 (25%)	1 (20%)
Diarrhoea	0	1 (25%)	1 (20%)
Gastrooesophageal reflux disease	0	1 (25%)	1 (20%)
Lower gastrointestinal haemorrhage	1 (100%)	0	1 (20%)
Vomiting	1 (100%)	0	1 (20%)
Face oedema	1 (100%)	0	1 (20%)
Injection site pain	0	1 (25%)	1 (20%)
Mucosal dryness	0	1 (25%)	1 (20%)
Pain	1 (100%)	0	1 (20%)
Graft versus host disease in skin	1 (100%)	0	1 (20%)
Dizziness postural	0	1 (25%)	1 (20%)
Headache	0	1 (25%)	1 (20%)
Hypoaesthesia	0	1 (25%)	1 (20%)
IIIrd nerve paresis	0	1 (25%)	1 (20%)
Immune effector cell-associated neurotoxicity syndrome	0	1 (25%)	1 (20%)
Neuralgia	1 (100%)	0	1 (20%)
Paraesthesia	0	1 (25%)	1 (20%)
Paresis	0	1 (25%)	1 (20%)
Somnolence	1 (100%)	0	1 (20%)
Alopecia	0	1 (25%)	1 (20%)

	Dose Confirmation		
Preferred Term, n (%)	**GSK3901961 (1-8) × 10^9 (N=1)**	**GSK3901961 (0.1-0.8) × 10^9 (N=4)**	**Total (N=5)**
Pruritus	0	1 (25%)	1 (20%)
Skin fissures	0	1 (25%)	1 (20%)
Decreased appetite	1 (100%)	0	1 (20%)
Hypercalcaemia	0	1 (25%)	1 (20%)
Muscle spasms	0	1 (25%)	1 (20%)
Pain in extremity	0	1 (25%)	1 (20%)
Malignant neoplasm progression	0	1 (25%)	1 (20%)
Metastases to central nervous system	0	1 (25%)	1 (20%)
Tumour pain	0	1 (25%)	1 (20%)
Cough	0	1 (25%)	1 (20%)
Dyspnoea	0	1 (25%)	1 (20%)
Pulmonary haemorrhage	0	1 (25%)	1 (20%)
Diplopia	0	1 (25%)	1 (20%)
Eyelid ptosis	0	1 (25%)	1 (20%)
Insomnia	0	1 (25%)	1 (20%)
Dysuria	1 (100%)	0	1 (20%)
Vaginal discharge	1 (100%)	0	1 (20%)

Source: Table 3.0140.
COVID-19=coronavirus disease 2019; mITT=Modified Intent-to-Treat; TEAE=treatment-emergent adverse event.
Note: Adverse events which started or worsened on or after T-cell infusion were classified as treatment emergent.
Note: Preferred terms are combined as shown in Table 3.0110.
Data as of 10 July 2023.

Grade ≥3 treatment-emergent adverse events:

All 5 participants experienced at least 1 Grade ≥3 TEAE (Table 8). The most common Grade ≥3 TEAEs, occurring in >50% of participants, were leukopenia/WBC decreased and neutropenia/neutrophil count decreased (80% each).

The following Grade 4 TEAEs were reported: neutropenia/neutrophil count decreased (80%) and leukopenia/WBC decreased (60%) (Source: Table 3.0150).

The following Grade 5 TEAE was reported: malignant neoplasm progression (20%) (Source: Table 3.0150).

Table 8 Grade ≥3 TEAEs by Actual Dose (mITT Population)

	Dose Confirmation Phase		
Preferred Term, n (%)	**GSK3901961 (1-8) × 10^9 (N=1)**	**GSK3901961 (0.1-0.8) × 10^9 (N=4)**	**Total (N=5)**
Any Grade ≥3 TEAE	**1 (100%)**	**4 (100%)**	**5 (100%)**
Leukopenia/White blood cell decreased	1 (100%)	3 (75%)	4 (80%)
Neutropenia/Neutrophil count decreased	1 (100%)	3 (75%)	4 (80%)
Alanine aminotransferase increased	1 (100%)	1 (25%)	2 (40%)
Anaemia/Red blood cell count decreased	1 (100%)	1 (25%)	2 (40%)
Rash/Rash maculo-papular	1 (100%)	1 (25%)	2 (40%)
Thrombocytopenia/Platelet count decreased	0	1 (25%)	1 (20%)
Aspartate aminotransferase increased	1 (100%)	0	1 (20%)
COVID-19	0	1 (25%)	1 (20%)
Pyrexia	1 (100%)	0	1 (20%)
C-reactive protein increased	0	1 (25%)	1 (20%)
Procalcitonin increased	0	1 (25%)	1 (20%)
Blood alkaline phosphatase increased	1 (100%)	0	1 (20%)
Diarrhoea	0	1 (25%)	1 (20%)
Eyelid ptosis	0	1 (25%)	1 (20%)
Hypercalcaemia	0	1 (25%)	1 (20%)
Hypoaesthesia	0	1 (25%)	1 (20%)
IIIrd nerve paresis	0	1 (25%)	1 (20%)
Leukocytosis	0	1 (25%)	1 (20%)
Lymphopenia/Lymphocyte count decreased	1 (100%)	0	1 (20%)
Malignant neoplasm progression	0	1 (25%)	1 (20%)
Metastases to central nervous system	0	1 (25%)	1 (20%)
Pain in extremity	0	1 (25%)	1 (20%)
Paresis	0	1 (25%)	1 (20%)
Serum ferritin increased	0	1 (25%)	1 (20%)
Unspecified GVHD - Skin	1 (100%)	0	1 (20%)

