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 2 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 dnTGF-βRII (GSK3845097) in Participants with NY-ESO-1 and/or LAGE-1a Positive Previously Treated Advanced (Metastatic or Unresectable) Synovial Sarcoma and Myxoid/Round Cell Liposarcoma
Phase:	1
Compound Number:	GSK3845097
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Subject: Safety, Recommended Phase 2 Dose, Synovial Sarcoma, Myxoid/Round Cell Liposarcoma, NY-ESO-1, LAGE-1a, dnTGF-βRII, Autologous T cells

Indication Studied: Synovial Sarcoma and Myxoid/Round Cell Liposarcoma

Initiation Date (Substudy 2): 05 May 2021

Completion Date: 24 October 2022

Sponsor Signatory: (and Medical Officer)
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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.

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Synopsis

Name of company: GSK Research & Development Limited

Name of finished product: not available at the time of this report

Name of active substance: GSK3845097

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 2 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 dnTGF-βRII (GSK3845097) in Participants with NY-ESO-1 and/or LAGE-1a Positive Previously Treated Advanced (Metastatic or Unresectable) Synovial Sarcoma and Myxoid/Round Cell Liposarcoma

Investigators: Multicenter study

Study centers: Substudy 2 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, 1 site in Germany, and 1 site in Sweden enrolled participants in Substudy 2.

Publication: None at the time of this report

Study Period: 05 May 2021 to 24 October 2022

Phase of Development: 1

Objectives and endpoints:

Below are the objectives and endpoints for protocol 209012 Substudy 2. The substudy was stopped for further treatment based on the protocol stopping and pausing provisions. Also, further screening and enrolment on master protocol 209012 was closed before further investigation on GSK3845097 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 2 SAP Section 1.1.

Objectives	Endpoints
Primary	
To assess the safety, tolerability and determine RP2D of GSK3845097 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, advanced (metastatic or unresectable) SS and MRCLS	• Frequency of DLTs • Frequency and severity of AEs, SAEs, and AESI; as defined in the core protocol

Objectives	Endpoints
Secondary - Efficacy	
To investigate the antitumor activity of GSK3845097 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, advanced (metastatic or unresectable) SS and MRCLS	• ORR (investigator assessed according to RECIST v1.1) • DoR
Secondary - Pharmacokinetics	
To characterize in vivo cellular PK profile (levels, expansion, persistence) of GSK3845097 over time	• Cmax • Tmax • AUC(0-t), as data permit
Exploratory	
To further evaluate safety and tolerability of GSK3845097 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, advanced (metastatic or unresectable) SS and MRCLS	• Changes in laboratory parameters; vital signs; ECOG PS; ECG • RCL • Instances of insertional oncogenesis
To further evaluate the antitumor activity of GSK3845097 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, advanced (metastatic or unresectable) SS and MRCLS	• OS

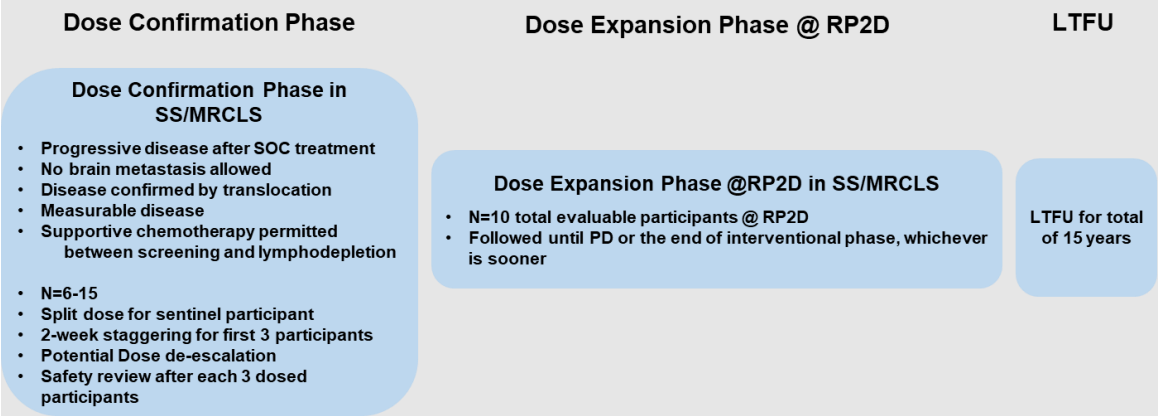
Methodology:

GSK3845097 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.

GSK3845097 is modified by multicomponent engineering to enable co-expression, alongside the NY-ESO-1^{c259} TCR, of the dnTGF-βRII receptor to decrease the potential inhibition of T-cell function by the TME.

This is an FTIH, single cohort, non-randomized, open-label substudy (part of a Master Protocol) to investigate GSK3845097 in previously treated participants with advanced (metastatic or unresectable) SS and MRCLS, 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 on 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 2 Design



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

Dose Confirmation Phase

Dose confirmation phase commenced first. Once all participants needed for dose confirmation (n=6-15) had been assigned, participants were to be assigned to dose expansion phase.

The primary objective of the dose confirmation phase was to identify the RP2D of GSK3845097. 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.

Dose Selection Committee review was to occur after the DLT period of 28 days after the last T-cell infusion in every 3 participants 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 2 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

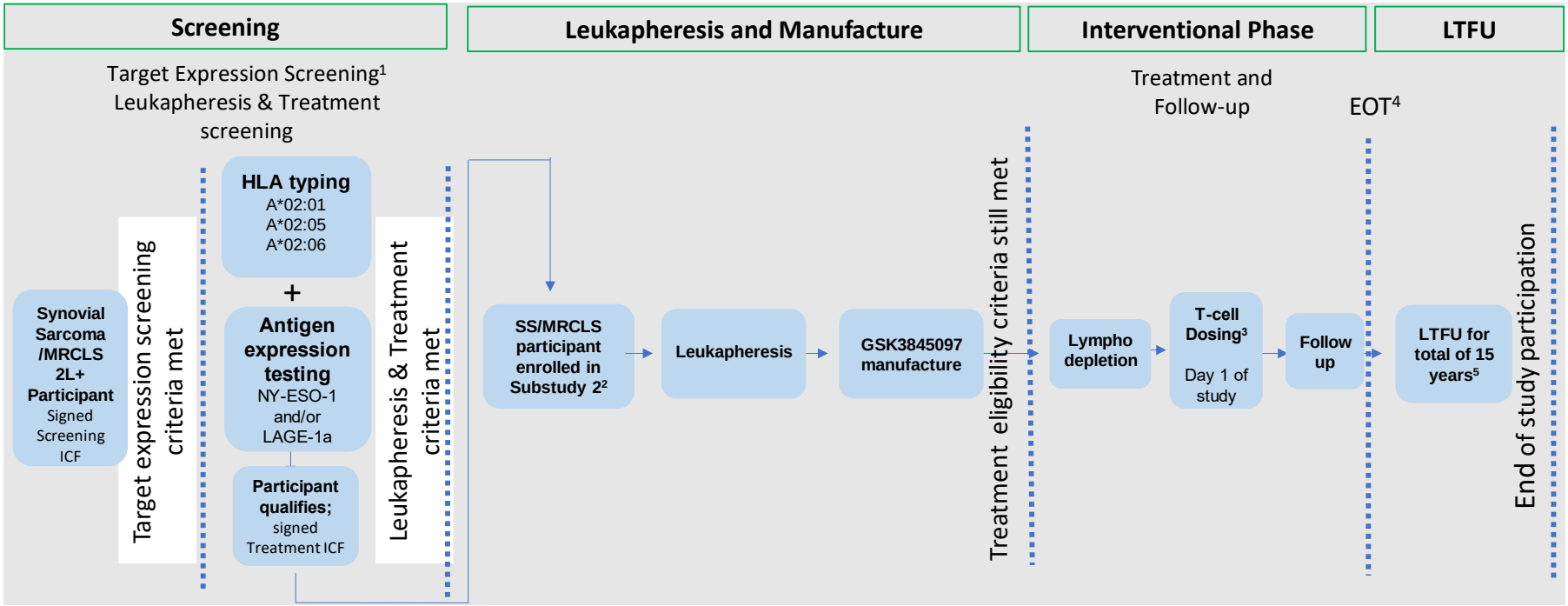
The dose expansion phase was to begin after determination of the RP2D. The cohort was to enroll additional participants to ensure 10 participants become evaluable at the RP2D. Evaluable participants were those who received T-cell infusion and completed at least 2 post-baseline disease assessments since 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 2 Protocol Section 5.1.3.

Figure 2 Participant Journey



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; 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 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 received the full dose as a single, i.e., one-time, infusion.
4. See Substudy 2 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: 5 participants (4 participants were dosed with GSK3845097 in the dose confirmation phase and 1 participant underwent leukapheresis but did not receive lymphodepletion chemotherapy or T-cell infusion)
- Analyzed: 4 participants in the dose confirmation phase

Note: Substudy 2 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 GSK3845097.

Key inclusion criteria:

Refer to Substudy 2 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.
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 11).
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.

<u>Leukapheresis eligibility screening:</u>

7. 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.

8. 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).
9. Participant had measurable disease according to RECIST v1.1.
10. Participant had evidence of radiographic or clinical disease progression.
11. Participant 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).
12. Participant had completed at least one standard of care treatment including anthracycline-containing regimen unless intolerant to or ineligible to receive the therapy.

