Statistical Analysis Plan Amendment 3

Study ID: 209012 Core

Official Title of Study: 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

NCTID: NCT04526509

Date of Document: 10 May 2023

Analysis Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

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
Study Number:	209012
Compound Number:	GSK3901961, GSK3845097, GSK4427296
Abbreviated Title:	Master Protocol of Autologous Enhanced T-Cell in Advanced Tumors

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s)

Registry	**ID**
IND Number	19751
EudraCT Number	2019-004446-14
Clinicaltrials.gov	NCT04526509

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Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP v1	18 May 2022	209012/ Amendment 3 (20-Dec-2021)	Not Applicable	Original version
SAP Amendment 1	14 Sep 2022	209012/ Amendment 4 (27-May-2022)	In addition to minor formatting changes, the following updates have been made: • Revision of the DLT analysis set definition to remove text relating to AEs leading to withdrawal since these are not permitted per protocol (SAP Section 3). • Updates on which analyses are to be presented by planned/actual dose (Table 1). • Correction to text relating to selection of RP2D (Section 4.1.4). • Added reverse Kaplan-Meier method for Duration of Response follow-up summary (Section 4.3.1). • Pneumonia was removed as an AESI to align with Protocol Amendment 4 (Section 4.5.1.7). • Additional information on the presentation of screen failure summaries (Section 6.1.1) as well as HLA status, NY-ESO-1 expression scores and LAGE-1a (Section 6.1.2). • Additional clarification added to the definition of anti-cancer therapy phases, and on-study follow-up phase now from lymphodepletion and not T-cell infusion to match lete-cell program (Section 6.1.5). Anti-cancer therapy phases table removed from Section 6.2 – will not be derived programmatically. • Revision of the prior and concomitant medication definitions to incorporate blood cell products and align the definition with the lete-cell program (Section 6.2.3.2).	Minor updates and corrections

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			• Combined terms and focused list updated from MedDRA Version 24.1 to 25.0 (Section 6.3) • Change to the definition of 'U' in the mTPI-2 table to indicate that dose will be de-escalated if possible, to match the corresponding update in 209012 Protocol Amendment 4 (Section 6.4).	
SAP Amendment 2	03 Apr 2023	209012/ Amendment 4 (27-May-2022)	In addition to minor typographical and formatting changes, the following updates have been made: Reduction in scope of original planned analyses as a result of study termination including: 1. Removal of analyses related to RP2D or based on the Evaluable Analysis Set (throughout document) 2. Clarification to the Duration of Response endpoint, if the 5 responder condition is not met then the DOR will be summarised using descriptive statistics instead of Kaplan-Meier estimates (Section 4.3.1). 3. Removed reverse Kaplan-Meier method for Duration of Response follow-up summary (Section 4.3.1) 4. Clarification that exploratory efficacy endpoints will not be analysed, although Overall Survival will be listed for the ITT analysis set (Section 4.4) 5. Reduction in scope of Safety analyses due to early study termination as well as additional safety analyses for disclosure and annual safety reporting requirements (Section 4.5). The majority of safety analyses (excluding adverse events, exposure, deaths and[redacted] are	Reduction in scope of original planned analyses as a result of study termination

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			to be listed instead of summarised 6. PCI categories for ECGs and Vital signs will not be derived (Section 4.5.3) 7. Subgroup analyses removed (Section 4.6.1) 8. Clarification that the protocol-planned Interim and Primary analyses will not be conducted (Section 4.7) 9. Documented changes to protocol defined analyses as a result of early termination of substudies (Section 4.8) 10. Reduction in scope of study population analyses (Section 6.1) 11. Summaries of anti-cancer therapies removed, only listings will be provided (Section 6.1.5) • Updated wording of DLT analysis set to DLT Evaluable analysis set (Section 3) • Added clarification that DLT rates (proportions) to be presented on actual treatment only and DLT frequency counts to be presented by planned and actual treatment. (Table 1 & Section 4.5.1.1) • Added disease characteristics at screening summary based on the screened population for HLA/NYESO results (Section 6.1.2). • Updated derivation of treatment emergent flag for adverse events to clearly classify AEs that occur on the same day as T-cell infusion (Section 6.2.3.4) • Combined terms and focused list updated from MedDRA Version 25.0 to 25.1 (Section 6.3)	

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP Amendment 3	10 May 2023	209012/ Amendment 4 (27-May-2022)	Formatting change to re-correct the heading titles and numbers	Administrative amendment, no changes were made to the content of the SAP

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to describe the planned analyses applicable to all substudies for Study 209012, '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'. Details of the planned analyses are provided.

The SAP is structured similarly to the protocol, with a core document which covers the common endpoints and analyses for all substudies and substudy-specific SAPs which cover the specific analyses for the corresponding substudy only. The combination of the analyses specified in this main SAP and substudy-specific SAPs will be included in the substudy specific clinical study report. However, it should be noted that due to early termination of all substudies, the purpose of this SAP is to describe the planned analyses for synoptic clinical study reports (CSRs). As a result, only a subset of the previously planned analyses that were to support full CSRs are now required. Additionally, some variables that were previously planned to be presented in summaries and/or figures will instead be presented in listing format since early termination has resulted in fewer participants than planned. Analyses required for synoptic CSRs are clearly indicated in this document. In general, exploratory endpoints will not be analysed, with exceptions clearly indicated. Additionally, since the substudies were terminated prior to the establishment of the recommended phase 2 dose (RP2D), no related analyses will be provided (e.g., analyses based on the Evaluable analysis set). The Interim and Primary analyses described in Protocol Amendment 4 Section will not be conducted, only the Final Analysis will be undertaken.

Note that additional details regarding data handling conventions and the specification of data displays are provided in the core and substudy-specific Output and Programming Specification (OPS) documents.

1.1. Objectives, Estimands, and Endpoints

The full list of objectives and endpoints below is the list given in the substudy-specific protocols (Amendment 4). It should be noted that due to termination of all substudies, only a subset of endpoints will be analysed, as detailed in Section 4. Discrepancies between the objectives and

endpoints stated here and those in the substudy specific SAP will not require amendment, instead those stated in the substudy-specific SAP will apply and take priority.

Additional pharmacokinetic (PK) and CCI exploratory analyses not described in this SAP will be detailed in separate PK and CCI reporting and analysis plans.

Due to the phase of the current study, estimand framework will not be used for this study.

Objectives	Endpoints
Primary	
To assess the safety, tolerability and determine recommended phase 2 dose (RP2D) of NY-ESO-1 and LAGE-1a specific T-cells, alone or in combination with other agents, in HLA-A*02 positive participants with NY-ESO-1 and/or LAGE-1a positive advanced tumors	• Frequency of dose-limiting toxicities (DLTs) • Frequency and severity of adverse events (AEs), serious adverse events (SAEs) and AEs of special interest (AESI; as defined in the core protocol)
Secondary - Efficacy	
To investigate the efficacy of NY-ESO-1 and LAGE-1a specific T-cells, alone or in combination with other agents, in HLA-A*02 positive participants with NY-ESO-1 and/or LAGE-1a positive advanced tumors	• Overall Response Rate (ORR) (investigator assessed according to RECIST v1.1) • Duration of Response (DoR)
Secondary – Pharmacokinetics (PK)	
To characterize in vivo cellular PK profile (levels, expansion, persistence) of NY-ESO-1 and LAGE-1a specific T-cells, alone or in combination with other agents, over time	• Maximum transgene expansion (Cmax) • Time to Cmax (Tmax) • Area under the time curve from zero to time t AUC(0-t), as data permit
Exploratory	

CCI

[redacted]

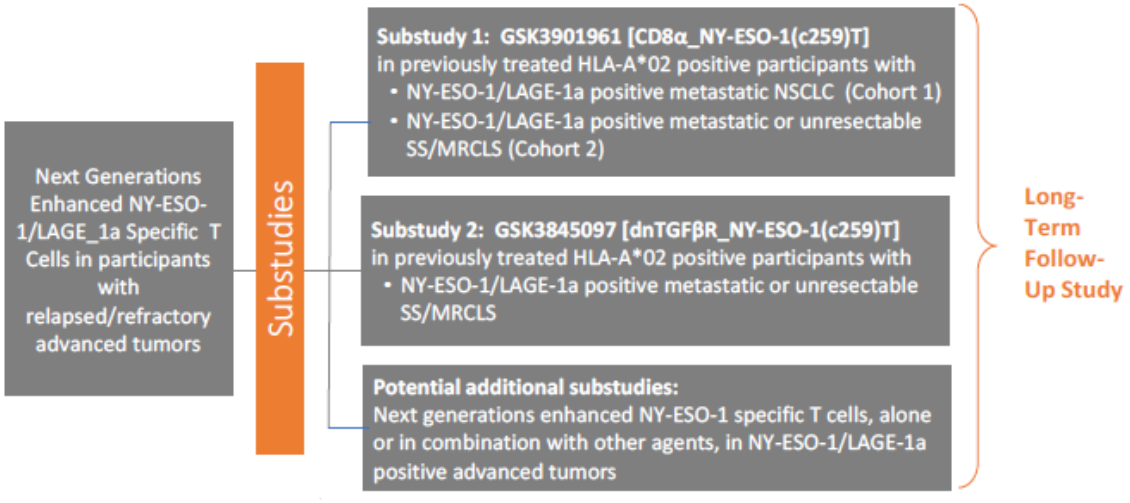
AE = adverse event/s; AESI = adverse event/s of special interest; AUC (0-t) = area under the time curve from zero to time t; Cmax = maximum concentration; CRS = Cytokine Release Syndrome; DLTs = dose-limiting toxicities; DNA = deoxyribonucleic acid ; DOR = duration of response; ECG = Electrocardiogram; HLA = human leukocyte antigen; ; NY-ESO-1 = New York esophageal antigen-1; ORR = overall response rate; ; RECIST = Response Evaluation Criteria In Solid Tumors; RNA = ribonucleic acid; RP2D = recommended phase 2 dose; SAE = serious adverse event; Tmax = Time to Cmax; TCR = T-cell receptor; ; † = PK and exploratory endpoints/analyses not covered in this SAP will be detailed in separate PK and reporting and analysis plans.

1.2. Study Design

1.2.1. Overall Study Design

This is a master protocol with multiple substudies. Refer to the substudy-specific SAP for the details of the design of the specific substudy.

Figure 1 Overall Study Design



Note: Figure 1 is for illustration, for additional substudies please refer to Core Protocol Section 12.12.

Each substudy will consist of two phases: Dose Confirmation Phase and Dose Expansion Phase.

Dose Confirmation Phase

In this phase, each next-generation NY-ESO-1 and LAGE-1a T-cell product will be evaluated to assess/confirm the RP2D to be used in further clinical investigations.

The RP2D will be determined as described in Section 5.1.1 of each substudy protocol.

Modified Toxicity Probability Interval–2 (mTPI-2) design is used for the dose confirmation phase. Details of the design are provided in Section 6.4.

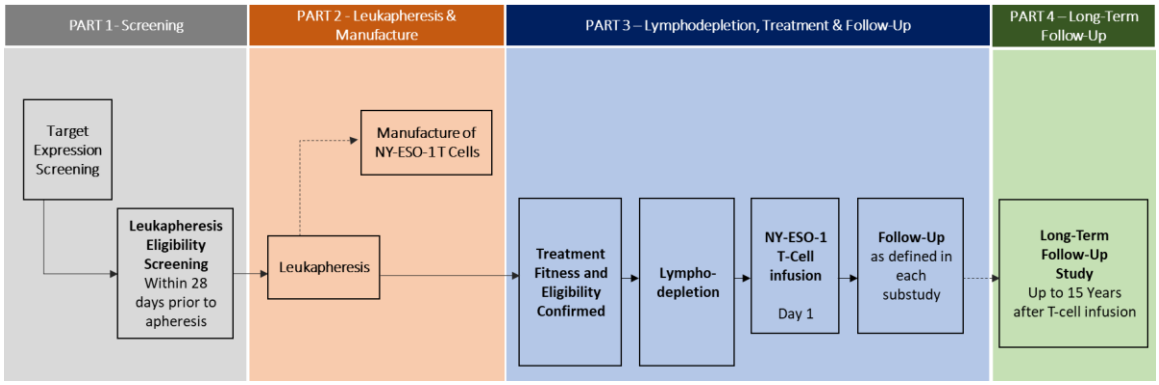
Dose Expansion Phase

After RP2D has been determined for a given T-cell product, the dose expansion phase will begin. In this phase, additional participants will be enrolled as necessary to meet the substudy requirements for the number of evaluable participants treated at the RP2D. Each substudy will define the maximal number of participants for this phase in the substudy-specific Section. If supported by safety and efficacy results, additional participants may be enrolled to confirm safety and efficacy in further cohort expansions. Additional details will be provided in each substudy-specific SAP.