Source: Table 3.0150.
COVID-19=coronavirus disease 2019; GVHD=graft versus host disease; mITT=Modified Intent-to-Treat; TEAE=treatment-emergent adverse event.
Note: Adverse events which started or worsened on or after T-cell infusion were classified as treatment emergent.
Note: Preferred terms are combined as shown in Table 3.0110.
Data as of 10 July 2023.

Treatment-emergent adverse events related to T-cell infusion:

All 5 participants had at least 1 TEAE related to T-cell infusion (Table 9). The most common T-cell infusion-related TEAE, occurring in >50% of participants, were CRS and neutropenia/neutrophil count decreased (80% each); and ALT increased, AST increased, and pyrexia (60% each).

Table 9 Treatment-Emergent T-cell-Related Adverse Events by Actual Dose (mITT Population)

	Dose Confirmation Phase		
Preferred Term, n (%)	**GSK3901961 (1-8) × 10^9 (N=1)**	**GSK3901961 (0.1-0.8) × 10^9 (N=4)**	**Total (N=5)**
Any T-cell-Related TEAE	**1 (100%)**	**4 (100%)**	**5 (100%)**
Cytokine Release Syndrome (CRS)	1 (100%)	3 (75%)	4 (80%)
Neutropenia/Neutrophil count decreased	1 (100%)	3 (75%)	4 (80%)
Alanine aminotransferase increased	1 (100%)	2 (50%)	3 (60%)
Aspartate aminotransferase increased	1 (100%)	2 (50%)	3 (60%)
Pyrexia	1 (100%)	2 (50%)	3 (60%)
Anaemia/Red blood cell count decreased	1 (100%)	1 (25%)	2 (40%)
Fatigue	1 (100%)	1 (25%)	2 (40%)
Leukopenia/White blood cell decreased	1 (100%)	1 (25%)	2 (40%)
Nausea	0	2 (50%)	2 (40%)
Thrombocytopenia/Platelet count decreased	1 (100%)	1 (25%)	2 (40%)
Blood alkaline phosphatase increased	1 (100%)	0	1 (20%)
Blood lactate dehydrogenase increased	1 (100%)	0	1 (20%)
C-reactive protein increased	0	1 (25%)	1 (20%)
Decreased appetite	1 (100%)	0	1 (20%)
Hypoalbuminaemia	1 (100%)	0	1 (20%)
Hypokalaemia	1 (100%)	0	1 (20%)
Immune effector cell-associated neurotoxicity syndrome (ICANS)	0	1 (25%)	1 (20%)
Mucosal dryness	0	1 (25%)	1 (20%)
Procalcitonin increased	0	1 (25%)	1 (20%)
Rash/Rash maculo-papular	1 (100%)	0	1 (20%)
Serum ferritin increased	0	1 (25%)	1 (20%)
Skin fissures	0	1 (25%)	1 (20%)
Troponin increased	1 (100%)	0	1 (20%)

	Dose Confirmation Phase		
Preferred Term, n (%)	**GSK3901961 (1-8) × 10^9 (N=1)**	**GSK3901961 (0.1-0.8) × 10^9 (N=4)**	**Total (N=5)**
Tumour pain	0	1 (25%)	1 (20%)
Unspecified GVHD - Skin	1 (100%)	0	1 (20%)

Source: Table 3.0160.
AE=adverse event; GVHD=graft versus host disease; mITT=Modified Intent-to-Treat; TEAE=treatment-emergent adverse event.
Note: Adverse events which started or worsened on or after T-cell infusion were classified as treatment emergent.
Note: T-cell related AEs were defined as AEs identified by the investigator as related to T-cell infusion.
Note: Preferred terms are combined as shown in Table 3.0110.
Data as of 10 July 2023.

T-cell infusion-related Grade ≥3 TEAEs occurred in 4 participants (80%). The following T-cell infusion-related Grade ≥3 TEAEs were reported: neutropenia/neutrophil count decreased (80%); ALT increased and leukopenia/WBC decreased (40% each); and AST increased, pyrexia, anemia/RBC count decreased, blood ALP increased, CRP increased, procalcitonin increased, rash/rash maculopapular, serum ferritin increased, and unspecified GVHD – skin (20% each). Notably, none of these events were Grade 5 (Source: Table 3.0160).

Treatment-emergent adverse events related to lymphodepletion:

Listed TEAEs related to lymphodepletion in this section may have also been reported as related to GSK3901961 T-cell infusion in the prior section. All 5 participants had at least 1 TEAE related to lymphodepletion. The most common lymphodepletion-related TEAEs, occurring in >50% of participants, were leukopenia/WBC decreased and neutropenia/neutrophil count decreased (60% each) (Source: Table 3.0170).