Treatment eligibility screening:

20. 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 2 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.
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:

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 target lesions had been irradiated within 3 months prior to lymphodepletion. A lesion with unequivocal progression 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 GSK3845097. Participants underwent leukapheresis to obtain starting material for the manufacture of GSK3845097. 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 Amendment 3). G-CSF was started on Day -3. The intended dose of GSK3845097 was 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 GSK3845097 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 4 dosed participants are listed in the table below:

Participant ID	Batch number	Manufacturer
110801	G0016	Miltenyi Biotec
110014	G0041	Miltenyi Biotec
110762	G0063	Miltenyi Biotec
110454	G0076	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 GSK3845097 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 GSK3845097 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 took place after each consecutive group of 3 participants had been dosed in the substudy and followed for the DLT period of 28 days.

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:

Only a subset of the previously planned analyses was performed as the study was closed for further screening and enrolment; and stopped for further treatment based on the protocol stopping and pausing provisions. The following are the key changes to previously planned analyses: 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 2 Protocol Section 10.5 were not conducted; only the Final Analysis was undertaken. 3) Most exploratory endpoints were not analyzed. 4) As appropriate, listings were produced in lieu of tables and figures given the low sample size. 5) No subgroup analyses were undertaken because of recruiting fewer participants than the planned target sample size.

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 2 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. 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.	• Study Population • Safety (where appropriate) • 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 = intention-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

The following analyses were planned and produced after the finalization of the SAP dated 10 May 2023 and post-database lock.

TLF	Title	Reason for change or addition
Table	Summary of Dose-Limiting Toxicities as per Protocol Definition (T-cell Related) by Actual Dose	Post-database lock, an error was found in the reporting of the primary endpoint for the frequency of DLTs. Participant 110014 had an AE of 'Lymphocyte Count Decreased' that was erroneously recorded as DLT in the database. This was confirmed as a transcription error by site. The AE onset was before any study treatment was administered and resolved 1 day following the start of lymphodepletion and prior to T-cell infusion. The AE relationship to study treatment was recorded 'No'. Per the SAP, reported DLTs were to be those collected on the eCRF. Hence an ad hoc analysis was added post-SAP approval to report the number of DLTs as per the protocol definition, which in brief considers a DLT to be: • At least possibly related to transduced T cells; AND • They occur within the DLT-assessment period of 28 days after the initial dosing of T cells. For participants receiving T cells as split dose, DLT assessment period would begin at the start of the first infusion and continue for 28 days after completion of the last infusion. The number of DLTs per the protocol definition also aligned with the DLTs that were agreed by the dose selection committee members.
Table	Summary of Dose-Limiting Toxicities as per Protocol Definition (T-cell Related) by Actual Dose and Planned Dose	

Summary:

Participant disposition:

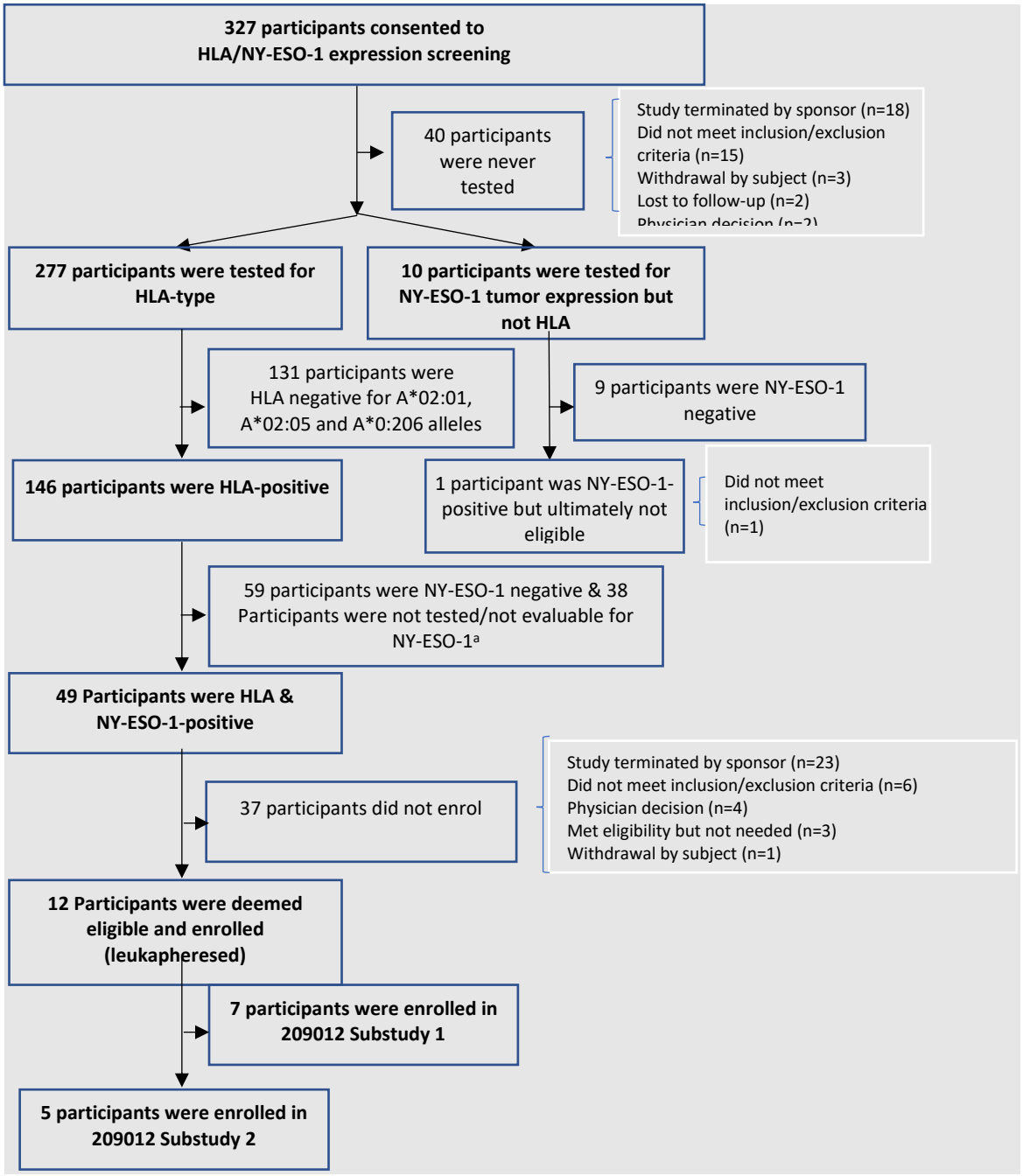
Participants in Substudy 2 were enrolled from 1 center in Germany (N=2), 1 center in Sweden (N=1), and 2 centers in the US (N=2) (Source: Table 1.0180).

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, 5 participants entered Substudy 2 (Figure 4). Of these 5 participants, 4 participants were treated with GSK3845097 and therefore included in the mITT population; 1 participant underwent leukapheresis but did not initiate treatment because the study was closed based on protocol stopping provisions. Two of the 4 participants treated with GSK3845097 died during the study and the other 2 participants were transferred to the LTFU study 208750 after confirmed disease progression.

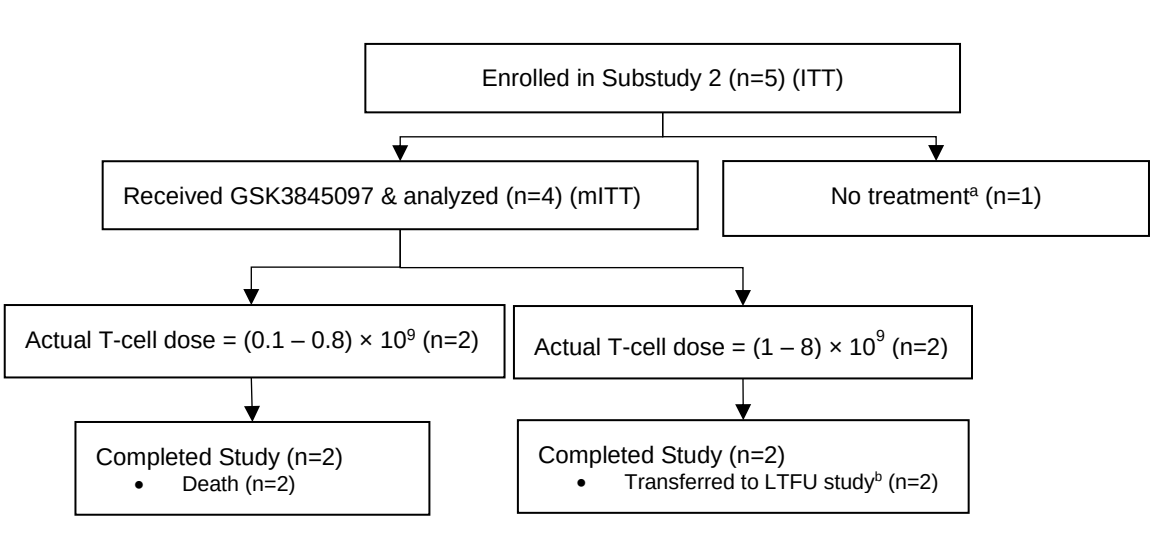
Figure 3 Participant Disposition up to Enrolment



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 12 May 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 underwent leukapheresis but did not initiate treatment because the study was closed based on protocol stopping provisions.
b Two participants had disease progression.
Data as of 12 May 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 3 participants ("study treatment not administered per protocol", "incomplete assessment", "missed assessment", and "informed consent/assent not signed and/or dated by the participant or legal representative", each in 1 participant).