1.2.2. Participant Journey

Participants will undergo stepwise enrolment followed by treatment according to defined phases within each substudy. The general patient journey is divided into four distinct parts: 1) Screening, 2) Leukapheresis/Manufacture, 3) Lymphodepletion/Treatment and Follow-up, and 4) Long-term follow-up.

Figure 2 Patient Journey Schema



Part 1: Screening

- Target expression Screening for the presence of HLA-A*02 positivity and tumor expression of NY-ESO-1 and/or LAGE-1a. For further details regarding HLA testing, please refer to the specific substudies.
- Leukapheresis eligibility screening phase to determine eligibility for undergoing leukapheresis beginning up to 28 days prior to leukapheresis.

Part 2: Leukapheresis/Manufacture

- Leukapheresis procedure.
  (Note: leukapheresis may have been performed under another GSK-sponsored protocol or substudy of this protocol.)

Part 3: Lymphodepletion, Treatment, and Follow-up

- Treatment fitness assessment and eligibility confirmation.
- Interventional phase including Lymphodepletion from Days -7 to -4, TCR engineered T-cell infusion on Day 1, and follow-up as defined in each specific substudy. (Note: TCR engineered T-cells may have been manufactured under another GSK-sponsored protocol or substudy of this protocol.)

Part 4: Long-Term Follow-Up (LTFU)

- Long-term follow-up phase for up to 15 years from the date of TCR engineered T-cell infusion

2. STATISTICAL HYPOTHESES

Substudy and, where applicable, cohort-specific null and alternate hypotheses for the overall response rate (ORR) during the dose expansion phase will be described in the substudy-specific SAP. No inferential statistical hypothesis testing will be conducted i.e., no p-values will be calculated.

2.1. Multiplicity Adjustment

No formal statistical hypothesis testing will be performed and therefore no multiplicity adjustment is required.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	All participants who signed an ICF to participate in the study.	• Screen Failures
Enrolled[1]	All participants who started leukapheresis procedure. Note: this analysis set will include 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 will include 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)
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 are part of the dose confirmation phase that either had a DLT (meeting the definition of a DLT as defined in Section 8.2 of the Core Protocol) or have completed the DLT assessment period of 28 days since last T-cell infusion. Note: For participants who receive a single dose, the DLT assessment period is up to and including Day 28, and for participants who receive split dose, the DLT assessment period is up to and including Day 28 after the second split-dose.	• Safety – summary of DLTs for dose confirmation phase
Modified ITT 90 (mITT 90)[2]	Participants in the mITT analysis set who have been followed-up for at least 90 days since the last T-cell infusion.	• Safety – summary of delayed AEs

Analysis Set	Definition / Criteria	Analyses Evaluated
Evaluable[3]	Participants in the mITT analysis set who received the RP2D and have completed at least 2 disease assessments after infusion or progressed or died or were withdrawn or lost to follow-up from the sub-study.	• 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, analysed, 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.
[1] Enrolled and ITT analysis sets are identical. The enrolled analysis set is required for disclosure reporting by EUdraCT.
[2] Note that mITT 90 analysis set will not be used since summary of delayed AEs will not be produced following termination of substudies.
[3] Note that all substudies were terminated prior to achieving RP2D and therefore the Evaluable Analysis Set is not required for analysis purposes.

4. STATISTICAL ANALYSES

4.1. General Considerations

References to T-cell infusion and T-cell infusion dates throughout the SAP documents are in reference to Study 209012 TCR T-cell therapies GSK3901961, GSK3845097, GSK4427296 but not GSK3377794 (letetresgene autoleucel, lete-cel), unless otherwise stated.

4.1.1. General Methodology

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

Details on the presentation of results are included in substudy-specific SAPs and OPS.

In general, and unless otherwise specified, participant data will be summarized overall and according to either the planned dose range, the actual dose range received, or both depending on the data type, as indicated in Table 1. See Section 4.1.5 on the handling of split-dose participants for summaries by actual treatment. Listings will be presented by actual treatment, unless otherwise specified.

Table 1 Presentation of Summaries by Planned/Actual Dose

	Present by Planned/Actual Treatment
Analysis Sets	Planned and Actual
T-Cell Infusion Status	Planned
Demographic and Baseline Characteristics	Actual
Exposure	Planned

	Present by Planned/Actual Treatment
Safety	Actual
DLT frequency counts	Actual & Planned
DLT Rates	Actual
Efficacy	Actual
PK	Actual

Confidence intervals (CI) will use 95% confidence levels unless otherwise specified.

Details of the planned displays, including those that will be presented for the Interim, Primary and Final analyses, are provided in the Core and substudy-specific OPS documents and are based on GSK data standards and statistical principles.

4.1.2. Baseline Definition

Among the participants with lymphodepleting chemotherapy, the baseline value is defined as the latest assessment with a non-missing value (including unscheduled visits) prior to initiating lymphodepletion (except as noted in Table 2). If time is not collected, assessments taken on the day of lymphodepleting chemotherapy are assumed to be taken prior to lymphodepletion and used as baseline. If a non-missing assessment within 10 days of initiating lymphodepletion is not available, then the last assessment with a non-missing value prior to initiating lymphodepletion would be used even if it occurred more than 10 days prior to initiating lymphodepletion.

For laboratory data, baseline will be defined as the most recent, non-missing value from a central laboratory prior to initiating lymphodepletion. If there are no central laboratory values collected for a substudy or a participant and the laboratory test is prior to lymphodepletion, the most recent, non-missing value from a local laboratory prior to initiating lymphodepletion will be defined as the baseline value.

For summaries of laboratory data by NCI-CTCAE v5.0 grade, missing baseline grades will be assumed as grade 0.

For ECG analyses, the participant level baseline is defined as the mean of the triplicate baseline assessments.

Unless otherwise stated, missing baseline data will not be imputed.

Table 2 Baseline Considerations

Parameter	Study Assessments Considered as Baseline		Baseline Used in Data Display
	Target Expression Screening	Treatment Eligibility Screening/ Baseline	
[Efficacy]			
Target and Non-target lesions		X	Prior to lymphodepletion
[Safety]			

Parameter	Study Assessments Considered as Baseline		Baseline Used in Data Display
	Target Expression Screening	Treatment Eligibility Screening/ Baseline	
Hematology, Chemistry, Additional Lab Parameters		X	Prior to lymphodepletion
Vital Signs, Physical Exam, ECOG		X	Prior to lymphodepletion
Electrocardiograms		X	Prior to lymphodepletion
Immunogenicity		X	Prior to lymphodepletion
[Demography]			
Demography	X		Target Expression Screening
[PK]			
T-cell persistence		X	Prior to lymphodepletion

4.1.3. Multicentre Studies

Data from all participating centres will be pooled prior to analysis.

It is anticipated that participant accrual will be spread thinly across centres and summaries of data by centre would be unlikely to be informative and will not, therefore, be provided.

Enrolment will be summarized by centre.

4.1.4. Selection of RP2D

As of Core SAP Amendment 2: Note that all substudies were terminated prior to the determination of RP2D. Any references to RP2D in the text are not applicable.

Selection of the RP2D will be based on the mTPI-2 approach described in Section 6.4. The Interim Analysis will be based on 10 evaluable participants within a cohort who received a cell dose infusion at the RP2D. Additional supplementary analyses may be performed, selecting participants based on similarity in PK cell expansion/persistence profile using parameters such C_{max} and AUC.

4.1.5. Split-dose Participants

The sentinel participant is the first study participant per substudy (if applicable for substudy) receiving NY-ESO-1 and/or LAGE-1a specific T-cells as two separate infusions, 7 days apart, in aliquots of ~30% (first infusion) and ~70% (second infusion) of the total manufactured dose, respectively. If DLTs are reported for sentinel participants receiving split doses, additional participants may be treated with a split-dose regimen.

For the purpose of summaries and listings presented by actual dose, split-dose participants will be summarised based on the actual cell dose received as follows:

- If both doses are infused, the actual cell dose would be the sum of the two doses.
- If only the first dose was infused, this would be actual cell dose.

Split-dose participants will be included in the RP2D provided the participant had received a cell dose infusion at the RP2D.

4.1.6. Participants Receiving Prior Letetresgene autoleucel (GSK3377794, lete-cel) Therapy

As of Core SAP Amendment 2: Due to early termination of the study during the dose confirmation phase this section of text is no longer applicable.

Participants who achieved a confirmed RECIST v1.1 response of complete response (CR) or partial response (PR), or stable disease (SD) ≥3 months following treatment with letetresgene autoleucel (GSK3377794, lete-cel) on another GSK sponsored study/substudy may be considered for eligibility for certain substudies (if applicable) following discussion with the Sponsor Medical Monitor.

For the applicable substudy, there will be no more than 3 participants who were previously treated with lete-cel to be permitted. These participants will not be permitted on a substudy until at least after the dose confirmation phase is complete, hence will not be included in the dose confirmation analyses used to determine the RP2D. These participants may be included in the 10 evaluable participants for the Interim Analysis.

4.2. Primary Endpoint(s) Analyses

4.2.1. Definition of endpoint(s)

The primary endpoints are frequency of dose-limiting toxicities (DLTs), frequency and severity of adverse events (AEs) and serious adverse events (SAEs) and frequency and severity of the AEs of special interest (AESIs).

DLTs are toxicities that are considered to be at least possibly related to transduced T-cells and that occur within the DLT-assessment period of 28 days after initial dosing of T cells. For participants receiving T cells as a split dose, the DLT assessment period will begin at the start of the first infusion and continue for 28 days after completion of the last infusion. Refer to Core Protocol Section 8.2 for the full definition of a DLT.

4.2.2. Main analytical approach

Refer to Safety Analyses Section 4.5.

4.2.3. Strategy for intercurrent events

Not applicable.

4.2.4. Sensitivity analyses

Not applicable.

4.2.5. Additional estimands

Not applicable.

4.3. Secondary Endpoint(s) Analyses

4.3.1. Efficacy secondary endpoint(s)

4.3.1.1. Definition of endpoint(s)

4.3.1.1.1. Overall Response Rate (ORR)

ORR is defined as the percentage of participants with a confirmed complete response (CR) or a confirmed partial response (PR) as the BOR (Best Overall Response) 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 assessment, or have non-measurable disease at baseline, or experience death prior to the first disease assessment will be treated as non-responders i.e., these participants will be included in the denominator when calculating the ORR and best confirmed response will be summarized as Not Evaluable (NE).

Best Overall Response (BOR) as per RECIST v1.1:

The investigator reported disease assessment, as assessed by RECIST v1.1, will be considered from best to worst in the order of Complete Response (CR) > Partial Response (PR) > Stable Disease (SD) > Progressive Disease (PD) > Not Evaluable (NE). The BOR will be derived as the best response recorded from the start of the treatment i.e., 1st T-cell infusion date until disease progression or initiation of new anti-cancer therapy, whichever is earlier.

- Note: Unconfirmed responses of CR or PR may be included as a supplementary BOR derivation and listed, in which case the BOR will be considered from best to worst in the order of CR > Unconfirmed CR > PR > Unconfirmed PR > SD > PD > NE.

Confirmation Criteria:

A response of CR or PR is confirmed if the criteria for each are met at a subsequent time point at least 28 days later but before disease progression or initiation of new anti-cancer therapy, excluding assessments that are not evaluable (NE).