Lymphodepletion-related Grade ≥3 TEAEs occurred in 4 participants (80%). The following lymphodepletion-related Grade ≥3 TEAEs were reported: leukopenia/WBC decreased and neutropenia/neutrophil count decreased (60% each); and anemia/RBC decreased, thrombocytopenia/platelet count decreased, and lymphopenia/lymphocyte count decreased (20% each) (Source: Table 3.0170).

Deaths

Of the 5 participants who received GSK3901961, 2 participants (40%) died and 3 participants (60%) were alive at the last contact in this study and follow-up was ended in this study (Table 10).

The primary cause of death was disease under study (Grade 5 SAE of malignant neoplasm progression) in Participant 110251. The time from T-cell infusion to death was 83 days. This event was considered not related to GSK3901961 (Source: Listing 39).

The primary cause of death was disease under study in Participant 110804. The secondary cause of death was COVID-19. The time from T-cell infusion to death was 263 days. This event was considered not related to GSK3901961 (Source: Listing 39).

Table 10 Summary of Deaths by Actual Dose (mITT Population)

	Dose Confirmation Phase		
	GSK3901961 (1-8) × 10^9 (N=1)	GSK3901961 (0.1-0.8) × 10^9 (N=4)	Total (N=5)
Subject Status, n (%)			
Dead	0	2 (50%)	2 (40%)
Alive at last contact, follow-up ended	1 (100%)	2 (50%)	3 (60%)
Primary Cause of Death, n (%)			
Cancer (Disease under study)	0	2 (50%)	2 (40%)
Time since T-cell infusion to Death, n (%)			
>30 days	0	2 (50%)	2 (40%)

Source: Table 3.0330.
mITT=Modified Intent-to-Treat.
Data as of 10 July 2023.

Serious adverse events:

No SAEs were reported in the lymphodepletion phase (Source: Table 3.0200).

Three (60%) of the 5 participants who received GSK3901961 experienced treatment-emergent SAEs (Source: Table 3.0220,Table 11):

- Participant 110804 experienced a treatment-emergent SAE of Grade 1 pulmonary hemorrhage, which was not considered by the investigator to be related to GSK3901961.

- Participant 110028 experienced treatment-emergent SAEs of Grade 3 pyrexia, Grade 3 rash/rash maculopapular, and Grade 3 GvHD – skin, all of which were considered related to GSK3901961 by the investigator. This participant also experienced a treatment-emergent SAE of Grade 2 non-cardiac chest pain, which was not considered by the investigator to be related to GSK3901961.

- Participant 110251 experienced a Grade 5 treatment-emergent SAE of malignant neoplasm progression and Grade 3 pain in extremity, which were not considered by the investigator to be related to GSK3901961.

Table 11 Treatment Emergent Serious Adverse Events by Actual Dose (mITT Population)

	Dose Confirmation Phase		
Preferred Term, n (%)	**GSK3901961 (1-8) × 10^9 (N=1)**	**GSK3901961 (0.1-0.8) × 10^9 (N=4)**	**Total (N=5)**
Any Serious TEAE	**1 (100%)**	**2 (50%)**	**3 (60%)**
Malignant neoplasm progression	0	1 (25%)	1 (20%)
Non-cardiac chest pain	1 (100%)	0	1 (20%)
Pain in extremity	0	1 (25%)	1 (20%)
Pulmonary haemorrhage	0	1 (25%)	1 (20%)
Pyrexia	1 (100%)	0	1 (20%)
Rash/Rash maculo-papular	1 (100%)	0	1 (20%)
Unspecified GVHD - Skin	1 (100%)	0	1 (20%)

Source: Table 3.0220.
GVHD=graft versus host disease; mITT=Modified Intent-to-Treat; TEAE=treatment-emergent adverse event.
Note: Adverse events which started or worsened on or after T-cell infusion were classified as treatment emergent.
Note: Preferred terms are combined as shown in Table 3.0110.
Data as of 10 July 2023.

Adverse events of special interest:

The AESIs included CRS, hematopoietic cytopenias (including pancytopenia and aplastic anemia), GvHD, ICANS, Guillain-Barre syndrome, pneumonitis, treatment-related inflammatory response at tumor site(s), and neutropenia Grade 4 lasting ≥28 days.

A focused list of MedDRA terms based on clinical review was used to identify each type of event. In addition, a focused and comprehensive list of MedDRA terms aligning with MedDRA SMQ list was also used for AESI reporting. Treatment-related inflammatory response at tumor site was not identified using the focused or comprehensive list. Treatment-related inflammatory response was reported as per investigator's assessment.

The following AESIs were reported: CRS (80% of patients), hematopoietic cytopenias (100%), GvHD (20%), and ICANS (20%) (Table 12). These AESIs are described in detail below. No AESIs were reported for Guillain-Barre syndrome, treatment-related inflammatory response at tumor site(s), pneumonitis, and neutropenia Grade 4 lasting ≥28 days.