Table 1 Important Protocol Deviations by Actual Dose

Participant ID	Protocol Deviation	Impact on Participant Eligibility	Impact on Primary Endpoint
110454[a]	Study treatment not administered per protocol: the site did a renal adjustment of 20 mg/m^2 of fludarabine, instead of 30 mg/m^2.	None	None
110014	Incomplete assessment: vital sign assessment not completed	None	None
	Missed assessment: central lab assessments were not performed at Weeks 3 and 4.	None	None
110762	Informed consent/assent not signed and/or dated by the participant or legal representative: the site did	None	None

Participant ID	Protocol Deviation	Impact on Participant Eligibility	Impact on Primary Endpoint
	not offer the optional genetic ICF to the participant so the participant could not sign the optional genetic ICF.		

Source: Listing 3.
ICF=informed consent form.
Data as of 12 May 2023.

a. Study treatment refers to lymphodepleting chemotherapy component. While fludarabine was administered at 20 mg/m^2 instead of 30 mg/m^2, T-cell dose was administered as intended.

One participant had a non-important protocol deviation of missed assessments 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 in Table 2. The age of the 4 participants was 53, 67, 27, and 31 years. All 4 participants were male and Not Hispanic or Latino. Three participants (75%) were White and 1 participant (25%) was Black or African American.

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

	Dose Confirmation Phase		
	GSK3845097 (1-8) × 10^9 (N=2)	GSK3845097 (0.1-0.8) × 10^9 (N=2)	Total (N=4)
Sex, n (%)			
Female	0	0	0
Male	2 (100%)	2 (100%)	4 (100%)
Age (Years)[a]			
Mean (SD)	29.0 (2.83)	60.0 (9.90)	44.5 (18.86)
Median (Min, Max)	29.0 (27, 31)	60.0 (53, 67)	42.0 (27, 67)
Ethnicity, n (%)			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	2 (100%)	2 (100%)	4 (100%)
Race Detail, n (%)			
Black or African American	1 (50%)	0	1 (25%)
White - White/Caucasian/European Heritage	1 (50%)	2 (100%)	3 (75%)
BMI (kg/m^2) at Leukapheresis Eligibility Screening			
Mean (SD)	22.018 (2.1560)	31.021 (1.0205)	26.520 (5.3769)
BSA (m^2) at Leukapheresis Eligibility Screening[b]			

	Dose Confirmation Phase		
	GSK3845097 (1-8) × 10^9 (N=2)	GSK3845097 (0.1-0.8) × 10^9 (N=2)	Total (N=4)
Mean (SD)	1.858 (0.0192)	2.249 (0.1549)	2.054 (0.2433)

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 GSK3845097 infusion date.
Data as of 12 May 2023.

A summary of disease characteristics at screening by actual dose for the mITT Population is provided in Table 3. Three participants had SS and 1 participant had MRCLS. All 4 participants were positive for at least 1 of 3 of the eligible HLA alleles (A*02:01, A*02:05, A*02:06). Three participants were HLA-A*02:01 positive (heterozygous) and 1 participant was HLA-A*02:01 - A*02:01 positive (homozygous). Three participants had 100% tumor cells positive and 1 participant had 60% tumor cells positive for NY-ESO-1 (2+/3+ per immunohistochemistry). All 4 participants had metastatic Stage IV disease at screening. The median time since diagnosis of metastatic disease to leukapheresis screening was 11.19 (range: 9.1, 14.8) months. One participant (25%) received prior radiotherapy before leukapheresis. Two participants (50%) received radiotherapy between leukapheresis and lymphodepletion. All 4 participants received prior systemic therapy in the advanced (metastatic/unresectable) setting before the start of lymphodepletion (3 participants received 1 prior regimen and 1 participant received 2 prior regimens). Best response to the most recent prior systemic therapy in the metastatic/advanced setting was PD in 1 participant and NE in 1 participant; best response was not recorded for the other 2 participants. One participant received bridging therapy between leukapheresis and lymphodepletion.

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

	Dose Confirmation Phase		
	GSK3845097 (1-8) × 10^9 (N=2)	GSK3845097 (0.1-0.8) × 10^9 (N=2)	Total (N=4)
Primary Tumor Type, n (%)			
Myxoid/Round Cell Liposarcoma	0	1 (50%)	1 (25%)
Synovial Sarcoma	2 (100%)	1 (50%)	3 (75%)
HLA Status, n (%)			
Positive	2 (100%)	2 (100%)	4 (100%)
One HLA Allele positive			
A*02:01 - other	1 (50%)	2 (100%)	3 (75%)
Two HLA Alleles positive			

	Dose Confirmation Phase		
	GSK3845097 (1-8) × 10^9 (N=2)	**GSK3845097 (0.1-0.8) × 10^9 (N=2)**	**Total (N=4)**
A*02:01 - A*02:01	1 (50%)	0	1 (25%)
NY-ESO-1 Status, n (%)			
Positive	2 (100%)	2 (100%)	4 (100%)
NY-ESO-1 Expression Score (2+/3+) (%)			
Min.	100	60	60
1st Quartile	100.0	60.0	80.0
Median	100.0	80.0	100.0
3rd Quartile	100.0	100.0	100.0
Max.	100	100	100
Extent of Disease at Screening, n (%)			
Metastatic	2 (100%)	2 (100%)	4 (100%)
Disease Stage at Screening, n (%)			
IV	2 (100%)	2 (100%)	4 (100%)
TNM Staging: Primary Tumor, n (%)			
n	1	2	3
TX	0	1 (50%)	1 (33%)
T3	1 (100%)	1 (50%)	2 (67%)
TNM Staging: Regional Lymph Nodes, n (%)			
n	1	2	3
NX	0	1 (50%)	1 (33%)
N0	1 (100%)	1 (50%)	2 (67%)
TNM Staging: Distant Metastasis, n (%)			
n	1	2	3
M1	1 (100%)	2 (100%)	3 (100%)
Grade at Screening, n (%)			
n	0	1	1
2	0	1 (100%)	1 (100%)
Status of Measurable Disease at Screening, n (%)			
Yes	2 (100%)	2 (100%)	4 (100%)
Non-target Lesions, n (%)			
Yes	1 (50%)	2 (100%)	3 (75%)
No	1 (50%)	0	1 (25%)

	Dose Confirmation Phase		
	GSK3845097 (1-8) × 10^9 (N=2)	**GSK3845097 (0.1-0.8) × 10^9 (N=2)**	**Total (N=4)**
NY-ESO-1 Tumor Biopsy Site, n (%)			
Primary	1 (50%)	2 (100%)	3 (75%)
Metastatic	1 (50%)	0	1 (25%)
Anatomical Location of Biopsy Site, n (%)			
Bone	1 (50%)	0	1 (25%)
Foot	0	1 (50%)	1 (25%)
Leg	0	1 (50%)	1 (25%)
Other	1 (50%)	0	1 (25%)
Number of Prior Radiotherapy Regimens Before Start of Leukapheresis, n (%)			
0	2 (100%)	1 (50%)	3 (75%)
>1	0	1 (50%)	1 (25%)
Radiotherapy Between Leukapheresis and Lymphodepletion, n (%)			
Yes	0	2 (100%)	2 (50%)
No	2 (100%)	0	2 (50%)
Number of Prior Systemic Therapy Regimens in the Metastatic/Advanced Setting Before Start of Lymphodepletion, n (%)			
1	2 (100%)	1 (50%)	3 (75%)
2	0	1 (50%)	1 (25%)
Best Response to Most Recent Prior Systemic Therapy in the Metastatic/Advanced Setting, n (%)			
n	1	1	2
Complete Response	0	0	0
Partial Response	0	0	0
Stable Disease	0	0	0
Progressive Disease	1 (100%)	0	1 (50%)
Not Evaluable	0	1 (100%)	1 (50%)
Neo-Adjuvant Therapy, n (%)			
Yes	1 (50%)	0	1 (25%)
No	1 (50%)	2 (100%)	3 (75%)
Adjuvant Therapy, n (%)			
No	2 (100%)	2 (100%)	4 (100%)

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 records with partial dates, "Time since" parameters were not calculated.
Note: For Participants 110014, 110762, and 110801, "Grade at Screening" was unknown.
Note: For Participant 110014, all "TNM Staging" parameters were unknown.
Note: For Participants 110454 and 110762, the best response to the most recent prior systemic therapy in the metastatic/advanced setting was not collected on the CRF when the intent was intermediate standard of care.
Data as of 12 May 2023.

Exposure:

Table 6 shows planned versus actual doses of GSK3845097. Of the 4 treated participants, the first 3 participants were to receive DL1 planned dose of (1 to 8) × 10^9 transduced cells. Per protocol, as 2 (66%) of the first 3 participants treated at DL1 experienced DLTs, the DSC decided to de-escalate the dose for the next set of participants (impacting the fourth participant) to the DL-1 planned dose of (0.1 to 0.8) × 10^9 transduced cells.