The following additional rules will be followed during the derivation:

- The date of disease progression is defined as the date of radiological disease progression based on imaging data per RECIST v1.1. For cases where symptomatic progression is documented by the investigator, the derived overall response based on RECIST v1.1 tumor assessment data will be utilized.
- To be assigned a status of PR or CR, a confirmatory disease assessment should be performed no less than 28 days after the criteria for response are first met.

- To be assigned a status of stable disease (SD), follow-up disease assessment must have met the SD criteria at least once after the start of treatment at a minimum interval of 28 days (Core Protocol Section 12.6.1). This period includes 1st T-cell infusion and assessment day +1.
- If the minimum time of 28 days for SD is not met, best response will depend on the subsequent assessments. For example, if an assessment of PD follows the assessment of SD, and SD does not meet the minimum time requirement, the best response will be PD. Alternatively, participants lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.
- Responses of CR/PR that do not meet the requirements of confirmed CR/PR are still eligible to be considered SD if they have met the SD criteria.
- Assessments that are not done or not evaluable should be disregarded.
- SD responses between two PR responses for a participant will be handled as follows:
    a) If there is one SD response between two PR responses (i.e., PR-SD-PR) then the best overall response will be confirmed PR, provided the participant meets the requirements of a confirmed PR.
    b) If there are two SD responses between two PR responses (i.e., PR-SD-SD-PR) then the best overall response will not be confirmed PR.
- Disease assessments after on-study start of new anti-cancer therapy will not be considered when deriving best overall response. On-study anti-cancer therapies are defined in Section 6.1.5.2.
- If time is not collected and anti-cancer therapy starts on the same day as the disease assessment, it is assumed that the disease assessment occurred first.
- Study inclusion criteria require participants to have measurable disease at baseline according to RECIST v1.1. If this is violated and a participant has no measurable disease at baseline, then the participant will be treated as a non-responder and included in the denominator when calculating the ORR. Participants with no disease assessments on-study will also treated as non-responders and included in the denominator when calculating the ORR.

Table 3 summarizes the derivation of confirmed response and BOR per RECIST v1.1.

Table 3 Best Overall Response per RECIST v1.1 and Additional Programming Notes

Overall response first time point	Overall response subsequent time point	Best overall response	Additional Programming Notes
CR	CR	CR	Confirmatory response of CR is required >=28 days after initial CR
CR	PR	SD provided minimum criteria for SD duration met**, otherwise, PD	SD (if >=28 days per SD criteria); otherwise PD

Overall response first time point	Overall response subsequent time point	Best overall response	Additional Programming Notes
CR	SD	SD provided minimum criteria for SD duration met**, otherwise, PD*	SD (if >= 28 days per SD criteria); Otherwise PD
CR	PD	SD provided minimum criteria for SD duration met**, otherwise, PD	SD (if >= 28 days per SD criteria); Otherwise PD
CR	NE	SD provided minimum criteria for SD duration met**, otherwise NE	SD (if >= 28 days per SD criteria); Otherwise NE
PR	CR	PR	Confirmatory response of PR is required >=28 days after initial CR
PR	PR	PR	Confirmatory response of PR is required >=28 days after initial PR
PR	SD	SD provided minimum criteria for SD duration met**, otherwise, NE	SD (if >= 28 days per SD criteria); Otherwise NE. Note: if after SD there is a PR (i.e., PR-SD-PR) then BOR is PR.
PR	PD	SD provided minimum criteria for SD duration met**, otherwise, PD	SD (if >= 28 days per SD criteria); Otherwise PD
PR	NE	SD provided minimum criteria for SD duration met**, otherwise, NE	SD (if >= 28 days per SD criteria); Otherwise NE
SD	CR	SD provided minimum criteria for SD duration met**, otherwise, NE	SD (if >= 28 days per SD criteria); Otherwise NE
SD	PR	SD provided minimum criteria for SD duration met**, otherwise, NE	SD (if >= 28 days per SD criteria); Otherwise NE. Note: if prior to SD there is a PR (i.e., PR-SD-PR) then BOR is PR.

Overall response first time point	Overall response subsequent time point	Best overall response	Additional Programming Notes
SD	SD	SD provided minimum criteria for SD duration met**, otherwise, NE	SD (if >= 28 days per SD criteria); Otherwise NE
SD	PD	SD provided minimum criteria for SD duration met**, otherwise, PD	SD (if >= 28 days per SD criteria); Otherwise PD
SD	NE	SD provided minimum criteria for SD duration met**, otherwise, NE	SD (if >= 28 days per SD criteria); Otherwise NE
NE	NE	NE	

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.

* If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met.

** Minimum criterion for SD disease duration is at least 4 weeks to qualify SD as BOR.

Note: If BOR is confirmed CR or PR, the subject is classified as a responder for the ORR analysis.

4.3.1.1.2. Duration of Response (DOR)

Duration of response (DOR) is 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.

Censoring rules for the DOR will follow those for PFS (Section 4.4.1.2) and as specified in Table 4.

4.3.1.2. Main Analytical Approach

4.3.1.2.1. ORR

The observed confirmed ORR along with the 95% Clopper-Pearson exact confidence intervals, will be summarized based on the mITT analysis set.

In addition, the number and percentage of participants with the BOR in the following response categories as per RECIST v1.1 will be summarized: CR, PR, SD, PD, NE, and overall response (CR+PR).

An overall listing of participant response data will be provided for the ITT analysis set. This listing will display all the investigator response evaluations, the best confirmed response, whether the participant is ongoing in the study, and whether the participant is in the mITT analysis set. All supporting lesion data will be listed.

Change in sum of target lesion diameters from baseline over time for the mITT analysis set will be shown in a spider plot where data from all available tumor assessments will be displayed. The BOR, disease progression (first PD and confirmed PD, where applicable) and initiation of new anti-cancer therapy will be indicated on the plot.

4.3.1.2.2. DOR

DOR will be summarized based on the mITT analysis set using the Kaplan-Meier method. The median, 25th and 75th percentiles of DOR will be estimated and corresponding 95% confidence intervals will be estimated using the (Brookmeyer-Crowley method, 1982) under a log-log transformation. The Kaplan-Meier estimates will only be produced for a cohort if there are 5 or more confirmed responses within that cohort. If this condition is not met, standard summary statistics will be presented. A supportive listing will be provided on the mITT analysis set.

4.3.1.3. Strategy for Intercurrent Events

For ORR

A composite strategy will be followed for participants who experience death prior to response assessments. These participants will be treated as non-responders (NE) i.e., they will be included in the denominator when calculating the ORR.

The intercurrent event of start of on-study/follow-up anti-cancer therapy is addressed using a while-on-treatment strategy, as the interest lies in the treatment effect of the investigational treatments before start of new anti-cancer therapy. Only tumor assessments performed before initiation on-study/follow-up anti-cancer therapy will be considered for BOR.

For DOR

A composite strategy will be followed for participants who experience death prior to response assessments. If death occurs it is considered a progression event and the end of response duration.

The intercurrent event of start of on-study/follow-up anti-cancer therapy started before documented PD or death is addressed using a hypothetical strategy, because the interest lies in the treatment effect attributable to the investigational treatments and not confounded by other anti-cancer therapies. Only tumor assessments performed before initiation of on-study/follow-up anti-cancer therapy will be considered for DOR.

4.3.2. Pharmacokinetics (PK) secondary endpoint(s)

4.3.2.1. Drug persistence

T-cell vector copies (expansion/persistence) in the peripheral blood will be measured in participants by quantitation of transduced cells by polymerase chain reaction (PCR) of transgene from DNA extracted from Peripheral blood mononuclear cell (PBMC). Persistence will be 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 will be applied in lieu of “concentration” to derive PK parameters.

4.3.2.2. Definition of endpoints

Maximum expansion/persistence (C_{max}), time to C_{max} (T_{max}), and area under the time curve from 1st T-cell infusion to 28 days ($AUC_{0\text{-}28d}$), are secondary pharmacokinetic endpoints that will be determined from the persistence-time data, as data permits.

Parameter	Parameter Description
$AUC_{0\text{-}28d}$	Area under the persistence-time curve from 1st T-cell infusion to 28 days will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
C_{max}	Peak cell expansion, determined directly from the persistence-time data.
T_{max}	Time to reach C_{max}, determined directly from the persistence-time data.

NOTES:

Additional parameters, such as area under the time curve from 1st T cell infusion to time t ($AUC_{0\text{-}t}$) may be included as required, as data permit.

4.3.2.3. Main analytical approach

All pharmacokinetic analyses will be based on the PK population. All raw persistence and derived PK parameters will be listed.

Pharmacokinetic parameters will be calculated using standard non-compartmental analyses according to current working practices and using appropriate software. All calculations of non-compartmental parameters will be based on actual sampling times.

For each of these parameters, except T_{max}, the following summary statistics will be calculated: median, minimum, maximum, arithmetic mean, 95% confidence interval for the arithmetic mean, standard deviation, coefficient of variation, geometric mean, 95% confidence interval for the geometric mean and standard deviation of logarithmically transformed data.

Note: Coefficient of variation (CV) = 100*(sqrt (exp(SD^2) - 1))), where SD = standard deviation of log transformed data.

For T_{max}, median, maximum, minimum, arithmetic mean, 95% confidence interval, and standard deviation will be calculated.

Spider plots will be used to graphically summarize persistence (copies/µg gDNA) over time for each participant.

All PK parameters will be reported to at least 3 significant digits, but to no more significant digits than the precision of the original data.

Drug Concentration Measures

The following calculations will be performed:

- copies/cell=(copies/µg) x (0.0000063 µg gDNA/cell)
- Percent gene marked peripheral blood mononuclear cells (PBMCs) =(copies/cell) *100

The final reported result of copies/µg gDNA is calculated as follows:

- copies/µg gDNA=copies per well/µg gDNA per well

For persistence values below LLOQ, the following rules will be applied:

Reported Copies per cell Result	Reported Copies per ug DNA Result	Interpretive Reported Result	Set Value for Copies per cell	Set Value for Copies per ug DNA
<0.0003	<50.0	Negative	0	0

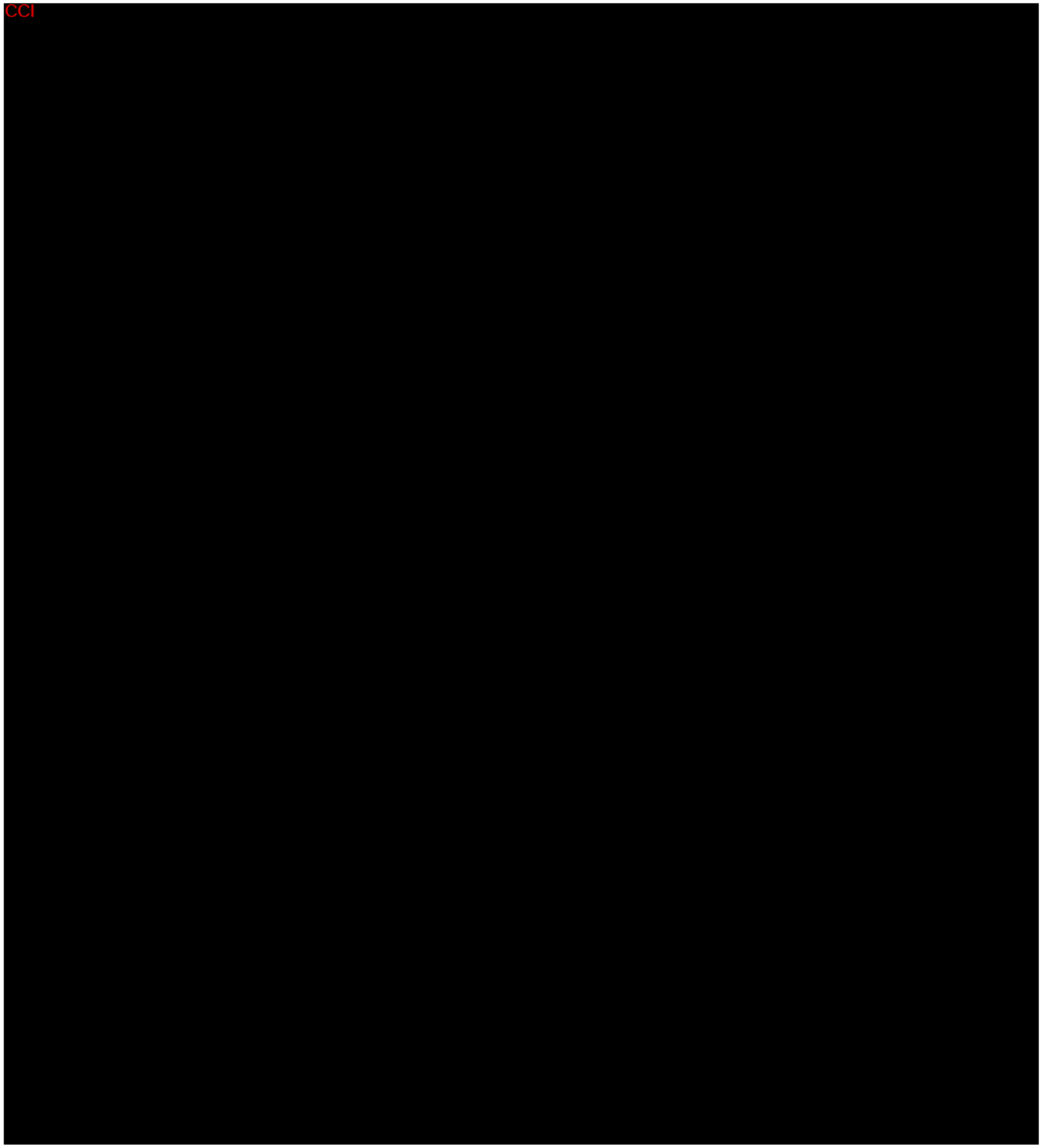
<0.0003	<50.0	Detectable, <LLOQ	0.0003	50