Table 12 Summary of Treatment-Emergent Adverse Events of Special Interest by Actual Dose (Focused List; mITT Population)

	Dose Confirmation Phase		
AESI Category Adverse Event, n (%)	**GSK3901961 (1-8) × 10^9 (N=1)**	**GSK3901961 (0.1-0.8) × 10^9 (N=4)**	**Total (N=5)**
Any AESI	1 (100%)	4 (100%)	5 (100%)
Cytokine release syndrome			
Any Event	1 (100%)	3 (75%)	4 (80%)
Cytokine Release Syndrome (CRS)	1 (100%)	3 (75%)	4 (80%)
Graft versus host disease			
Any Event	1 (100%)	0	1 (20%)
Unspecified GVHD - Skin	1 (100%)	0	1 (20%)
Haematopoietic cytopenias (including pancytopenia and aplastic anaemia)			
Any Event	1 (100%)	4 (100%)	5 (100%)
Leukopenia/White blood cell decreased	1 (100%)	3 (75%)	4 (80%)
Neutropenia/Neutrophil count decreased	1 (100%)	3 (75%)	4 (80%)
Thrombocytopenia/Platelet count decreased	1 (100%)	3 (75%)	4 (80%)
Anaemia/Red blood cell count decreased	1 (100%)	2 (50%)	3 (60%)
Lymphopenia/Lymphocyte count decreased	1 (100%)	0	1 (20%)
Immune Effector-Cell Associated Neurotoxicity Syndrome (ICANS)			
Any Event	0	1 (25%)	1 (20%)
Immune effector cell-associated neurotoxicity syndrome (ICANS)	0	1 (25%)	1 (20%)

Source: Table 3.0250.
AESI=adverse event of special interest; GVHD=graft versus host disease; mITT=Modified Intent-to-Treat.
Note: Adverse events which started or worsened on or after T-cell infusion were classified as treatment emergent.
Note: Preferred terms are combined as shown in Table 3.0110.
Data as of 10 July 2023.

Four (80%) of 5 treated participants had CRS (total 4 events) after GSK3901961 infusion. All events were considered related to T-cell infusion. No participant had an SAE of CRS. Two participants had Grade 2 CRS and 2 participants had Grade 1 CRS. CRS resolved in all 4 participants. Two participants required treatment with tocilizumab; 1 of these 2 participants also received steroids (dexamethasone) (Source: Listing 26). The median time to onset of CRS was 2.5 days (range: 2, 5), and the median duration of CRS was 3 days (range: 2, 7) (Source: Table 3.0260).

All 5 treated participants had hematopoietic cytopenias after GSK3901961 infusion. The following hematopoietic cytopenias were reported: leukopenia/WBC decreased,

neutropenia/neutrophil count decreased, and thrombocytopenia/platelet count decreased (80% each); anemia/RBC count decreased (60%); and lymphopenia/lymphocyte count decreased (20%) (Table 12). All 5 participants had Grade ≥3 hematopoietic cytopenias (Source: Table 3.0250). The following events were considered related to T cells: neutropenia/neutrophil count decreased (80%); and anemia/RBC count decreased, leukopenia/WBC decreased, and thrombocytopenia/platelet count decreased (40% each) (Table 9). None of these hematopoietic cytopenias were reported as SAEs (Table 11). All these events resolved except anemia and leukopenia in Participant 110251 and lymphocyte count decreased in Participant 110028, which did not resolve. The time to onset of hematopoietic cytopenias ranged from 1 to 120 days, and the duration of hematopoietic cytopenias ranged from 2 to 81 days (Source: Listing 20).

No participants had a lymphodepletion-emergent or treatment-emergent event of pancytopenia or aplastic anemia.

No participant had persistent cytopenia (neutropenia, thrombocytopenia, anemia) beyond 28 days post T-cell infusion (Week 5) based on the laboratory results (Source: Listing 51).

One participant (110028) had GvHD after GSK3901961 infusion. This participant had serious, Grade 3, T-cell related GvHD in skin with an onset of 40 days after the T-cell infusion. The participant received topical steroids and mepolizumab and the event resolved 14 days after onset (Source: Listing 29).

One participant (110456) had ICANS after GSK3901961 infusion. This participant had nonserious, Grade 1, T-cell related ICANS with an onset of 2 days after the T-cell infusion. The participant was treated with tocilizumab (in the context of CRS) as the participant had an ongoing CRS and the event resolved 2 days after onset (Source: Listing 27).

Clinical laboratory evaluations:

Listing of all laboratory data by actual dose for the ITT Population is provided in Listing 33. Plots of hemoglobin, neutrophils, and platelets over time for individual participants in the mITT Population are provided in Figure 3.0360. Worst-case post-baseline of Grade 3 was observed for the following clinical chemistry parameters: ALT increased (3 participants); and high calcium, ALP increased, and AST increased (1 participant each). Worst-case post-baseline of Grade ≥3 was observed for the following hematology parameters: lymphocyte count decreased (5 participants), neutrophil count decreased, WBC decreased (4 participants each), anemia (2 participants), and platelet count decreased (1 participant).

Listing of urinalysis data by actual dose for the ITT Population is provided in Listing 34.

Participants meeting hepatobiliary laboratory criteria post-baseline by actual dose for the mITT Population are listed in Listing 35. No participant met Hy's law criteria.

Three participants had liver events: 2 participants (110456,110028) met liver monitoring criteria level 2 and 1 participant (110804) met liver stopping criteria (Source: Listing 36,

Listing 37). Narratives of these participants are provided in the CASE NARRATIVES section.