A summary of exposure to study treatment by planned dose for the mITT Population is presented in Table 4. All 4 participants received the standard lymphodepletion regimen according to the protocol (including dose reduction provisions):

- Participant 110801 was less than 60 years old and met all criteria to receive the standard lymphodepletion chemotherapy regimen per protocol (Amendment 1) and received:
  - fludarabine 30 mg/m^2 × 4 days and cyclophosphamide 1800 mg/m^2 × 2 days

- Participants 110014 and 110762 were less than 60 years old and met all criteria to receive the updated standard lymphodepletion chemotherapy regimen per protocol (under Protocol Clarification Letter of Protocol Amendment 1 and under Protocol Amendment 3, respectively) and received:
  - fludarabine 30 mg/m^2 × 4 days and cyclophosphamide 900 mg/m^2 × 3 days

- Participant 110454 was more than 60 years old and had intermittent creatinine clearance between 50 and 80 mL/min. Following Protocol Amendment 3 dose reduction guidelines, the participant received:
  - fludarabine 20 mg/m^2 × 3 days and cyclophosphamide 600 mg/m^2 × 3 days.

The median cumulative dose of cyclophosphamide was 2700 mg/m^2 (range: 1800, 3600), and the median cumulative dose of fludarabine was 120 mg/m^2 (range: 60, 120).

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

	Dose Confirmation Phase		
Dose	GSK3845097 DL1 (N=3)	GSK3845097 DL-1 (N=1)	Total (N=4)
Cyclophosphamide Cumulative Dose (mg/m^2)			
Median (Min, Max)	2700.0 (2700, 3600)	1800.0 (1800, 1800)	2700.0 (1800, 3600)
Fludarabine Cumulative Dose (mg/m^2)			
Median (Min, Max)	120.0 (120, 120)	60.0 (60, 60)	120.0 (60, 120)
Actual Transduced Cell Dose Received			
<0.1 (× 10^9 cells)	0	0	0
≥0.1 to ≤0.8 (× 10^9 cells)	1 (33%)	1 (100%)	2 (50%)
>0.8 to <1 (× 10^9 cells)	0	0	0
≥1 to ≤8 (× 10^9 cells)	2 (67%)	0	2 (50%)
>8 (× 10^9 cells)	0	0	0
Median (Min, Max)	1.884 (0.80, 4.90)	0.800 (0.80, 0.80)	1.342 (0.80, 4.90)

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 12 May 2023.

The first participant (110801) to receive GSK3845097 was a sentinel participant and planned to receive the target GSK3845097 dose at the DL1 dose level to be infused in 2 aliquots (at Day 1 [~30%] and Day 8 [~70%]). However, the participant experienced toxicities that precluded them from receiving the second aliquot. The actual dose received was 0.8×10^9 transduced cells.

Because of the DLT reported for the first sentinel participant, the second participant (110014) was also dosed as a sentinel and received the planned dose of 1.884×10^9 transduced cells in 2 aliquots: 0.746×10^9 transduced cells on Day 1 and 1.138×10^9 transduced cells on Day 8 (Table 5). Because no DLTs were reported for the second sentinel participant, all subsequent participants treated with GSK3845097 received the full planned transduced T cell dose as a single infusion.

Ultimately, 2 participants received GSK3845097 at the dose of (1 to 8) × 10^9 cells and 2 participants at the dose of (0.1 to 0.8) × 10^9 cells. Overall, the median number of transduced T cells was 1.342×10^9 cells (range: 0.80×10^9, 4.90×10^9).

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
110801	0.8	0	0.8
110014[a]	0.746	1.138	1.884
110762	4.9	NA	4.9
110454	0.8	NA	0.8

Source: Listing 15.
mITT=Modified Intent-to-Treat; NA=not applicable.
Note: Participants 110801 and 110014 were sentinel participants to receive split doses.
a This participant received a non-conforming batch.
Data as of 12 May 2023.

Concomitant medications

A summary of concomitant medications by actual dose for the mITT Population is presented in Table 1.0270. All 4 participants received concomitant medications during the study. Overall, the most common concomitant medications (received by >50% of participants) were dexamethasone, fluconazole, G-CSF, magnesium sulfate, ondansetron, paracetamol, and tocilizumab (each reported in 3 participants [75%]).

Safety results:

Dose-limiting toxicities:

DLTs were reported in all 4 participants; however, 1 participant (110014) had a non-serious Grade 3 AE of lymphocyte count decreased prior to treatment (Day -17) indicated as unrelated to study treatment, which was erroneously recorded as a DLT due to a transcription error at site. This AE does not fulfil the DLT definition given in the protocol (Source: Listing 19).

Three out of 4 (75%) participants had reported T-cell related events that met protocol defined DLT criteria and were endorsed by the DSC (Source: Table 3.0101 and Table 6).

The following DLTs were reported: 1 participant (110801) had ALT increased (onset 8 days, duration 72 days, nonserious, Grade 3, related to T-cell infusion, resolved); 1 participant (110762) had ICANS (onset 3 days, duration 5 days, serious, Grade 4, related to T cell infusion, resolved); and 1 participant (110454) had GVHD in skin (onset 18 days, serious, Grade 3, related to T-cell infusion, not resolved), GVHD in gastrointestinal tract (onset 19 days, serious, Grade 3, related to T-cell infusion, not resolved), hemophagocytic lymphohistiocytosis (onset 37 days, serious, Grade 4, related to T-cell infusion, not resolved), and systemic inflammatory response syndrome (onset 39 days, duration 1 day, serious, Grade 5, related to T-cell infusion, fatal) (Source: Listing 19).

Table 6 Summary of Dose-Limiting Toxicities Per Protocol Definition (T-cell Related) by Actual Dose and Planned Dose (DLT Evaluable Population)

GSK3845097		Planned Dose		
	Actual Dose	DL1 (N=3)	DL-1 (N=1)	Total (N=4)
n [No. of Participants with DLT]	(1-8) × 10^9 (N=2)	2[a] [1]	0 [0]	2 [1]
	(0.1-0.8) × 10^9 (N=2)	1[b] [1]	1 [1]	2 [2]

Source: Table 3.0106.
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. One participant (110014) had a non-serious Grade 3 AE of lymphocyte count decreased prior to treatment (Day -17) indicated as unrelated to study treatment, which was erroneously recorded as a DLT due to a transcription error at site. This AE resolved prior to the start of lymphodepletion, does not fulfil the DLT definition given in the protocol and therefore is not counted here.
b. The sentinel participant 110801 in DL1 (planned dose level 1-8 × 10^9) did not receive the second dose of T cells on Day 8; participant 110801 only received total of 0.8 × 10^9 transduced T cells and is consequently summarized under actual dose level (0.1-0.8) × 10^9.
Note: DLTs assigned where "Is this event a DLT" was "Yes" and based on timing and relatedness per the protocol definition.
Data as of 12 May 2023.

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

The pre-lymphodepletion phase includes AEs that started before the first day of lymphodepletion chemotherapy. During the pre-lymphodepletion phase (ITT Population), 4 of 5 enrolled participants (80%) had at least 1 AE (Source: Table 3.0120). None of these AEs were considered related to study procedure. Two participants had SAEs and Grade 3 AEs, which were considered not related to study procedure (Source: Listing 20).

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 4 treated participants (75%) had at least 1 AE (Source: Table 3.0130). Two participants had Grade ≥3 AEs; 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 4 participants had TEAEs. Overall, the most common TEAEs occurring in >50% of participants were ALT increased, anemia/RBC count decreased, AST increased, CRS, and thrombocytopenia/platelet count decreased (100% each) and neutropenia/neutrophil count decreased (75%).

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

	Dose Confirmation Phase		
Preferred Term, n (%)	**GSK3845097 (1-8) × 10^9 (N=2)**	**GSK3845097 (0.1-0.8) × 10^9 (N=2)**	**Total (N=4)**
Any TEAE	**2 (100%)**	**2 (100%)**	**4 (100%)**
Alanine aminotransferase increased	2 (100%)	2 (100%)	4 (100%)
Anaemia/Red blood cell count decreased	2 (100%)	2 (100%)	4 (100%)
Aspartate aminotransferase increased	2 (100%)	2 (100%)	4 (100%)
Cytokine release syndrome	2 (100%)	2 (100%)	4 (100%)
Thrombocytopenia/Platelet count decreased	2 (100%)	2 (100%)	4 (100%)
Neutropenia/Neutrophil count decreased	1 (50%)	2 (100%)	3 (75%)
Febrile neutropenia	1 (50%)	1 (50%)	2 (50%)
Hyponatraemia	2 (100%)	0	2 (50%)
Hypophosphataemia	2 (100%)	0	2 (50%)
Immune effector cell-associated neurotoxicity syndrome	1 (50%)	1 (50%)	2 (50%)
Leukopenia/White blood cell decreased	1 (50%)	1 (50%)	2 (50%)
Pancytopenia	1 (50%)	1 (50%)	2 (50%)
Pyrexia	1 (50%)	1 (50%)	2 (50%)
Unspecified GVHD - gut (liver and intestine)	1 (50%)	1 (50%)	2 (50%)
Unspecified GVHD - skin	1 (50%)	1 (50%)	2 (50%)
Anxiety	1 (50%)	0	1 (25%)
Aplastic anaemia	1 (50%)	0	1 (25%)
Blood alkaline phosphatase increased	1 (50%)	0	1 (25%)
Blood creatinine increased	0	1 (50%)	1 (25%)
Blood glucose increased	0	1 (50%)	1 (25%)
Blood lactate dehydrogenase increased	1 (50%)	0	1 (25%)
Blood sodium increased	0	1 (50%)	1 (25%)
Blood urea increased	0	1 (50%)	1 (25%)
Chest pain	0	1 (50%)	1 (25%)
Cough	1 (50%)	0	1 (25%)
COVID-19 pneumonia	1 (50%)	0	1 (25%)
C-reactive protein increased	0	1 (50%)	1 (25%)
Decreased appetite	1 (50%)	0	1 (25%)
Diarrhoea	1 (50%)	0	1 (25%)
Dyspnoea	0	1 (50%)	1 (25%)