Note, sometimes values for copies per cell and copies per ug DNA might be different than above as it depends on the input of DNA, but rule would be the same:

- If interpretive reported result is “Negative”, set values at 0.
- If interpretive reported result is “Detectable, <LLOQ”, set values at LLOQ (If <XXX, set at XXX).

4.4. Exploratory Endpoint(s) Analyses

CCI



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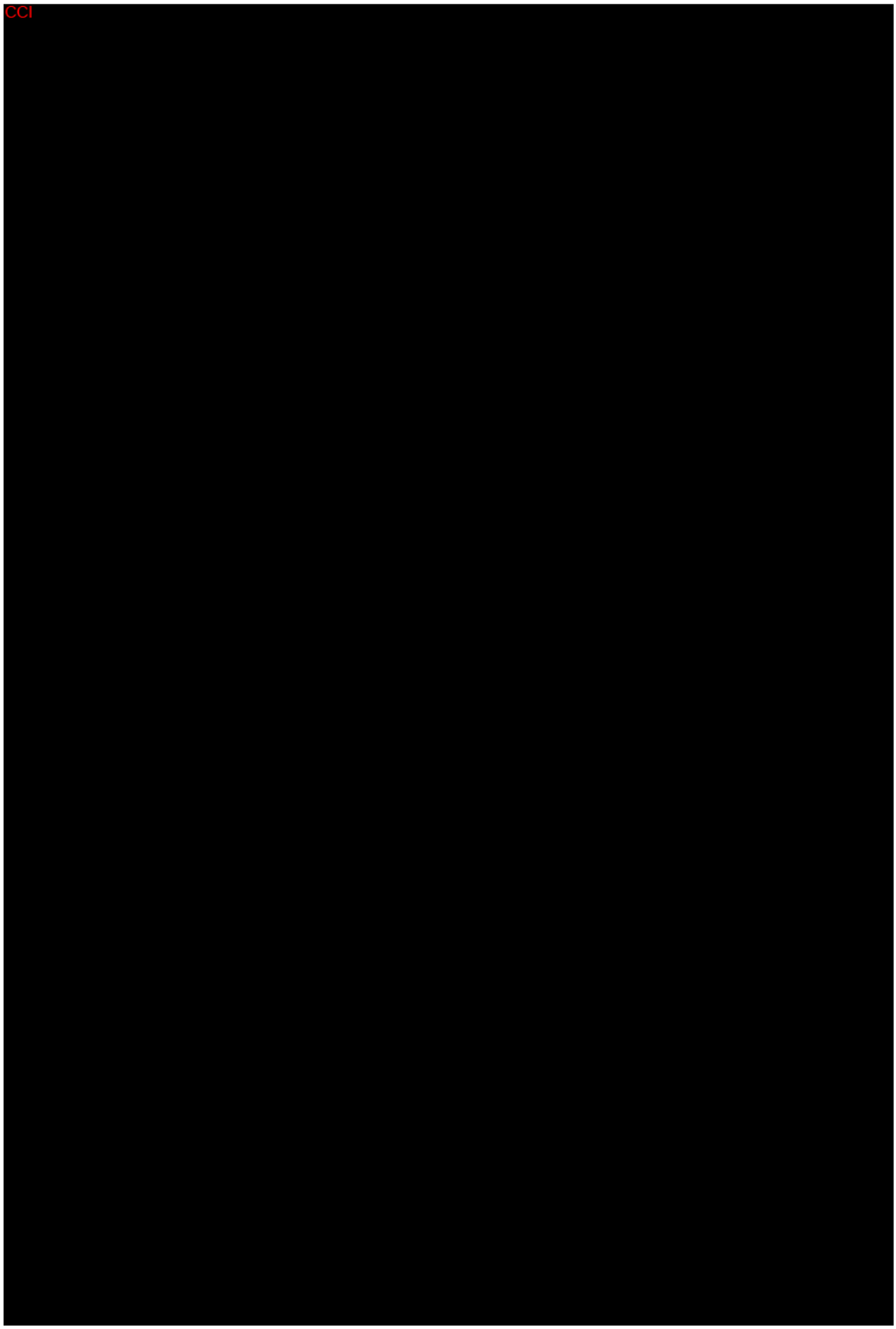

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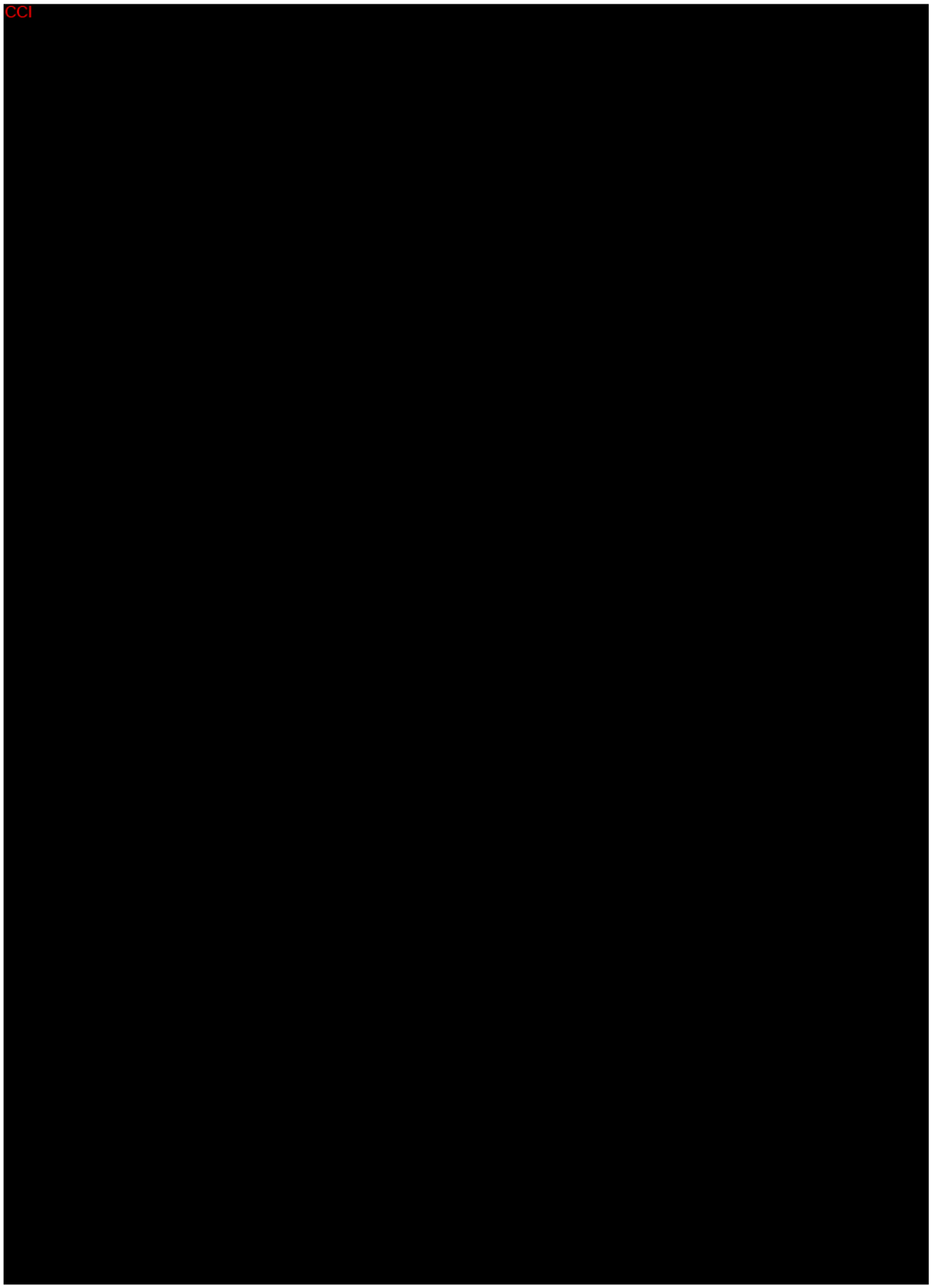

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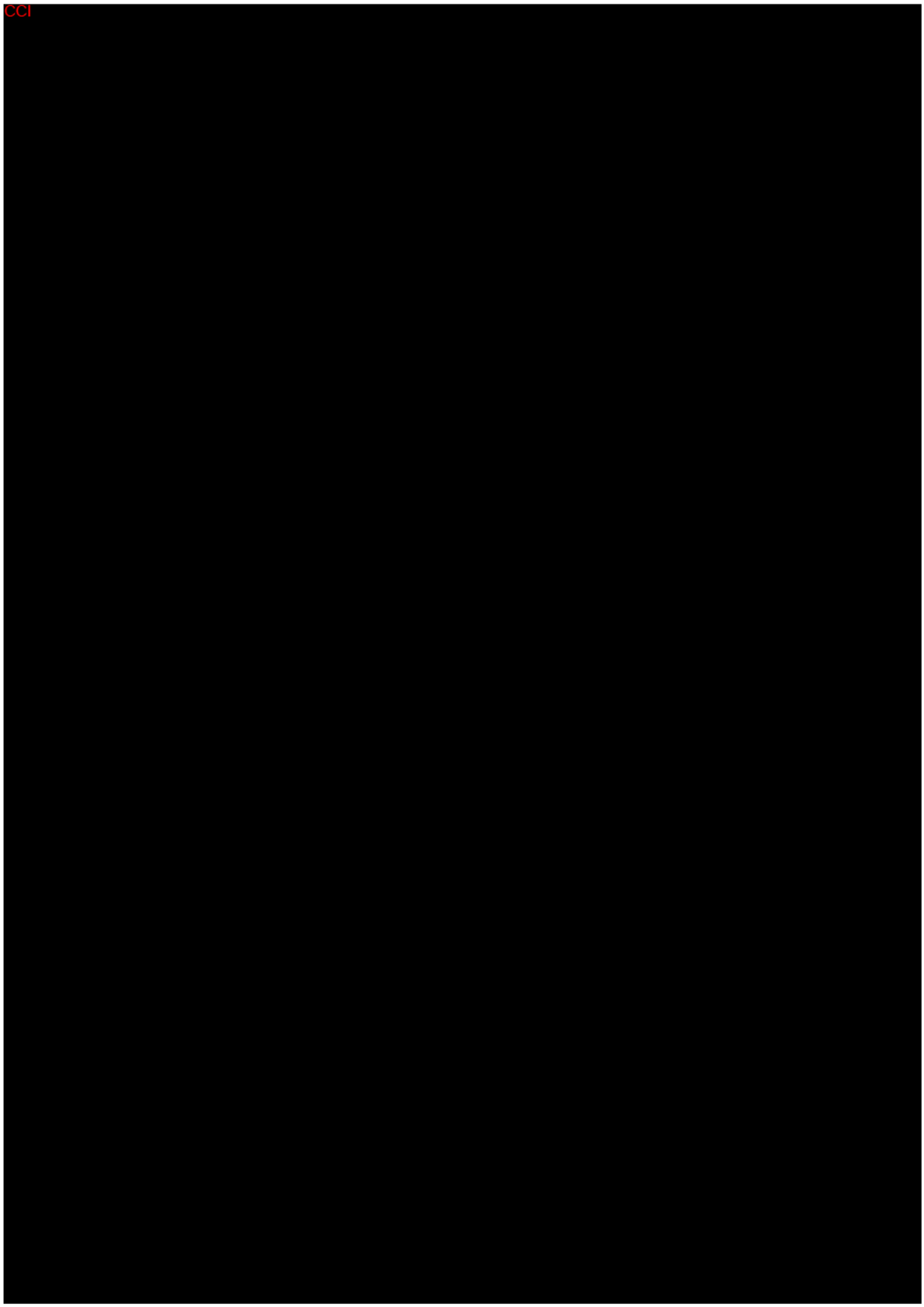