Vital signs:

Listing of all vital signs by actual dose for the ITT Population is provided in Listing 43. All clinically significant high or low values for blood pressure, temperature, and heart rate are in line with reported AEs or SAEs.

ECOG PS:

All 5 treated participants had ECOG PS of 0 (indicating full activity) or 1 (restricted in strenuous activity) at baseline (pre-lymphodepletion). ECOG PS worsened post-baseline to 4 (completely disabled; cannot carry on any self-care; totally confined to a bed or chair) in 1 participant, which did not improve by the last assessment since the participant died (Listing 40). The remaining 4 participants had worsened postbaseline value of 1, of which 2 participants improved to 0 by their last assessment.

Electrocardiogram:

Clinically significant ECG findings were noted for 1 participant (110028) during the study. This participant had sinus arrhythmia on Day 41 and sinus tachycardia (heart rate 121 beats/minute) on Day 111 (Source: Listing 42). A narrative of this participant is provided in the CASE NARRATIVES section.

Worst-case post-baseline of QTcB interval ≥450 msec was reported for 2 participants: Participant 110251 had QTcB interval of 458 msec at Day 6 and Participant 110028 had QTcB interval of 450 msec at Day 41 and 452 msec on Day 111. No participant had an increase in QTcB interval >501 msec or QTcF interval ≥450 msec. QRS was low (<70 msec) for Participant 110804 on Day 4 and for Participant 110916 on Day 8 (Source: Listing 41).

Anti-GSK3901961 antibodies:

All participants were tested at least once and were negative at all timepoints during the study (Source: Listing 63).

Replication competent lentivirus:

All 5 treated participants were tested for RCL post T-cell infusion at least once, and no participant tested positive for RCL. Two participants (110251, 110916) had results reported for baseline only by the DBL date, but each participant had a post T-cell infusion RCL result (at Week 8 for 110251 and Week 12 for 110916) that was obtained post DBL and confirmed negative (Source: Table 3.0350, Listing 61, and Memo Document TMF-17012146).

Insertional oncogenesis:

No integration site analysis was performed as no participant remained in the study 1-year post-treatment (Source: Listing 62).

Efficacy results:

A summary of investigator-assessed best response with confirmation per RECIST 1.1 by actual dose is presented in Table 13. The ORR was 60% (95% CI: 14.7%, 94.7%), with 3 participants achieving confirmed PR. SD was noted in 1 participant (20%).

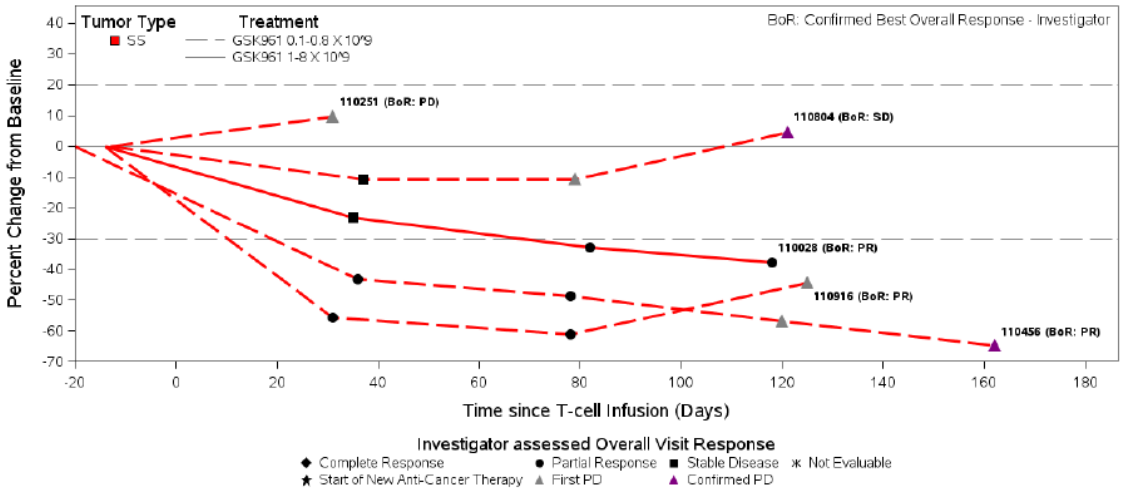
Table 13 Summary of Investigator-Assessed Best Response with Confirmation (RECIST 1.1 Criteria) by Actual Dose (mITT Population)

	Dose Confirmation Phase		
	GSK3901961 $(1\text{-}8) \times 10^9$ (N=1)	GSK3901961 $(0.1\text{-}0.8) \times 10^9$ (N=4)	Total (N=5)
Best Response			
Complete Response	0	0	0
Partial Response	1 (100%)	2 (50%)	3 (60%)
Stable Disease	0	1 (25%)	1 (20%)
Progressive Disease	0	1 (25%)	1 (20%)
Not Evaluable	0	0	0
Response Rate			
[CR + PR]	1 (100.0%)	2 (50.0%)	3 (60.0%)
95% Confidence Interval[a]	(2.5%, 100.0%)	(6.8%, 93.2%)	(14.7%, 94.7%)

Source: Table 2.0100.
CI=confidence interval; CR=complete response; PR=partial response; mITT=Modified Intent-to-Treat; RECIST=response evaluation criteria in solid tumors.
a. CIs were calculated using the exact (Clopper-Pearson) method.
Data as of 10 July 2023.