	Dose Confirmation Phase		
Preferred Term, n (%)	**GSK3845097 (1-8) × 10^9 (N=2)**	**GSK3845097 (0.1-0.8) × 10^9 (N=2)**	**Total (N=4)**
Dysuria	1 (50%)	0	1 (25%)
Fatigue	1 (50%)	0	1 (25%)
Haematocrit decreased	0	1 (50%)	1 (25%)
Haemoglobin decreased	0	1 (50%)	1 (25%)
Haemophagocytic lymphohistiocytosis	0	1 (50%)	1 (25%)
Herpes zoster	1 (50%)	0	1 (25%)
Hyperbilirubinaemia	1 (50%)	0	1 (25%)
Hypoaesthesia	1 (50%)	0	1 (25%)
Hypokalaemia	0	1 (50%)	1 (25%)
Interleukin level increased	0	1 (50%)	1 (25%)
International normalised ratio increased	1 (50%)	0	1 (25%)
Lymphoedema	1 (50%)	0	1 (25%)
Mucosal inflammation	1 (50%)	0	1 (25%)
Muscular weakness	0	1 (50%)	1 (25%)
Pericardial effusion	0	1 (50%)	1 (25%)
Pneumonia	1 (50%)	0	1 (25%)
Procalcitonin increased	0	1 (50%)	1 (25%)
Protein total decreased	0	1 (50%)	1 (25%)
Pulmonary embolism	0	1 (50%)	1 (25%)
Respiratory failure	0	1 (50%)	1 (25%)
Rash/Rash maculo-papular	1 (50%)	0	1 (25%)
Staphylococcal bacteraemia	1 (50%)	0	1 (25%)
Stomatitis	0	1 (50%)	1 (25%)
Supraventricular tachycardia	0	1 (50%)	1 (25%)
Syncope	0	1 (50%)	1 (25%)
Systemic inflammatory response syndrome	0	1 (50%)	1 (25%)
Tachycardia	1 (50%)	0	1 (25%)
Vomiting	0	1 (50%)	1 (25%)

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 12 May 2023.

Grade ≥3 treatment-emergent adverse events:

All 4 participants experienced at least 1 Grade ≥3 TEAE (Table 8). The most common Grade ≥3 TEAEs, occurring in >50% of participants, were anemia/RBC count decreased and thrombocytopenia/platelet count decreased (100% each) and neutropenia/neutrophil count decreased (75%).

The following Grade 4 TEAEs were reported: thrombocytopenia/platelet count decreased (100%); neutropenia/neutrophil count decreased (75%); leukopenia/WBC decreased and pancytopenia (50% each); and anemia/RBC count decreased, ICANS, aplastic anemia, and hemophagocytic lymphohistiocytosis (25% each) (Source: Table 3.0150).

The following Grade 5 TEAEs were reported: respiratory failure and systemic inflammatory response syndrome (25% each) (Source: Table 3.0150).

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

	Dose Confirmation Phase		
Preferred Term, n (%)	**GSK3845097 (1-8) × 10^9 (N=2)**	**GSK3845097 (0.1-0.8) × 10^9 (N=2)**	**Total (N=4)**
Any Grade ≥3 TEAE	**2 (100%)**	**2 (100%)**	**4 (100%)**
Anaemia/Red blood cell count decreased	2 (100%)	2 (100%)	4 (100%)
Thrombocytopenia/Platelet count decreased	2 (100%)	2 (100%)	4 (100%)
Neutropenia/Neutrophil count decreased	1 (50%)	2 (100%)	3 (75%)
Alanine aminotransferase increased	1 (50%)	1 (50%)	2 (50%)
Febrile neutropenia	1 (50%)	1 (50%)	2 (50%)
Leukopenia/White blood cell decreased	1 (50%)	1 (50%)	2 (50%)
Pancytopenia	1 (50%)	1 (50%)	2 (50%)
Aspartate aminotransferase increased	0	1 (50%)	1 (25%)
Immune effector cell-associated neurotoxicity syndrome	1 (50%)	0	1 (25%)
Unspecified GVHD - gut (liver and intestine)	0	1 (50%)	1 (25%)
Unspecified GVHD - skin	0	1 (50%)	1 (25%)
Aplastic anaemia	1 (50%)	0	1 (25%)
Blood creatinine increased	0	1 (50%)	1 (25%)
Blood glucose increased	0	1 (50%)	1 (25%)
Blood urea increased	0	1 (50%)	1 (25%)
C-reactive protein increased	0	1 (50%)	1 (25%)
COVID-19 pneumonia	1 (50%)	0	1 (25%)
Dyspnoea	0	1 (50%)	1 (25%)
Haematocrit decreased	0	1 (50%)	1 (25%)

	Dose Confirmation Phase		
Preferred Term, n (%)	**GSK3845097 (1-8) × 10^9 (N=2)**	**GSK3845097 (0.1-0.8) × 10^9 (N=2)**	**Total (N=4)**
Haemoglobin decreased	0	1 (50%)	1 (25%)
Haemophagocytic lymphohistiocytosis	0	1 (50%)	1 (25%)
Herpes zoster	1 (50%)	0	1 (25%)
Procalcitonin increased	0	1 (50%)	1 (25%)
Protein total decreased	0	1 (50%)	1 (25%)
Pulmonary embolism	0	1 (50%)	1 (25%)
Respiratory failure	0	1 (50%)	1 (25%)
Syncope	0	1 (50%)	1 (25%)
Systemic inflammatory response syndrome	0	1 (50%)	1 (25%)

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 12 May 2023.

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

All 4 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 ALT increased and CRS (100% each) and anemia/RBC count decreased, AST increased, neutropenia/neutrophil count decreased, and thrombocytopenia/platelet count decreased (75% each).

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

	Dose Confirmation Phase		
Preferred Term, n (%)	**GSK3845097 (1-8) × 10^9 (N=2)**	**GSK3845097 (0.1-0.8) × 10^9 (N=2)**	**Total (N=4)**
Any T-cell-Related TEAE	**2 (100%)**	**2 (100%)**	**4 (100%)**
Alanine aminotransferase increased	2 (100%)	2 (100%)	4 (100%)
Cytokine release syndrome	2 (100%)	2 (100%)	4 (100%)
Anaemia/Red blood cell count decreased	1 (50%)	2 (100%)	3 (75%)
Aspartate aminotransferase increased	1 (50%)	2 (100%)	3 (75%)
Neutropenia/Neutrophil count decreased	1 (50%)	2 (100%)	3 (75%)
Thrombocytopenia/Platelet count decreased	1 (50%)	2 (100%)	3 (75%)
Febrile neutropenia	1 (50%)	1 (50%)	2 (50%)

	Dose Confirmation Phase		
Preferred Term, n (%)	**GSK3845097 (1-8) × 10^9 (N=2)**	**GSK3845097 (0.1-0.8) × 10^9 (N=2)**	**Total (N=4)**
Immune effector cell-associated neurotoxicity syndrome	1 (50%)	1 (50%)	2 (50%)
Leukopenia/White blood cell decreased	1 (50%)	1 (50%)	2 (50%)
Pancytopenia	1 (50%)	1 (50%)	2 (50%)
Unspecified GVHD - gut (liver and intestine)	1 (50%)	1 (50%)	2 (50%)
Unspecified GVHD - skin	1 (50%)	1 (50%)	2 (50%)
Anxiety	1 (50%)	0	1 (25%)
Aplastic anaemia	1 (50%)	0	1 (25%)
Blood alkaline phosphatase increased	1 (50%)	0	1 (25%)
Blood creatinine increased	0	1 (50%)	1 (25%)
Blood urea increased	0	1 (50%)	1 (25%)
C-reactive protein increased	0	1 (50%)	1 (25%)
COVID-19 pneumonia	1 (50%)	0	1 (25%)
Cough	1 (50%)	0	1 (25%)
Dyspnoea	0	1 (50%)	1 (25%)
Fatigue	1 (50%)	0	1 (25%)
Haematocrit decreased	0	1 (50%)	1 (25%)
Haemoglobin decreased	0	1 (50%)	1 (25%)
Haemophagocytic lymphohistiocytosis	0	1 (50%)	1 (25%)
Hyperbilirubinaemia	1 (50%)	0	1 (25%)
Interleukin level increased	0	1 (50%)	1 (25%)
Mucosal inflammation	1 (50%)	0	1 (25%)
Muscular weakness	0	1 (50%)	1 (25%)
Pericardial effusion	0	1 (50%)	1 (25%)
Procalcitonin increased	0	1 (50%)	1 (25%)
Protein total decreased	0	1 (50%)	1 (25%)
Pyrexia	0	1 (50%)	1 (25%)
Rash/Rash maculo-papular	1 (50%)	0	1 (25%)
Stomatitis	0	1 (50%)	1 (25%)
Supraventricular tachycardia	0	1 (50%)	1 (25%)
Systemic inflammatory response syndrome	0	1 (50%)	1 (25%)

Source: Table 3.0160.