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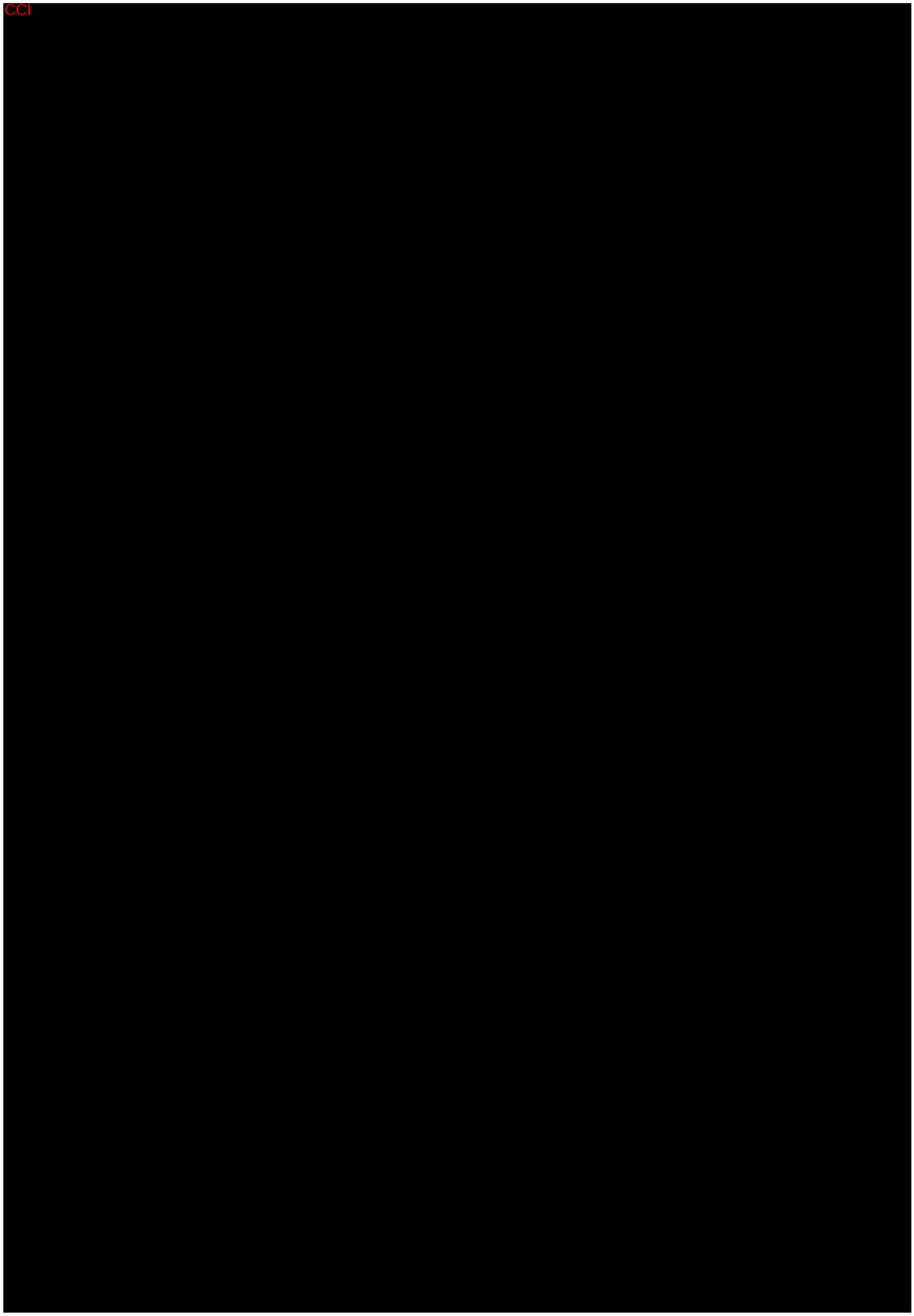

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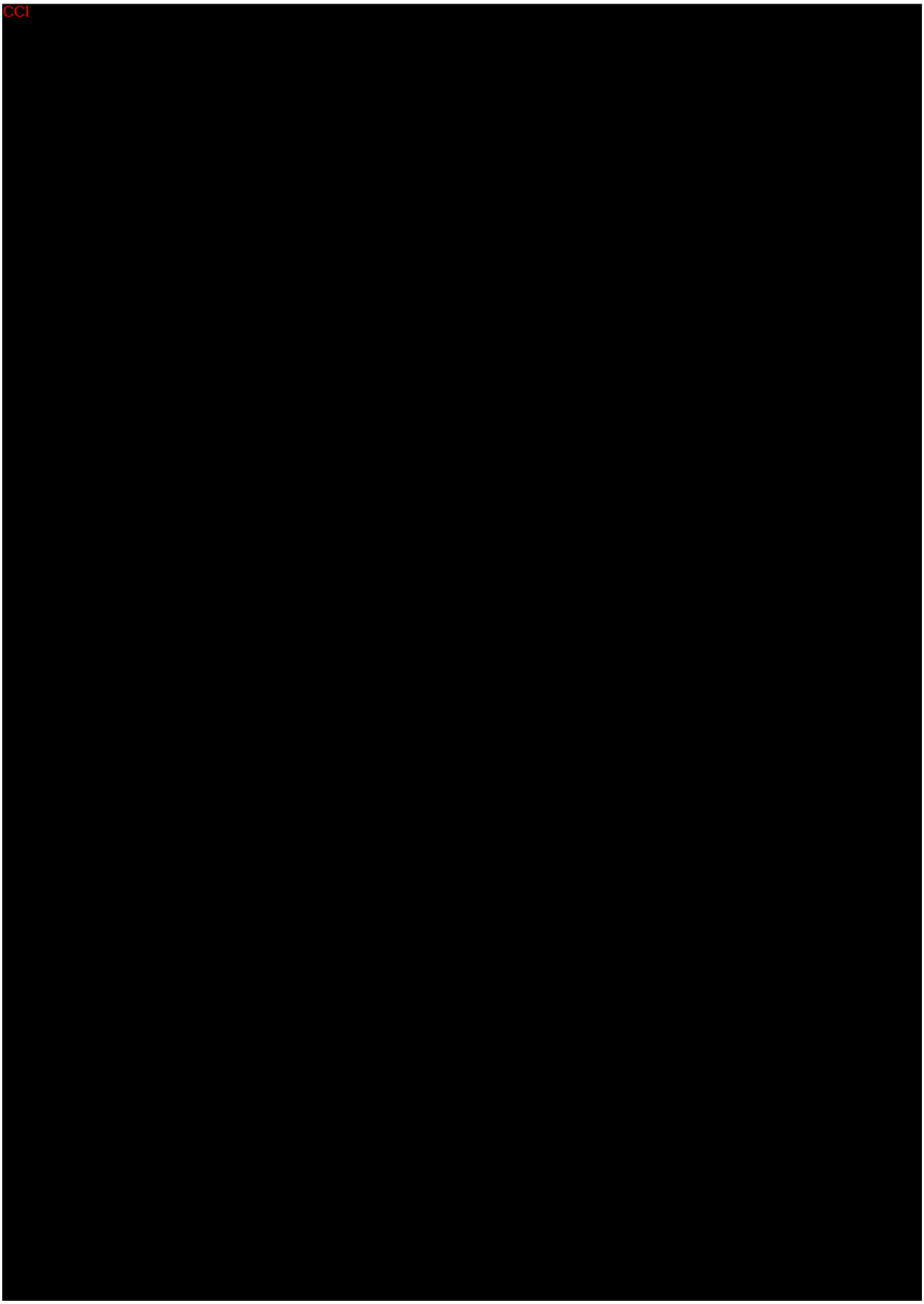

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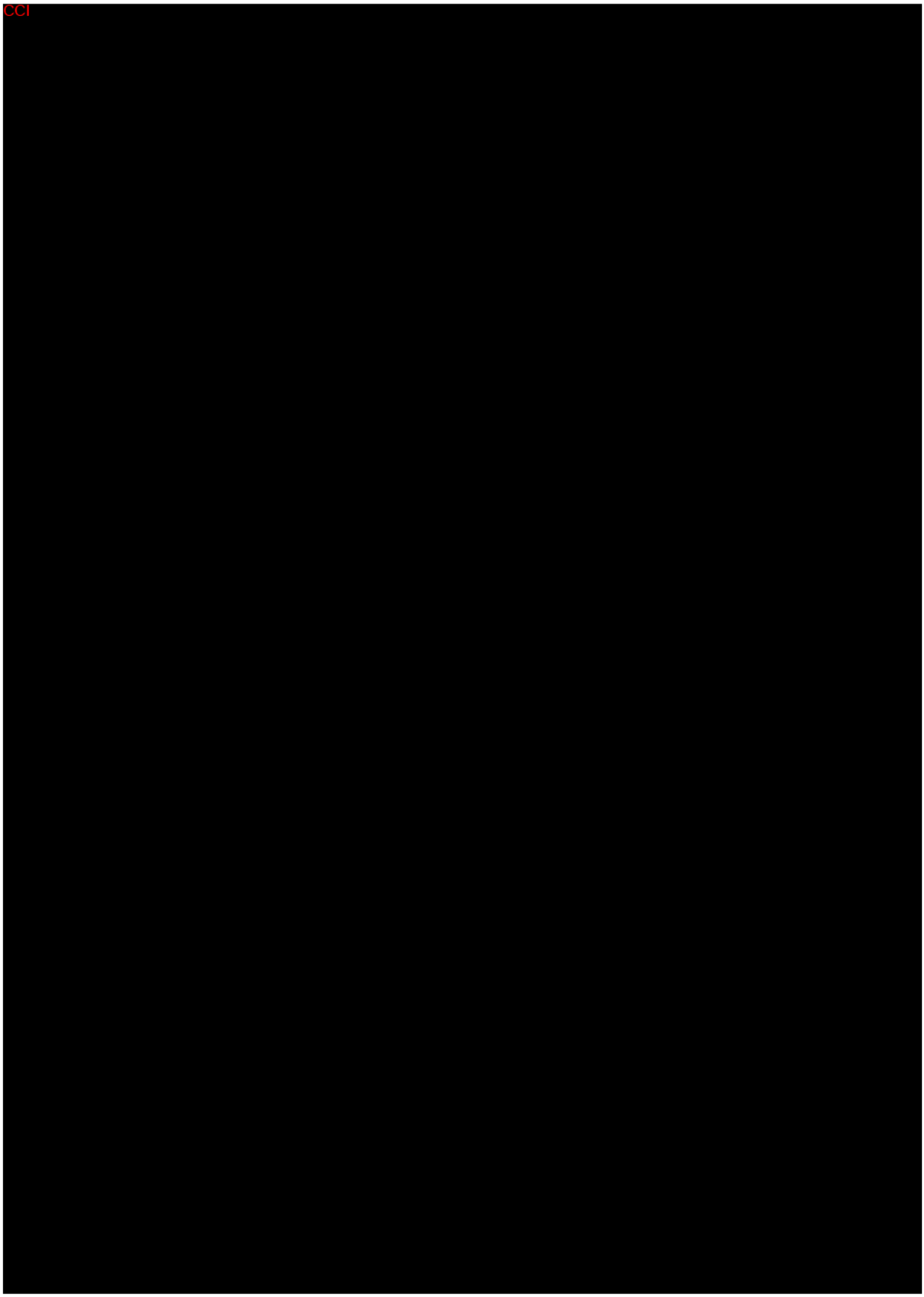

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4.5. Safety Analyses

The primary safety analysis will be based on the modified ITT population. Additional analyses will be presented using the DLT Evaluable, ITT and Lymphodepletion populations, as appropriate. Adverse events analyses will be based on different analysis sets for different AE phases as summarized in Table 7.