Spider plots of percentage change from baseline in target lesions are shown in Figure 5. Three participants had a decrease in target lesion diameters of ≥30% (at Weeks 6, 12, and 18 for Participant 110916; at Weeks 6, 12, 18, and 24 for Participant 110456; and at Weeks 12 and 18 for Participant 110028) and achieved confirmed PR.

Figure 5 Spider Plot of Investigator-Assessed Percent Change from Baseline in Target Lesion Diameter by Actual Dose (mITT Population)



Source: Figure 2.0120.
BoR=best overall response; mITT=Modified Intent-to-Treat; PD=progressive disease; PR=partial response; SD=stable disease; SS=synovial sarcoma.
Note: Participant 110456 had first PD recorded at Week 18 due to a new non-target tumor and confirmed PD recorded at Week 24 due to a non-target tumor enlargement from nadir.
Note: Participant 110251 had first PD recorded at Week 6 due to a non-target tumor enlargement from nadir and then did not have any target lesions measured again after that visit. The participant had 2 further unscheduled visits on Days 43 and 64, the latter of which confirmed the Week 6 PD due to a new non-target lesion.
Note: Participant 110916 had first PD recorded at Week 18 due to a new non-target tumor. No further tumor assessments were performed due to interventional phase closing.
Note: Participant 110916 had an incorrect Week18 assessment date of 29 May 2023 per site entry for new non-target lesions. Correct date was 26 May 2023; hence, the first PD date was reported as 3 days later than it was.
Data as of 10 July 2023.

A summary of investigator-assessed DoR per RECIST 1.1 by actual dose is presented in Table 14. Of the 3 confirmed responders, 2 participants had disease progression and 1 participant was censored at the last tumor assessment due to study withdrawal. The DoR for Participant 110456 was 2.8 months until progression, DoR for Participant 110916 was 3.1 months until progression, and DoR for Participant 110028 was censored at 1.2 months (Source: Listing 45).

Table 14 Summary of Investigator-Assessed Duration of Response (RECIST 1.1 Criteria) by Actual Dose (mITT Population)

	Dose Confirmation Phase		
	GSK3901961 $(1\text{-}8) \times 10^9$ (N=1)	GSK3901961 $(0.1\text{-}0.8) \times 10^9$ (N=4)	Total (N=5)
Number of Subjects			
n	1	2	3
Progressed or Died (event)	0	2 (100%)	2 (67%)

	Dose Confirmation Phase		
	GSK3901961 (1-8) × 10^9 (N=1)	GSK3901961 (0.1-0.8) × 10^9 (N=4)	Total (N=5)
Censored, follow-up ended	1 (100%)	0	1 (33%)
Summary Statistics for Duration of Response (Months)			
n	1	2	3
Mean	1.22	2.96	2.38
StD		0.232	1.019
Median	1.22	2.96	2.79
Minimum	1.2	2.8	1.2
Maximum	1.2	3.1	3.1

Source: Table 2.0110.
CR=complete response; mITT=Modified Intent-to-Treat; PD=progressive disease; PR=partial response; RECIST=response evaluation criteria in solid tumors; StD=standard deviation.
Note: Duration of response was defined as the interval between the initial date of the confirmed response (PR/CR) and the date of PD or death among participants with a confirmed response per RECIST 1.1.
Note: Minimum criterion of ≥5 confirmed responders for presentation of Kaplan-Meier statistics had not been met; summary statistics are presented instead.
Note: Participant 110916 had an incorrect Week 18 assessment date of 29 May 2023 per site entry for new non-target lesions. Correct date was 26 May 2023; hence, duration of response was reported as 3 days longer than it was.
Data as of 10 July 2023.

OS data are not mature. Two participants have died and 3 participants were alive as per the last contact date in the study. The 2 deaths occurred at 2.7 and 8.6 months after T cell infusion (Source: Listing 46). A summary of the deaths is provided in Table 10.

Pharmacokinetic results:

The geometric mean AUC(0-28d) (%CV) was 537,038.02 (366.447) copies per µg gDNA times days, the geometric mean AUC(0-tlast) (%CV) was 775,822.56 (446.020) copies per µg gDNA times days, and the geometric mean Cmax (%CV) was 38,713.78 (341.948) copies per µg gDNA (Table 15). The median Tmax was 8 days (range: 1, 21) (Source: Table 4.0100).