AE=adverse event; 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: 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 12 May 2023.

T-cell infusion-related Grade ≥3 TEAEs occurred in 3 participants (75%). The following T-cell infusion-related Grade ≥3 TEAEs were reported: anemia/RBC count decreased and thrombocytopenia/platelet count decreased (75% each); ALT increased, neutropenia/neutrophil count decreased, febrile neutropenia, leukopenia/WBC decreased, and pancytopenia (50% each); and AST increased, ICANS, unspecified GVHD - gut (liver and intestine), unspecified GVHD – skin, aplastic anemia, blood creatinine increased, Blood urea increased, CRP increased, COVID-19 pneumonia, dyspnea, hematocrit decreased, hemoglobin decreased, hemophagocytic lymphohistiocytosis, procalcitonin increased, protein total decreased, and systemic inflammatory response syndrome (25% each). The event of systemic inflammatory response syndrome led to death (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 GSK3845097 T-cell infusion in the prior section. Three of 4 participants (75%) had at least 1 TEAE related to lymphodepletion (Source: Table 3.0170). The most common lymphodepletion-related TEAEs, occurring in >50% of participants, were anemia/RBC count decreased and thrombocytopenia/platelet count decreased (75% each).

Lymphodepletion-related Grade ≥3 TEAEs occurred in 3 participants (75%). The following lymphodepletion-related Grade ≥3 TEAEs were reported: anemia/RBC decreased and thrombocytopenia/platelet count decreased (75% each); neutropenia/neutrophil count decreased (50%); and leukopenia/WBC decreased and pancytopenia (25% each). No lymphodepletion-related deaths were reported (Source: Table 3.0170).

Deaths

Of the 4 participants, 2 participants (50%) died and 2 participants (50%) 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 hemorrhage in the right lung secondary to pulmonary embolism and disease under study in Participant 110801. The participant had developed a Grade 5 SAE of respiratory failure. The time from T-cell infusion to death was 94 days. The SAE of respiratory failure had an onset of 93 days after T-cell infusion. This event was considered not related to GSK3845097 (Source: Listing 39).

The primary cause of death was systemic inflammatory response syndrome (Grade 5 SAE) in Participant 110454. The time from T-cell infusion to death was 39 days. This event was considered related to GSK3845097 (Source: Listing 39).

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

	Dose Confirmation Phase		
	GSK3845097 (1-8) × 10^9 (N=2)	GSK3845097 (0.1-0.8) × 10^9 (N=2)	Total (N=4)
Subject Status, n (%)			
Dead	0	2 (100%)	2 (50%)
Alive at last contact, follow-up ended	2 (100%)	0	2 (50%)
Primary Cause of Death, n (%)			
Haemorrhage	0	1 (50%)	1 (25%)
Other Non-Cardiovascular Cause[a]	0	1 (50%)	1 (25%)
Time since T-cell infusion to Death, n (%)			
>30 days	0	2 (100%)	2 (50%)

Source: Table 3.0330.
AE=adverse event; mITT=Modified Intent-to-Treat.
a Participant 110454: primary cause of death was "systemic inflammatory response syndrome".
Data as of 12 May 2023.

Serious adverse events:

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

Treatment-emergent SAEs occurred in 3 participants (75%) (Table 11); Participant 110014 did not experience any treatment-emergent SAE. Treatment-emergent SAEs of febrile neutropenia were reported in 2 participants; all other SAEs occurred in 1 participant.

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

	Dose Confirmation Phase		
Preferred Term, n (%)	GSK3845097 (1-8) × 10^9 (N=2)	GSK3845097 (0.1-0.8) × 10^9 (N=2)	Total (N=4)
Any Serious TEAE	**1 (50%)**	**2 (100%)**	**3 (75%)**
Febrile neutropenia	1 (50%)	1 (50%)	2 (50%)
Alanine aminotransferase increased	1 (50%)	0	1 (25%)
Aplastic anaemia	1 (50%)	0	1 (25%)
COVID-19 pneumonia	1 (50%)	0	1 (25%)
Haemophagocytic lymphohistiocytosis	0	1 (50%)	1 (25%)
Herpes zoster	1 (50%)	0	1 (25%)
Hyperbilirubinaemia	1 (50%)	0	1 (25%)

	Dose Confirmation Phase		
Preferred Term, n (%)	**GSK3845097 (1-8) × 10^9 (N=2)**	**GSK3845097 (0.1-0.8) × 10^9 (N=2)**	**Total (N=4)**
Immune effector cell-associated neurotoxicity syndrome	1 (50%)	0	1 (25%)
International normalised ratio increased	1 (50%)	0	1 (25%)
Pancytopenia	1 (50%)	0	1 (25%)
Pulmonary embolism	0	1 (50%)	1 (25%)
Pyrexia	1 (50%)	0	1 (25%)
Respiratory failure	0	1 (50%)	1 (25%)
Systemic inflammatory response syndrome	0	1 (50%)	1 (25%)
Thrombocytopenia/Platelet count decreased	0	1 (50%)	1 (25%)
Unspecified GVHD - gut (liver and intestine)	0	1 (50%)	1 (25%)
Unspecified GVHD - skin	0	1 (50%)	1 (25%)

Source: Table 3.0220.
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 12 May 2023.

All treatment-emergent SAEs were Grade ≥3, except INR increased and hyperbilirubinemia (Grade 2) and pyrexia (Grade 1). Two SAEs were fatal: respiratory failure and systemic inflammatory response syndrome (Source: Table 3.0220).

The following treatment-emergent SAEs were considered related to T-cell infusion: febrile neutropenia (50%), ALT increased, aplastic anemia, COVID-19 pneumonia, hemophagocytic lymphohistiocytosis, hyperbilirubinemia, ICANS, pancytopenia, systemic inflammatory response syndrome, thrombocytopenia/platelet count decreased, unspecified GVHD - gut (liver and intestine), and unspecified GVHD – skin (25% each) (Source: Table 3.0230).

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 (100% of patients), hematopoietic cytopenias (100%), GVHD (50%), and ICANS (50%) (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 (%)	**GSK3845097 (1-8) × 10^9 (N=2)**	**GSK3845097 (0.1-0.8) × 10^9 (N=2)**	**Total (N=4)**
Any event	2 (100%)	2 (100%)	4 (100%)
Cytokine release syndrome			
Any Event	2 (100%)	2 (100%)	4 (100%)
Cytokine Release Syndrome (CRS)	2 (100%)	2 (100%)	4 (100%)
Haematopoietic cytopenias (including pancytopenia and aplastic anaemia)			
Any Event	2 (100%)	2 (100%)	4 (100%)
Anaemia/Red blood cell count decreased	2 (100%)	2 (100%)	4 (100%)
Thrombocytopenia/Platelet count decreased	2 (100%)	2 (100%)	4 (100%)
Neutropenia/Neutrophil count decreased	1 (50%)	2 (100%)	3 (75%)
Febrile neutropenia	1 (50%)	1 (50%)	2 (50%)
Leukopenia/White blood cell decreased	1 (50%)	1 (50%)	2 (50%)
Pancytopenia	1 (50%)	1 (50%)	2 (50%)
Aplastic anaemia	1 (50%)	0	1 (25%)
Haematocrit decreased	0	1 (50%)	1 (25%)
Haemoglobin decreased	0	1 (50%)	1 (25%)
Graft versus host disease (GVHD)			
Any Event	1 (50%)	1 (50%)	2 (50%)
Unspecified GVHD - Gut (Liver and Intestine)	1 (50%)	1 (50%)	2 (50%)
Unspecified GVHD - Skin	1 (50%)	1 (50%)	2 (50%)
Immune Effector-Cell Associated Neurotoxicity Syndrome (ICANS)			
Any Event	1 (50%)	1 (50%)	2 (50%)
Immune effector cell-associated neurotoxicity syndrome (ICANS)	1 (50%)	1 (50%)	2 (50%)

Source: Table 3.0250.
AESI=adverse event of special interest; 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 12 May 2023.

All 4 treated participants had CRS (total 4 events) after GSK3845097 infusion. All events were considered related to T-cell infusion. No participant had an SAE of CRS.

Three participants had Grade 2 CRS and 1 participant had Grade 1 CRS. CRS resolved in all 4 participants. Three participants required treatment with tocilizumab; 1 of these 3 participants also received steroids (dexamethasone) (Source: Listing 26). The median time to onset of CRS was 1.5 days (range: 1, 2), and the median duration of CRS was 4.5 days (range: 3, 10) (Source: Table 3.0260).