4.5.1. Adverse Events

4.5.1.1. Dose Limiting Toxicities

Dose-limiting toxicities (DLTs) will be listed for each subject and summarized by frequency and proportion by actual treatment (see Table 1). Additionally a summary of the frequency of DLTs broken down by the actual treatment within each planned treatment cohort will be presented. Reported DLTs will be those collected on the eCRF. Summaries will be based on the DLT Evaluable population.

4.5.1.2. AE Standards and Grading Criteria

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs), AEs related to study-treatment (lymphodepletion chemotherapy and T-cell infusion), SAEs related to study-treatment and other significant AEs will be based on GSK Core Data Standards.

AEs will be graded according to National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 5.0 or higher unless otherwise specified in the protocol. For instance, the grading of Cytokine Release Syndrome (CRS) and ICANS will be performed using the American Society for Transplantation and Cellular Therapy (ASTCT) grading criteria (Lee, 2019); see Core Protocol Section 12.7.5 and Section 12.7.8.1. For the grading of Graft versus Host Disease (GVHD), see Core Protocol Section 12.7.6.2. AEs will be coded using the latest version of the Medical Dictionary for Regulatory Affairs (MedDRA).

Per GSK standard, AEs that have grade changes over the course of the event are entered in the same record within the eCRF, with grade changes indicated within. Other attributes of the event (e.g., seriousness, relatedness) are attributed to the overall event.

For specific AE displays, Preferred Terms are combined and will be reported together as one term. The combined terms for MedDRA Version 25.1 are listed in Section 6.3. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional combined terms, therefore the list of combined preferred terms will be based on the safety review team (SRT) agreements in place at the time of reporting. A table showing the relationship between the combined preferred term and contributing preferred terms will be produced. Tables that summarize AEs by SOC and PT will use MedDRA preferred terms. Most other Tables will summarize AEs using the combined term in Section 6.3, unless otherwise specified.

4.5.1.3. AE Phases

AEs will be summarized in the following phases amongst participants which have entered the phase (Table 7). These phases are defined in more detail in Section 4.5.1.5. The analyses for each phase are presented in Section 4.5.1.5.

Table 7 AE phases

Phase	Definition	Population
Pre-Lymphodepletion Phase	AEs which start prior to lymphodepletion chemotherapy	Intent-to-Treat Population
Lymphodepletion Phase	AEs which start or worsen on or after the start of lymphodepletion chemotherapy until prior to 1st T-cell infusion	Lymphodepletion Population
T-cell Phase (Treatment-Emergent)	AEs which start or worsen on or after 1st T-cell infusion	mITT Population

4.5.1.4. General AE summaries

AEs which start within the phase or worsen after initiation of the phase (maximum grade after initiation of the phase is larger than the maximum grade before initiation of the phase) will qualify to be summarized in the phase. AEs may be summarized in multiple phases (ex: A Grade 2 AE after lymphodepletion increases to Grade 3 after T-cell infusion and is therefore summarized as a Grade 2 in the lymphodepletion phase and a Grade 3 in the T-cell Phase).

The primary analysis of AEs will be performed for AEs which started or worsened in the T-cell Phase i.e., treatment-emergent AEs. However additional analyses will be performed in the phases above. The full definition of treatment emergence by phase are detailed in Section 6.2.3.4.

All AEs collected in the ITT population will be listed and the phase assigned to the AE will be indicated in the listing. AEs which led to study treatment withdrawal, interruption, delay, or reduction of any study treatment (cyclophosphamide, fludarabine, or T-cell infusion) will be flagged in the listing as collected in the eCRF. Additionally, a listing of participant IDs for each individual AE will be produced.

SAEs will be included in the listing of all AEs, but also separate supportive listings with participant-level details will be generated for:

- Fatal SAEs
- Non-fatal SAEs
- Reasons for considering AE as serious

AEs will be summarized and displayed in descending order of total incidence by SOC and PT. In the SOC row, the number of participants with multiple events under the same system organ class will be counted once.

Summaries of number and percentage of participants with AEs by maximum grade will also be produced. AEs will be sorted by combined PT in descending order of total incidence. The summary will use the following algorithms for counting the participant:

- **Combined preferred term row**: Participants experiencing the same combined preferred term several times with different grades will only be counted once with the maximum grade.
- **Any event row**: Each participant with at least one adverse event will be counted only once at the maximum grade no matter how many events they have.

Summaries will be provided for lymphodepletion-related and T-cell-related AEs separately. These study treatment-related AEs are defined as an AE for which the investigator classifies the relationship to study treatment as "Yes". For example, lymphodepletion-related AEs include lymphodepletion or treatment-emergent AEs that are reported as related to fludarabine and/or cyclophosphamide per investigators; T-cell-related AEs include AEs that are reported as related to T-cell per investigators. A worst case scenario approach will be taken to handle missing relatedness data i.e., the summary table will include events with the relationship to study treatment as 'Yes' or missing.

A summary of common non-serious AEs that occurred in 5% of the participants or above will be provided (no rounding for the percentage will be used in terms of 5% threshold, e.g., events with 4.9% incidence rate should not be included in this Table). This summary will contain the number of subjects and occurrences of participants with common non-serious AEs. The summary table will be displayed by SOC and PT.

A summary of All Serious Adverse Events by System Organ Class (SOC) and Preferred Term (PT) will also be created to detail the number of participants and occurrences of each event.

4.5.1.5. AE summaries by Phase

In the AE summaries mentioned below, it refers to all AEs including those collected in the non-serious AE page and SAE page from eCRF.

Analyses for all AEs:

- Common non-serious AEs (number of subjects and occurrences)
- SAEs (number of subjects and number of occurrences of SAEs, T-cell related SAEs, Fatal SAEs and T-cell related Fatal SAEs)

Analyses for AEs in the Pre-Lymphodepletion Phase will include:

- Summary by maximum grade
  - AEs and SAEs

Analyses for AEs in the Lymphodepletion Phase will include:

- Summary by maximum grade
  - AEs
  - SAEs

Analyses for treatment-emergent AEs will include:

- Summary of AEs by System Organ Class and Preferred Term (using PT term)

- AEs and SAEs

- Summary by maximum grade
  - AEs
  - SAEs
  - T-cell related AEs
  - Lymphodepletion related AEs and SAES
  - T-cell related SAEs

- Descending frequency (using Preferred Term)
  - Non serious T-cell related AEs
  - Serious fatal and non-fatal T-cell related AE

4.5.1.6. Delayed AEs

Delayed AEs as defined in the FDA 2020 Guidance- Long Term Follow-Up After Administration of Human Gene Therapy Products [FDA, 2020a] are identified through sponsor adjudication as the primary method of reporting. Sponsor adjudication will focus on AEs starting 90 days after administration of T-cell therapy that fall into one of following categories:

- New malignancies
- New incidence or exacerbation of a pre-existing neurological disorder
- New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
- New incidence of an immune related hematologic disorder
- Serious infections or non-serious pulmonary or opportunistic infections
- Unanticipated illness or hospitalization deemed related to gene modified cell therapy

Events that meet the criteria above, are study-treatment related events and are serious and/or Grade $\geq$3 will be the primary focus of sponsor adjudication, although adjudication is not limited to these criteria.

Delayed AEs are also identified by the investigator and captured in the CRF. Delayed AEs as adjudicated by the sponsor (provided from external data source) and identified by the investigator will be listed separately on the mITT analysis set.

4.5.1.7. Adverse Events of Special Interest

Adverse events of special interest (AESIs) covered in this SAP include:

- Cytokine Release Syndrome (CRS)
- Haematopoietic cytopenias (including pancytopenia and aplastic anaemia)
- Graft versus Host Disease (GvHD)
- Immune Effector-Cell Associated Neurotoxicity Syndrome (ICANS)
- Guillain-Barre Syndrome (GBS)
- Pneumonitis
- Treatment-related inflammatory response at tumor site(s)

All analyses of AESIs will be performed in the T-cell Phase (treatment emergent) using the mITT analysis set, unless otherwise stated. Each summary will only be produced if there are ≥3 corresponding AESIs.

A focused list of MedDRA terms based on clinical review will be used to identify each type of event and will be used for AESI reporting. In addition, a comprehensive list of MedDRA terms aligning with MedDRA SMQ list will also be used for AESI reporting (data set only, no tables or listings). Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies highlight additional adverse events of special interest, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the safety review team (SRT) agreements in place at the time of reporting.

The protocol-identified AESI, treatment-related inflammatory response at tumor site, is non-specific and will not be identified using the focused or comprehensive list. Investigator identified AEs which may be related to this event will be used to characterize this AESI.

The number and percentage of participants with treatment emergent AESIs and serious treatment emergent AESIs will be summarized by categories of AESI, combined preferred term, and grade using the focused list . Haematopoietic cytopenias will be summarized using the focused list, and presented overall, as well as by cell lines Neutropenia, Thrombocytopenia and Anemia.

Cytokine Release Syndrome

The following analyses will be provided:

- Among subjects which experienced CRS, a summary of onset and duration of the first occurrence of CRS identified using the focused list will be provided.

A supporting CRS listing profile will be provided to detail the CRS adverse event, display the procedures and medications received to treat CRS and display symptoms associated with the event.

Haematopoetic Cytopenias

The following analyses will be provided:

- Summary of onset and duration of the first occurrence of febrile neutropenia.
- Listing of persistent cytopenias
    - Persistent cytopenias will be based on laboratory values. Please refer to Section 4.5.2.

A supporting Pancytopenia listing profile will be provided to detail these events.

Graft versus Host Disease (GvHD)

The following analyses will be provided:

- Summary of onset and duration of the first occurrence of GvHD identified using the focused list.

A supporting GvHD listing profile will be provided to detail these events.

Immune Effector-Cell Associated Neurotoxicity Syndrome (ICANS)

The following analyses will be provided:

- Summary of onset and duration of the first occurrence of ICANS identified using the focused list.

A supporting ICANS listing profile will be provided to detail these events.

Guillain-Barre Syndrome (GBS)

A supporting GBS listing profile will be provided to detail these events.

Pneumonitis

The following analyses will be provided:

- Summary of onset and duration of the first occurrence of Pneumonitis identified using the focused list.

A supporting Pneumonitis listing profile will be provided to detail these events. Note that in 209012 Protocol Amendment 3, pneumonia was also included as an AESI. Pneumonia will be listed in a separate profile listing but will not be summarized as an AESI.

4.5.1.8. COVID-19 Assessment and COVID-19 AEs

Separate summaries of COVID-19 AEs will not be produced. The incidence of COVID-19 AEs at individual PT level can be obtained from the standard AE/SAE summaries and listings. COVID-19 AEs leading to study drug discontinuation and study withdrawal can be found in the associated listing.

4.5.2. Clinical Laboratory Analyses

The tests detailed below will be performed by the laboratory.