Table 15 Derived Log-Transformed GSK3901961 Pharmacokinetic Parameters (Pharmacokinetic Population)

Parameter	Treatment	N	n	Geometric Mean	95% CI (Lower, Upper)	SD (logs)	%CV
AUC(0-28d) (Copies/µg gDNA times days)	GSK3901961 1-8 × 10^9	1	1	-	-	-	-
	GSK3901961 0.1-0.8 × 10^9	4	4	374,639.00	(27,495.49, 5,104,631.96)	1.641	371.441
	Total	5	5	537,038.02	(70,631.76, 4,083,288.13)	1.634	366.447

Parameter	Treatment	N	n	Geometric Mean	95% CI (Lower, Upper)	SD (logs)	%CV
AUC(0-tlast) (Copies/µg gDNA times days)	GSK3901961 1-8 × 10^9	1	1	-	-	-	-
	GSK3901961 0.1-0.8 × 10^9	4	4	485,941.21	(37,470.56, 6,301,983.10)	1.610	351.791
	Total	5	5	775,822.56	(89,051.07, 6,759,049.75)	1.743	446.020
Cmax (Copies/µg gDNA)	GSK3901961 1-8 × 10^9	1	1	-	-	-	-
	GSK3901961 0.1-0.8 × 10^9	4	4	29,058.02	(1989.83, 424,343.00)	1.685	401.296
	Total	5	5	38,713.78	(5348.97, 280,195.22)	1.594	341.948

Source: Table 4.0110.

AUC(0-28d)=area under the persistence–time curve from 1st T cell infusion to 28 days; AUC(0-tlast)=area under the persistence–time curve from 1st T cell infusion to last timepoint; CI=confidence interval; Cmax=maximum observed persistence; CV=coefficient of variation; LLOQ=lower limit of quantitation; N=number of participants in the population for the treatment and group; n=number of participants in the population for the treatment and group with data; PCR=polymerase chain reaction; PK=pharmacokinetics; RCL=replication-competent lentivirus; SD=standard deviation.

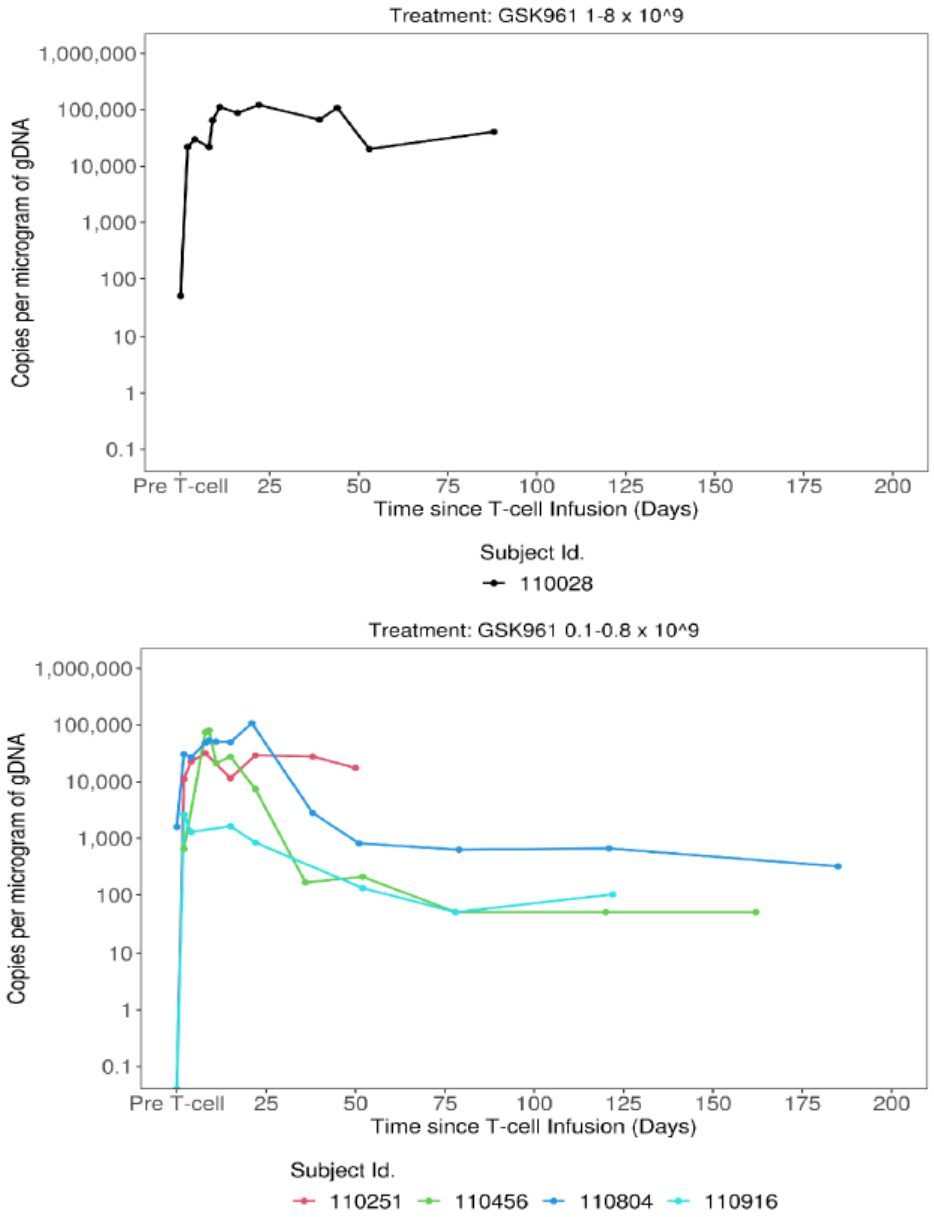
Note: Statistics were not calculated for 'n'=1; refer to Listing 68 for all PK parameters results.