All 4 treated participants had hematopoietic cytopenias after GSK3845097 infusion. The following hematopoietic cytopenias were reported: anemia/RBC count decreased and thrombocytopenia/platelet count decreased (100% each); neutropenia/neutrophil count decreased (75%);, leukopenia/WBC decreased, and pancytopenia (50% each); and aplastic anemia, hematocrit decreased, and hemoglobin decreased (25% each) and febrile neutropenia (50%) (Table 12). All these events were of maximum Grade 3 or 4 (Source: Table 3.0250). All these events resolved except pancytopenia in Participant 110454 and thrombocytopenia in Participant 110454, which did not resolve. The following events were considered related to T cells: pancytopenia and thrombocytopenia (Participant 110454); anemia and neutrophil count decreased (Participant 110801); and pancytopenia, aplastic anemia, and febrile neutropenia (Participant 110762). The following events were considered serious: thrombocytopenia (Participant 110454) and pancytopenia, aplastic anemia, and febrile neutropenia (Participant 110762). Participant 110801 who experienced platelet count decreased, neutrophil count decreased, and anemia required antimicrobial prophylaxis/therapy and high-dose corticosteroids. The time to onset of hematopoietic cytopenias ranged from 2 to 36 days and the duration of hematopoietic cytopenias ranged from 2 to 135 days (Source: Listing 20, Listing 28).

All 4 (100%) participants had a lymphodepletion-emergent or treatment-emergent pancytopenia:

- Participant 110454 had a nonserious pancytopenia that started on Day 18 with a maximum severity of Grade 4 that did not resolve (G-CSF reinitiated, immunosuppressant therapy not given);
- Participant 110762 had a serious pancytopenia that started on Day 11 with a maximum severity of Grade 4 that resolved after 27 days (G-CSF reinitiated, immunosuppressant therapy not given). This participant also had a serious aplastic anemia that started on Day 22 with a maximum severity of Grade 4 that resolved after 16 days and a serious febrile neutropenia that started on Day 25 with a maximum severity of Grade 3 that resolved after 3 days (G-CSF reinitiated, immunosuppressant therapy not given for both events);
- Participant 110014 had a nonserious pancytopenia with started on Day 1 with a maximum severity of Grade 4 that resolved after 23 days (G-CSF or immunosuppressant therapy not given);
- Participant 110801 had a nonserious pancytopenia that started on Day 2 with intermittent neutropenia/neutrophil count decreased of maximum severity of Grade 4 and thrombocytopenia/platelet count decreased of maximum severity of Grade 4 that resolved respectively after 35 and 65 days and intermittent anemia/RBC count decreased of maximum severity of Grade 3 from Day 4 until Day 76 (G-CSF

reinitiated, antimicrobial prophylaxis/therapy and high-dose corticosteroids were given).

Three participants (75%) had persistent cytopenia (neutropenia, thrombocytopenia, anemia) beyond 28 days post T-cell infusion (Week 5) based on the laboratory results. Persistent cytopenias resolved after 1 to 2 months in 2 of these 3 participants and did not resolve in 1 participant as this participant died due to systemic inflammatory response syndrome (see the narrative for Participant 110454 for more details) (Source: Listing 51).

Two participants (50%) had GVHD after GSK3845097 infusion. Participant 110454 had serious, Grade 3, T-cell related GVHD in skin and gastrointestinal tract with an onset of 18 days post-T-cell infusion for skin and 19 days post-T-cell infusion for gastrointestinal tract; the participant received both topical and systemic corticosteroids and ruxolitinib and the events had not resolved at time of death. Participant 110762 had non-serious, Grade 2, T-cell related GVHD in liver and skin with an onset of 20 days post-T-cell infusion; the patient received topical corticosteroids and the events resolved with sequelae 40 days after onset (Source: Listing 29).

Two participants (50%) had ICANS after GSK3845097 infusion. Participant 110454 had non-serious, Grade 1, T-cell related ICANS with an onset of 3 days post-T-cell infusion; the event resolved 2 days after onset. Participant 110762 had serious, Grade 4, T-cell related ICANS with an onset of 3 days post-T-cell infusion; the event was treated with IV dexamethasone from Days 3 to 7 and the event resolved 5 days after onset. Of note, Participant 110762 received levetiracetam from Days -1 to 37 (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: AST increased (2 participants), ALT increased (2 participants), low albumin (1 participant), high magnesium (1 participant), and high sodium (1 participant). Worst-case post-baseline of Grade 3 or 4 was observed for the following hematology parameters: low hemoglobin (4 participants), low leukocytes (4 participants), low lymphocytes (4 participants), low neutrophils (4 participants), and low platelets (4 participants).

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.

Three participants had liver events: 1 participant (110014) met liver monitoring criteria level 1; 1 participant (110762) met liver monitoring criteria level 2, and 1 participant (110801) met liver stopping criteria. None of these 3 participants met Hy's law criteria. Narratives of these participants are provided in the CASE NARRATIVES section. The liver monitoring level 2 profile of Participant 110762 is provided in Listing 36. The liver stopping event profile of Participant 110801 is provided in Listing 37. Liver

monitoring/stopping event reporting details for Participants 110801, 110014, and 110762 are provided in Listing 38.

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 4 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 2 (restricted in work activity but ambulatory and capable of self-care) in 2 participants (Listing 40).

Electrocardiogram

No clinically significant ECG findings were noted for any participant during the study (Source: Listing 42).

Worst-case post-baseline of QTcB interval ≥450 msec was reported for 2 participants: Participant 110454 had QTcB interval of 456 msec at Day 1 and Participant 110762 had QTcB interval of 455 msec at Day 1. No participant had an increase in QTcB interval >501 msec. QRS was low (<70 msec) for Participant 110454 on Day 1 (Source: Listing 41).

Replication competent lentivirus:

Of 3 participants tested for RCL post-baseline, no participant tested positive for RCL (Source: Table 3.0350).

Insertional oncogenesis:

No integration site analysis was performed as no participant remained in the study 1-year post-treatment.

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 25% (95% CI: 0.6%, 80.6%), with 1 participant achieving confirmed PR. Stable disease was noted in 3 participants (75%).

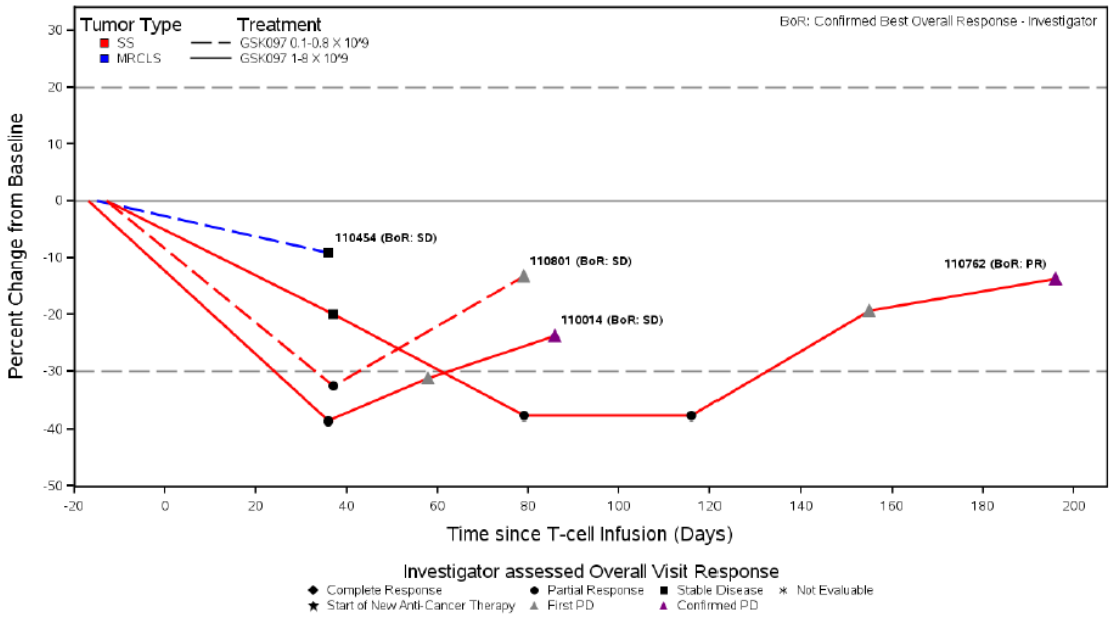
Table 13 Summary of Investigator-Assessed Best Response with Confirmation (RECIST 1.1 Criteria) by Actual Dose (mITT Population)

	Dose Confirmation		
	GSK3845097 $(1\text{-}8) \times 10^9$ (N=2)	GSK3845097 $(0.1\text{-}0.8) \times 10^9$ (N=2)	Total (N=4)
Best Response, n (%)			
Complete Response	0	0	0
Partial Response	1 (50%)	0	1 (25%)
Stable Disease	1 (50%)	2 (100%)	3 (75%)
Progressive Disease	0	0	0
Not Evaluable	0	0	0
Response Rate			
[CR + PR], n (%)	1 (50.0%)	0 (0.0%)	1 (25.0%)
95% Confidence Interval[a]	(1.3%, 98.7%)	(0.0%, 84.2%)	(0.6%, 80.6%)

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 12 May 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 Week 6 for 2 participants and at Weeks 12 and 18 for 1 participant). The initial PR at Week 6 for Participants 110801 and 110014 was followed by PD at the next assessment, hence neither met the criteria of confirmed PR. For Participant 110762, the initial confirmed response of PR occurred at 2.6 months (Day 79) after T-cell infusion with a duration of 2.5 months until confirmed progression. A summary of investigator-assessed DoR per RECIST 1.1 by actual dose is presented in Table 2.0110.