Laboratory Assessments	**Parameters**			
Haematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: • MCV • MCH • Reticulocytes		WBC count with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Flow cytometry	CD3/CD4/CD8			
Clinical Chemistry[a]	BUN[b]	Potassium	AST (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose [nonfasting]	Calcium	Alkaline phosphatase	Chloride
	Albumin	Phosphorus	LDH	Urea

Laboratory Assessments	Parameters			
		Magnesium	Bicarbonate	
Coagulation	INR, PT, and aPTT, Fibrinogen			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Tests	• CMV IgG and PCR • TSH with free T4 • CRP • Uric acid • GFR or 24 hour Urine • Follicle-stimulating hormone (as needed in women of non-childbearing potential only) • Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[c] • HIV, HBV, HCV, HTLV, EBV, and syphilis (spirochete bacterium). • Ferritin • Serum troponin • NT-proBNP / BNP			

a. Details of liver chemistry monitoring criteria and required actions and follow-up assessments after liver monitoring event are given in Core Protocol Section 8.2.1. All events of ALT ≥3 × ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and INR >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE.
b. Either BUN or UREA tests are acceptable.
c. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Note: All study-required laboratory safety assessments will be performed by a local laboratory, exception of alleles HLA-A*02:01, A*02:05, or A*02:06 and NY-ESO-1/LAGE-1a expression. The results of each test must be entered into the eCRF.

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = Aspartate aminotransferase; BUN = blood urea nitrogen; CMV = cytomegalovirus; CRP = C-reactive protein; EBV = Epstein Barr virus; GFR = glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HTLV = human T-lymphotropic virus; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; NT-proBNP = N-terminal group pro-BNP; PCR = polymerase chain reaction; PT = prothrombin time; RBC = red blood cells; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; T4 = thyroxine; TSH = thyroid stimulating hormone; WBC = white blood cells.

A listing of all laboratory data and urinalysis data for participants will be provided. All laboratory values, including pre-baseline values, will be included in the listing.

Laboratory grades will be reported using NCI-CTCAE v5.0 or higher. Missing baseline grade will be assumed as grade 0. For laboratory tests that are not gradable by NCI-CTCAE v5.0 or higher, values outside the normal range will be provided. Missing baseline grade will be assumed to be normal.

Spider plots including neutrophils, platelets, and hemoglobin in the same plot will be created by participant.

Persistent cytopenias

Persistent cytopenias are defined as neutropenia, thrombocytopenia, or anemia at Grade 3 or above at the Week 5 visit (Day 29 ± 3 days). If the subject does not have a Week 5 laboratory assessment, the latest assessment before the Week 5 visit will be analysed. The percentage of subjects with any cytopenia, as well as any persistent neutropenia, thrombocytopenia, or anemia at Week 5 will be provided separately. If a subject has multiple laboratory values within the Week 5 visit window, the worst case grade will be used to define persistent cytopenia. Unscheduled visits will be incorporated in the analysis. Grading of cytopenias are reported according to NCI-CTCAE v5.0 or higher criteria for neutropenia, anemia, and thrombocytopenia.

Among the subset of subjects with persistent cytopenias defined above, a listing of time to resolution to grade 2 or below will be provided. The time from 1st T-cell infusion to the first reduction to Grade 2 after Week 5 will be reported. Resolution to Grade 2 may occur within the Week 5 visit window if multiple laboratory assessments are collected. If the participant did not achieve resolution to grade 2 at the last laboratory assessment, they will be censored at the last laboratory assessment. If a subject is censored, the result for unresolved cytopenia will be displayed (death, interventional phase follow-up ended, cytopenia ongoing). Cytopenias may worsen to Grade 3 again at a later point in time. Recurrences are not captured in this analysis.

4.5.2.1. Analysis of Liver Function Test (LFT)

A listing of subjects with liver monitoring/stopping event reporting will be provided.

A listing of subjects meeting hepatobiliary laboratory abnormalities aligned with the Protocol liver monitoring criteria will be provided. The intent of this listing is to identify subjects, in particular possible Hy's Law subjects, for clinical review.

A liver monitoring level 2 event profile will be provided for subjects who met level 2 monitoring criteria, and the event did not result in stopping study treatment. An additional liver stopping event profile will be provided to facilitate medical review of subjects with liver stopping events.

4.5.3. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified.

4.5.3.1. Deaths

All deaths will be summarized based on the number and percentage of participants on the ITT and mITT analysis sets. This summary will classify participants by time of death relative to the date of 1st T-cell infusion as a categorical (>30 days or ≤30 days) and primary cause of death displayed in the order it appears in the CRF.

An individual subject profile listing for participants who died will be generated, which will include fatal SAE(s).

4.5.3.2. ECOG Performance Status

A listing of the subject's ECOG score (0,1,2,3,4-5) will be provided.

4.5.3.3. ECG

A listing of participants who had normal and abnormal (clinically significant and not clinically significant) ECG findings will be presented. A listing of ECG values for all participants will also be presented. The categories of potential clinical importance for ECG values (see Section 6.2.2.2) will not be presented. Instead, these thresholds will be provided in the listing footnotes for reference.

4.5.3.4. Vital Signs

A listing of all vital signs (heart rate, diastolic blood pressure, systolic blood pressure, temperature, pulse oximetry) will be presented. The categories of potential clinical importance for all vital signs (see Section 6.2.2.3) will not be presented. Instead, these thresholds will be provided in the listing footnotes for reference.

Pregnancy

The investigator will report all pregnancies immediately to the Sponsor. If participants or participants' partner become pregnant while on the study, the information will be included in the narratives. A supportive listing of those subjects or partners of subjects that became pregnant during the study will be produced to support the case narratives.

4.5.3.5. Cardiovascular Events

As required by the GSK Global Safety Board, profile displays for the following nine cardiovascular events will be produced if an event occurs and the appropriate CV event form has been completed in the CRF.

- Arrythmias
- Congestive Heart Failure
- Cerebrovascular Events Stroke (CVA) and Transient Ischemic Attack (TIA)
- Deep Vein Thrombosis (DVT)/Pulmonary Embolism (PE)
- Unstable Angina / Myocardial Infarction
- Peripheral Arterial Thromboembolism
- Pulmonary Hypertension
- Revascularisation
- Valvulopathy

4.5.3.6. CCI [redacted] and Integration Site Analysis

CCI [redacted]

For any participant who has greater than 1% gene marked PBMCs at least 1 year or beyond post-infusion, Integration Site Analysis will be performed on PBMCs to assess clonality. Insertional oncogenesis will be evaluated if any clones represent >20% of the total.

For subjects that undergo Integration Site Analysis, a supportive listing will be provided to report, if data are available. Two diversity indices, Shannon diversity index and Gini index (GI), will be reported in the data listing. Shannon diversity is a measurement that represents the

uncertainty about the identity of a single species within a population. Therefore, the greater number of unique species within a population, the less certain the measure is of the "identity" of any one species, resulting in a higher value of Shannon diversity. Likewise, the less complex the population, the lower the value of Shannon diversity. When Shannon diversity is calculated it takes into account the number of distinct clones ("species") as well as the abundance of each clone. A low value of Shannon diversity has been previously reported in the literature as being associated with clonal expansion and a reduction in overall clonal diversity (Braun, 2014).

The GI is a measure for detecting inequality in the distribution of clone sizes. A GI value of 0 indicates complete equality across the population i.e., all clones have the same abundance. A value of 1 would indicate complete inequality i.e., one clone is much more abundant than the others. Therefore, as GI approaches 1 this indicates that one clone is highly abundant. It has previously been used for insertion site analysis (as the oligoclonality index, Gillet, 2011) to describe clonal populations where the dominance of a single clone is seen (e.g., leukaemia).

4.5.4. Extent of Exposure

A listing of study treatment based on mITT population will be provided, including total number of T-cell infusion bags, T-cell infusion bag start and stop date, route of synthesis and whether it was a split dose, total cell dose, average vector copy number per cell in the cell product, total number of transduced cells and percent of cells transduced. The listing will also include information pertaining partially infused bag(s) and reason(s) for pausing or discontinuing infusion. The total number of transduced T-cells will be summarized for the mITT population using mean, standard deviation, median and range. Also, the total number of transduced T-cells will be categorized into:

- $<0.1 \times 10^9$
- $\geq 0.1 \times 10^9$ to $\leq 0.8 \times 10^9$ (i.e., lower planned T-cell dose range)
- $>0.8 \times 10^9$ to $<1 \times 10^9$
- $\geq 1 \times 10^9$ to $\leq 8 \times 10^9$ (i.e., higher planned T-cell dose range)
- $>8 \times 10^9$

All dose administration data for T-cell therapy and lymphodepletion chemotherapy will be presented in a data listing based on the ITT population. Supportive listings to report dose reductions, delay, stoppages, interruption, and dose escalation of lymphodepletion chemotherapy, as well as reasons for these, may be provided in addition to cumulative dose, if appropriate. Additional displays may be provided if several participants require reductions.

As detailed in the respective substudy Protocol Schedule of Activities, lymphodepletion doses are to be delivered on consecutive days -7, -6, -5 and -4. The duration of lymphodepletion dose delay will be calculated for lymphodepletion doses subsequent to the first lymphodepletion dose. Lymphodepletion dose delay is defined as the difference between the expected start date of dose and actual start date of dose (i.e., actual start date of dose - expected start date of dose), where the expected start date of dose = actual start date of previous dose + 1.

CCI [redacted]

4.5.6. Immunogenicity

Serum samples for determination of antibodies against NY-ESO-1 and LAGE-1a specific T-cells are taken from all participants for anti-drug antibody (ADA) testing.

The anti-drug antibody results (positive or negative), including titers, will be reported for all participants in a data listing if data are available.

4.6. Other Analyses

4.6.1. Subgroup analyses

As of Core SAP Amendment 2: Due to early termination of all substudies, subgroup analyses will not be conducted.

4.6.2. Other variables and/or parameters

Not Applicable

4.7. Interim Analyses

As of Core SAP Amendment 2: Protocol-planned analyses include an Interim, Primary and Final analysis. However, due to the early termination of all substudies, only a final analysis will be conducted.

4.7.1. Interim Analysis

Refer to the substudy-specific SAP for details.

4.7.2. Primary Analysis

The primary analyses will be performed for each cohort (in each substudy) after the completion of the following sequential steps:

1. Enrolment to the cohort is complete and all enrolled participants have received T-cell infusion, and
2. At least 80% of participants dosed at the RP2D (part of the mITT) have confirmed disease progression or died or were withdrawn or lost to follow-up from the substudy, and
3. All remaining T-cell infused participants (mITT), including those treated at non-RP2D dose have completed 2 post baseline disease assessments since T-cell infusion or have confirmed disease progression or died or were withdrawn or lost-follow-up from the substudy.
4. All required database cleaning activities have been completed and database release (DBR) and database freeze (DBF) has been declared by Data Management.

More details if applicable will be provided in the substudy-specific SAPs.

4.7.3. Final Analysis

The final analyses will be performed for each cohort (in each substudy) after the completion of the following sequential steps:

1. Enrolment to the cohort is complete and all enrolled participants have received T-cell infusion, and
2. All participants have completed the substudy.

- Completed the substudy for each cohort is defined as when all enrolled participants in the cohort have transferred to the separate LTFU protocol, declined consenting to the LTFU protocol, completed LTFU requirement in the applicable study, have been lost to follow-up, or withdrawn or died.

3. All required database cleaning activities have been completed and database release (DBR) and database lock (DBL) has been declared by Data Management.

More details if applicable will be provided in the substudy-specific SAPs.

4.8. Changes to Protocol Defined Analyses

As of Core SAP Amendment 2: As a result of the early termination of all substudies the following changes to the protocol defined analyses have been made:

- Due to early termination of all substudies prior to establishing RP2D, the interim analyses described in the substudy-specific Protocols (Amendment 4) Section 10.5.1 will not be conducted, as described in Section 4.7. The Primary analysis will also not be conducted.
- Safety summaries will be based on the DLT Evaluable, Lymphodepletion, ITT and mITT as applicable (note that the Core Protocol Amendment 4 Section 10.5.2.1 states that all safety analyses will be performed on the ITT and mITT populations).
- Serially collected (exploratory) safety endpoints (e.g., laboratory tests, vital signs, ECGs) will in general be listed and not summarised, with full details given in this document.
- Summaries of Characteristics of AESIs will not be presented but instead will be listed.

5. SAMPLE SIZE DETERMINATION

Refer to substudy-specific SAPs for the detail.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

Unless otherwise specified, the analyses specified in this Section will be based on the ITT population.