Note: A PCR analysis (duplex assay) was developed to quantify Vector Copy Number of Psi sequence and VSV-G to monitor T cell persistence and RCL, respectively. The Baseline sample from Participant 110804 was tested and showed a positive result in Vector Copy Number (Psi sequence) by PCR analysis. This observation was detectable and above the lower limit of quantification (<50 copies/µg of genomic DNA) and had a measured value of 1595.8 copies/µg. After a thorough investigation, potential root causes of this notable result were unclear and unlikely to be identified (refer to the BAL memo). This baseline value would not affect the calculation of PK parameters (Cmax, Tmax, and AUC as secondary study endpoints) for this individual as noncompartmental analysis for this cell therapy does not include baseline persistence values. Therefore, there is no impact on persistence/PK conclusions of this patient. Furthermore, since this is a duplex assay for monitoring T cell persistence and RCL, inclusion of this data point does not affect this participant's safety conclusions as their post-treatment RCL results were all negative. Taken together, data for both persistence and RCL at baseline of this participant is accepted and its inclusion in our data sets is preserved.

Data as of 10 July 2023.

GSK3901961 PK concentration-time plot by actual dose for the PK Population is presented in Figure 6. AUC and Cmax were comparable between dosed participants from dose levels of (1-8) $\times 10^9$ or (0.1-0.8) $\times 10^9$ transduced T cells. The highest AUC and Cmax values were recorded for Participant 110028 who received GSK3901961 at the dose of 1-8 × 10^9 T cells. Although 1 participant (110028) followed split dosing regimen and the follow-up duration for Participants 110251 and 110028 were shorter, there were no relevant differences in Cmax or AUC when compared with other participants.

Figure 6 GSK3901961 Pharmacokinetic Concentration-Time Plot by Actual Dose (Pharmacokinetic Population)



Source: Figure 4.0120.
LLOQ=lower limit of quantitation; PCR=polymerase chain reaction; PK=pharmacokinetics.
Note: Y-axis is log-transformed. For each participant, baseline is plotted at zero (pre-T-cell) on the x-axis.
Note: Values reported as "<50" were assigned based on the reported interpretation. If interpretive reported result was "Negative", values were set to 0. If interpretive reported result was "Detectable", values were set to 50.
Note: One baseline sample from Participant 110804 showed a positive Vector Copy Number result by PCR analysis above the LLOQ (<50 copies/µg of gDNA). After a thorough investigation, potential root causes of this notable result were unclear and unlikely to be identified. However, baseline samples are not included in the noncompartmental analysis, therefore this sample had no effect on the PK parameters.
Data as of 10 July 2023.

Conclusions:

Seven participants with SS entered Substudy 1 and 5 participants were treated with GSK3901961. Two of the 5 treated participants died of non-treatment related causes during the study (disease under study), 2 participants were transferred to the LTFU study after confirmed disease progression, and 1 participant was withdrawn due to physician decision (because of poor compliance).

Because this substudy was stopped as screening and enrollment on master protocol 209012 was closed, the RP2D for GSK3901961 could not be determined due to an insufficient number of dosed participants.

Safety monitoring for the 5 dosed participants revealed that 2 participants (40%) had a DLT, and 1 participant (20%) had a fatal SAE (not related to T-cell infusion). The AESIs reported for the 5 dosed participants included CRS, hematopoietic cytopenia, ICANS, and GvHD. Four participants (80%) had a treatment-emergent T-cell related CRS (all Grade <3, all nonserious). One participant had a serious, Grade 3, T-cell related treatment-emergent GvHD in skin. One participant had a nonserious, Grade 1, T-cell related, treatment-emergent ICANS. Four participants had at least 1 nonserious, Grade 4, T-cell related hematopoietic cytopenia and 1 participant had a least one nonserious non-T-cell related, Grade 3 hematopoietic cytopenia.

There was a signal of clinical activity (confirmed PR) in 3 participants; the duration of the response was 2.8 and 3.1 months until progression for 2 participants, and 1 participant was censored after 1.2 months due to withdrawal from the study. One of these 3 participants with confirmed PR was treated with GSK3901961 at a dose level of $(1\text{-}8) \times 10^9$ transduced T cells and the other 2 participants were treated with GSK3901961 at a dose level of $(0.1\text{-}0.8) \times 10^9$ transduced T cells. Two of these 3 participants exited the interventional phase of the study and were transferred to the LTFU study 208750 post disease progression. One participant was withdrawn from the study by the investigator due to poor compliance.

Overall, the small population treated in this study is not sufficient to draw a conclusive summary even though there may be an indication of benefit of treatment under the study with a manageable safety profile.

The PK profile of GSK3901961 was similar to the PK profile observed in the prior lete-cel studies. No participant was positive for RCL. No integration site analysis was performed as no participant remained in the study 1-year post-treatment.

Although the SRT determined the benefit/risk of GSK3901961 remains positive, GSK decided to stop the development of GSK3901961 on 28 November 2022 due to portfolio-prioritization.

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