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; MRCLS=myxoid/round cell liposarcoma; PD=progressive disease; PR=partial response; RECIST=response evaluation criteria in solid tumors; SD=stable disease; SS=synovial sarcoma.
Note: Participant 110454 had only 1 imaging evaluation as the participant died on Study Day 39.
Note: For Participant 110014, the first PD was due to a non-target lesion progression.
Data as of 12 May 2023.

OS data are not mature. Two participants have died and 2 participants were alive as per the last contact date in the study. The 2 deaths occurred at 1.3 and 3.1 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 984,320.98 (82.086) copies per µg gDNA times days; the geometric mean AUC(0-tlast) (%CV) was 1,183,090.87 (96.939) copies per µg gDNA times days, and the geometric mean Cmax (%CV) was 75,882.06 (96.071) copies per µg gDNA (Table 14). The median Tmax was 10.5 days (range: 7, 21) (Source: Table 4.0100).

Table 14 Derived Log-Transformed GSK3845097 Pharmacokinetic Parameters (Pharmacokinetic Population)

Parameter	Treatment	N	n	Geom. Mean	95% CI (Lower, Upper)	SD (logs)	%CV
AUC(0-28) (Copies/ug gDNA times days)	GSK3845097 1-8 × 10^9	2	2	730937.83	(40.61, 13157696626.43)	1.091	151.154
	GSK3845097 0.1-0.8 × 10^9	2	2	1325540.63	(915979.55, 1918228.36)	0.041	4.115
	Total	4	4	984320.98	(314165.86, 3084000.91)	0.718	82.086
AUC(0-tlast) (Copies/ug gDNA times days)	GSK3845097 1-8 × 10^9	2	2	943274.74	(6.02, 147723636698.64)	1.331	221.024
	GSK3845097 0.1-0.8 × 10^9	2	2	1483877.35	(605905.16, 3634053.88)	0.100	9.994
	Total	4	4	1183090.87	(323980.00, 4320340.80)	0.814	96.939
Cmax (Copies/ug gDNA)	GSK3845097 1-8 × 10^9	2	2	54606.56	(4.71, 632476668.59)	1.041	139.944
	GSK3845097 0.1-0.8 × 10^9	2	2	105446.79	(265.02, 41955927.13)	0.666	74.752
	Total	4	4	75882.06	(20957.22, 274754.34)	0.809	96.071

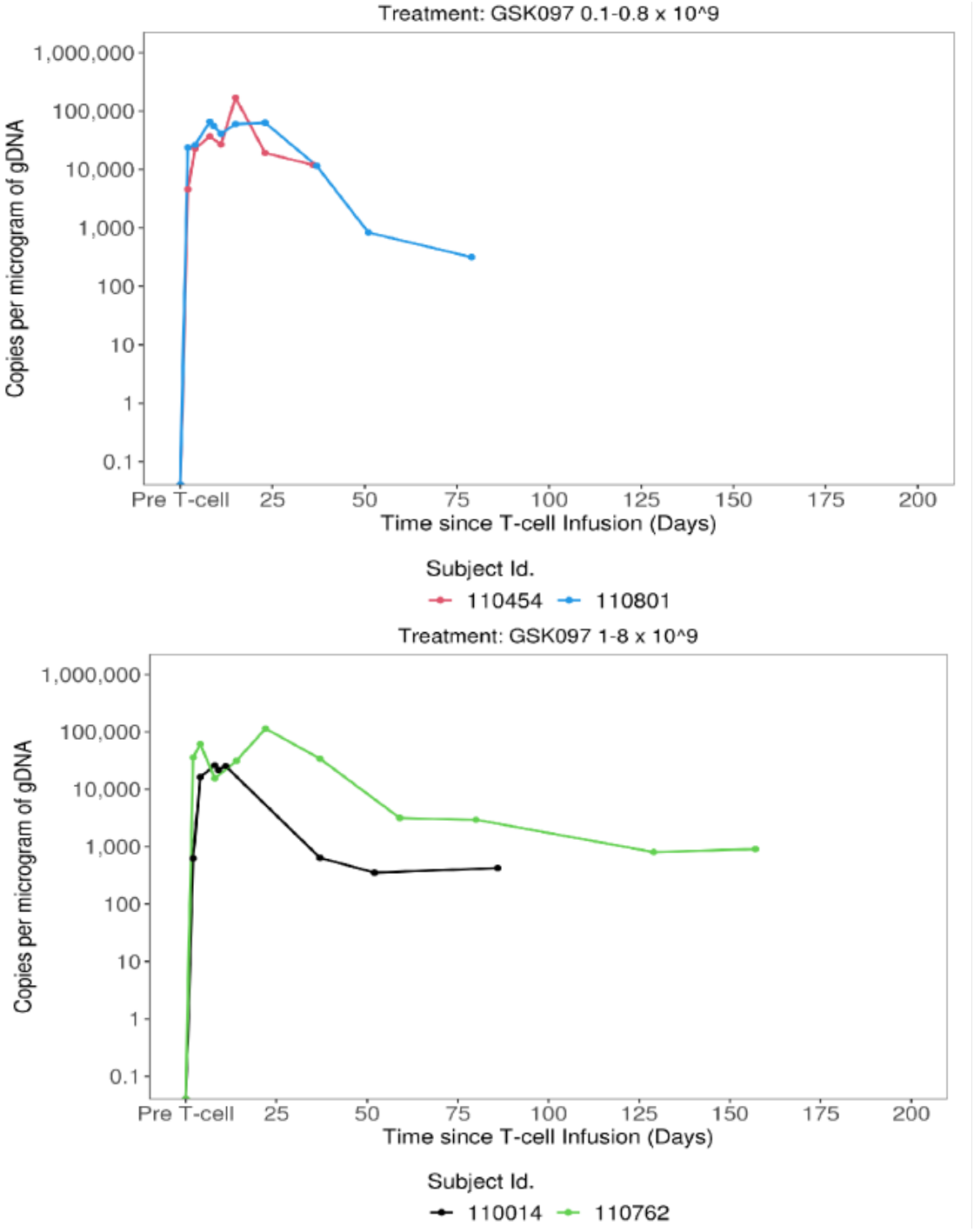
Source: Table 4.0110.

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; 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; SD=standard deviation.

Data as of 12 May 2023.

GSK3845097 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. Although 1 participant (110014) followed split dosing regimen and the duration for Participant 110454 (fatal SAE related to T-cell infusion) was shorter, there were no relevant differences in Cmax or AUC when compared to other participants.

Figure 6 GSK3845097 Pharmacokinetic Concentration-Time Plot by Actual Dose (Pharmacokinetic Population)



Source: Figure 4.0120.
Note: Y-axis is log-transformed.
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: For each participant, baseline is plotted at zero (pre-T-cell) on the x-axis
Data as of 12 May 2023.

Conclusions:

Five participants entered Substudy 2 and 4 participants were treated with GSK3845097. Two of the 4 participants died during the study and the other 2 participants were transferred to the LTFU study after confirmed disease progression.

Because this substudy was stopped for further treatment based on protocol stopping provisions and because screening and enrollment on master protocol 209012 was closed, the RP2D for GSK3845097 could not be determined due to an insufficient number of dosed participants.

Safety monitoring for the 4 dosed participants revealed that 3 participants (75%) had a DLT, and 2 participants (50%) had a fatal SAE, of which 1 event was T-cell related (systemic inflammatory response syndrome). The AESIs reported on the 4 dosed participants included CRS, hematopoietic cytopenia (including pancytopenia and aplastic anemia), ICANS, and GvHD. All 4 participants had a treatment-emergent T-cell related CRS (3 Grade 1, 1 Grade 2, all nonserious) and a maximum Grade 4 treatment-emergent pancytopenia, 1 of these participants had a serious Grade 4 aplastic anemia.
Two participants had a treatment-emergent GvHD (1 Grade 3 serious; 1 Grade 2 nonserious) involving 2 different organs for each participant. Two participants had a treatment-emergent ICANS (1 Grade 4 serious, 1 Grade 1 nonserious). All participants had treatment-emergent ALT increased (2 Grade 2, 2 Grade 3) and AST increased (2 Grade 1, 1 Grade 2, 1 Grade 3).

There was a signal of clinical activity (confirmed PR) in a participant with locally advanced/metastatic SS; the duration of the response was 2.5 months. The participant with confirmed PR was treated with GSK3845097 at a dose level of (1-8) $\times 10^9$ transduced T cells; this patient completed the interventional phase in Substudy 2 and has been transferred to the LTFU study. Notably, 3 participants (75%) had a decrease in the target lesion diameters of ≥30% (2 of these participants had an initial PR that was not confirmed due to disease progression at subsequent assessment).

The PK profile of GSK3845097 was similar to the PK profile observed in the prior lete-cel studies, including the participant with the T-cell related fatal SAE. No participant was positive for RCL. No integration site analysis was performed as no participant remained in the study 1-year post-treatment.

Based on the fatality in a participant who received GSK3845097 and the decision to place Substudy 2 on voluntary clinical hold, the benefit/risk profile for GSK3845097 is considered unfavourable until further evaluation.

Document Date: 18 August 2023