6.1.1. Participant Disposition

A summary of the number of participants in each of the analysis sets described in Section 3 will be provided by both planned and actual treatment (see Table 1). A listing of participants excluded from any analysis sets will also be provided, based on the Screened population.

Number of participants will be summarized by country and study site ID using the enrolled and mITT populations.

A summary and listing of screening status and screen failures will be provided using the Screened population and will be summarised separately for target expression screening status and leukapheresis eligibility screening status. Target expression screening will be reported for all substudies combined i.e., not separately for each substudy. Where applicable, leukapheresis eligibility screening failures will be presented by indication. If indication data for target expression screening are available then target expression screen failures will also be presented by indication, where applicable. An additional summary of screen failures by each subject's HLA or Antigen results will be presented. Per GSK reporting standards, participants who were rescreened will appear once in these displays according to their final status.

A summary of interventional phase status (see Section 6.2.3) will be produced using both the Lymphodepletion and mITT analysis sets, with reasons for completion and study withdrawal summarized in the order they are displayed in the CRF. Participant status will be displayed with the categories and subcategories: Completed study, Ongoing, or Withdrawn (reasons from the CRF).

Overall study disposition, including long term follow up, will also be summarized for the ITT and mITT population. An additional table will be created to summarize the number of participants in the ITT population who did and did not receive T-cell infusion, as well as the reason for not receiving T-cell infusion. A supportive listing of reason for study withdrawal will be created, using the ITT population.

6.1.2. Demographic and Baseline Characteristics

Demographic characteristics including race, age, gender, ethnicity, height, body weight at leukapheresis eligibility screening, body mass index (kg/m^2), and body surface area (BSA) per the DuBois & Dubois formula will be summarized with descriptive statistics. Age, height, weight, BMI and BSA will be summarised using mean, standard deviation, minimum, median, and maximum; gender, ethnicity and race will be summarized using number and percentage. In addition, age will also be categorized and summarized by <18, 18-64, 65-84 and ≥85 using EudraCT and also by GSK IDSL standard as ≤18, 19-64, ≥65. The summary of demographic characteristics will be produced on the ITT and mITT analysis sets, with the listing on the ITT analysis set.

A supportive summary of age ranges on the enrolled analysis set and a listing of race on the ITT will also be produced.

Disease characteristics at initial diagnosis and screening will be listed as collected in the CRF on the ITT analysis set. Disease characteristics at screening will be summarized on the mITT analysis set. The summary and listings will include primary tumor type under study, disease stage at initial diagnosis and screening, time since initial diagnosis (months), time since last recurrence (months), extent of disease at screening, TNM (tumor, node, metastasis) staging, visceral/non-visceral disease, progression on therapy (yes/no). Also, a summary of HLA status (including the number and phenotype of HLA alleles positive) and NY-ESO-1/LAGE-1a status (by indication and including a descriptive summary of the NY-ESO-1 Expression H-score and P-score), LAGE-1a expression and NY-ESO-1 tumor site and anatomical location will be produced. In addition to those stated above, date of initial diagnosis and date of last recurrence for the primary tumor, and date of blood collection and biopsy for antigen testing will be listed. For detail on substudy specific disease characteristics refer to the substudy SAPs.
An additional disease characteristics at screening table will be summarized on the Screened analysis set, presenting only the HLA status/phenotype and NY-ESO-1 status/expression information described above.

A listing of metastatic disease at screening will be provided based on the ITT analysis set. Refer to Section 6.2.1 for time since initial diagnosis, time since last recurrence and time since diagnosis of metastatic disease derivation rules.

Past medical conditions and current medical conditions as of screening will be listed using the ITT analysis set.

6.1.3. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarized on both the ITT and mITT analysis sets and listed on the ITT analysis set.

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to freezing the database to ensure all important deviations (where possible without knowing the study intervention details) are captured and categorised in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

A separate listing of all inclusion/exclusion criteria deviations will also be provided using the Screened population. This listing will be based on data as recorded on the Eligibility page of the eCRF.

6.1.4. Prior and Concomitant Medications

Prior and concomitant medications are as defined in Section 6.2.3.2.

Concomitant medications will be coded using both the GSK Drug and WHO Drug dictionaries. However, the summary (mITT analysis set) and listing (ITT analysis set) will be based on GSK

Drug dictionary only. The summary of concomitant medications will be provided by ingredient i.e., multi-ingredient medications will be summarized for each individual ingredient rather than a combination of ingredients. The summary will be created using ingredient base names, i.e., ingredients with the same base name but different salt will appear under one base name in the summary. Anatomical Therapeutic Chemical (ATC) classifications will not appear in the summary.

In the summary of concomitant medications, each participant is counted once within each unique ingredient. For example, if a participant takes Amoxycillin on two separate occasions, the participant is counted only once under the ingredient 'Amoxycillin'. In the summary of concomitant medications, the ingredients will be summarized by the base only.

Blood products and blood supportive care products will be listed separately from concomitant medications .

6.1.5. Anti-cancer therapies

Anti-cancer therapy includes systemic therapy (coded using the GSK Drug coding dictionary), radiotherapy, and cancer-related surgery.

Anti-cancer therapies will be classified into prior, bridging, and on-study phases as described below. Therapies will be identified using the corresponding CRF pages.

Type of Therapy	Definition
Prior	Prior therapy is defined as any line of systemic therapy, radiotherapy, and cancer-related surgeries given before start of lymphodepletion. Note: Intermediate systemic therapies are included in this definition, supportive chemotherapy is excluded from this definition.
Bridging	Bridging therapy is defined as prior systemic therapy given between leukapheresis and start of lymphodepletion to maintain disease control (not considered a line of therapy). Note: This definition captures supportive chemotherapies as bridging therapies.
On-Study/Follow-up	On-study and follow-up therapies are defined as systemic therapy, radiotherapy, or cancer related surgery given on or after the start of lymphodepletion.

A listing of systemic therapy will be provided and labelled as prior, bridging, or on-study. Radiotherapies and cancer-related surgeries will be listed separately and labelled as prior or on-study. Both listings will be based on the ITT analysis set.

6.1.5.1. Prior Anti-cancer therapy

A summary of the number of prior systemic anti-cancer therapy regimens in the advanced/metastatic setting (as reported in the Intent field of the *prior anti-cancer therapy eCRF page*), the number of prior radiotherapy regimens and the best response to the most

recent prior therapy will be provided. Prior therapy and bridging therapy will be coded using the GSK Drug coding dictionary.

Systemic anti-cancer therapy regimens initiated between leukapheresis and lymphodepletion as reported in the *intermediate and supportive therapy eCRF page* are categorized as either bridging (supportive chemotherapy regimens administered to maintain/stabilize the participant until T-cell infusion) or full lines of therapy (intermediate standard of care regimens administered with the intent of disease effect). Full lines are summarized as prior therapies – supportive chemotherapies are not considered in the number of prior lines.

6.1.5.2. On-study Anti-cancer therapy

On-study systemic therapies will be coded using GSK Drug coding dictionary.

6.1.6. Additional Analyses Due to the COVID-19 Pandemic

6.1.6.1. Participant Disposition

A country level listing of the dates of the COVID-19 Pandemic measures will be produced. For the definition of the phases of the COVID-19 pandemic measures see Section 6.2.3.3.

The 'Summary of Subject Status and Subject Disposition for the Study Conclusion Record' will be repeated, with the reason for withdrawal/discontinuation categorized as due to the COVID-19 pandemic, or non-due to the COVID-19 pandemic based on information collected on the COVID-19 Pandemic Study Impact form. The summaries will be based on GSK Core Data Standards.

6.1.6.2. Protocol Deviations

In addition to the overall summary of important protocol deviations, a separate summary will be produced for important protocol deviations related to COVID-19 based on the ITT analysis set. Non-important PDs due to the COVID-19 pandemic will be listed using the ITT analysis set.

Visits and assessments missed due to the COVID-19 pandemic, together with visits conducted remotely, will be listed using the ITT analysis set.

6.1.6.3. Additional Displays for Participants with COVID-19 Infection

A participant is defined as having a suspected, probable, or confirmed COVID-19 infection during the study if the answer is "Confirmed", "Probable" or "Suspected" to the case diagnosis question from the COVID-19 coronavirus infection assessment eCRF. A comprehensive profile listing of COVID-19 assessments, symptom assessments and epidemiological factors (travel to high-risk countries, health care contact, etc) for subjects with COVID-19 adverse events will be provided.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Derived and transformed data

6.2.1.1. General

Change from Baseline
Change from Baseline = Post-Baseline Visit Value – Baseline % Change from Baseline= 100 x (Post-Baseline Visit Value – Baseline) / Baseline Maximum Increase/Decrease from Baseline = maximum (Increase/Decrease from Baseline) If either the Baseline or Post-Baseline Visit Value is missing, Change from Baseline and % Change from Baseline are set to missing
Date of Response
For post-baseline disease assessments, the date of response (PR, CR) is assigned to the latest date of tumor assessments; for other response categories (SD, NE, PD), the date of response is assigned to the earliest date of disease assessments.
Date of New Anti-Cancer Therapy
Derived as the earliest date of new on study anti-cancer therapy, radiotherapy (where applicable, excluding palliative radiotherapy) or cancer-related surgical procedure (where applicable). Missing or partial dates will be imputed for derivation of new anti-cancer therapy following rules specified in Section 6.2.7.

6.2.1.2. Study Population

Age
For participants with a T-cell infusion date, age is derived using 1st T-cell infusion date as the reference date. For ITT participants without a T-cell Infusion date, date of eligibility for apheresis is used as the reference date.
BMI
Weight (kg) at baseline / (Height (m) at leukapheresis eligibility screening)^2
Body Surface Area (BSA) (m2) DuBois & DuBois Formula
0.007184 * Height(cm)$^{0.725}$ × Weight(kg)$^{0.425}$
Time since Initial Diagnosis to Screening
Calculated as the number of Months from the Date of Initial Diagnosis: Leukapheresis Eligibility Screening Visit Date = Missing → Elapsed Time = Missing Date of Initial Diagnosis = Completely/partially Missing → Elapsed Time = Missing Otherwise → Elapsed Time = (Leukapheresis Eligibility Screening Visit Date – Date of Initial Diagnosis + 1) /30.4375
Time since Last Recurrence to Screening
Calculated as the number of Months from the Date of Last Recurrence: Leukapheresis Eligibility Screening Visit Date = Missing → Elapsed Time = Missing Date of Last Recurrence = Completely/partially Missing → Elapsed Time = Missing Otherwise → Elapsed Time = (Leukapheresis Eligibility Screening Visit Date – Date of Last Recurrence+ 1) /30.4375
Time since Metastatic Disease to Screening
Calculated as the number of Months from the Date of Metastatic Disease was first diagnosed: Leukapheresis Eligibility Screening Visit Date = Missing → Elapsed Time = Missing Date of Metastatic Disease was first diagnosed = Completely/partially Missing → Elapsed Time = Missing Otherwise → Elapsed Time = (Leukapheresis Eligibility Screening Visit Date – Date of Metastatic Disease was first diagnosed + 1) /30.4375

6.2.1.3. Safety

Adverse Events
Duration of AE
Calculated as the number of days from AE Start Date to AE Stop Date: AE Start Date = Missing → Elapsed Time = Missing AE Stop Date = Missing → Elapsed Time = Missing Otherwise → Elapsed Time = AE Stop Date – AE Start Date + 1 Imputed dates will not be used to calculate AE duration
Clinical Laboratory Parameters
If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<=' or '=>' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value. Example 1: 2 significant digits = '<= x' becomes x – 0.01 Example 2: 1 significant digit = '=> x' becomes x + 0.1 Example 3: 0 significant digits = '<=x' becomes x - 1

6.2.1.4. Efficacy

Date of Last Known Contact
• Last date in all SDTM domains • If a patient died, the last contact date should be the death date. • Dates after date of death will be excluded. • Specific SDTM domains and variables will be excluded from the date of last known contact derivation. This also includes excluding any other external source data dates as seen necessary. For more details refer to the OPS. • Partial and missing dates will not be imputed for the purpose of deriving date of last contact.

6.2.2. Criteria for Potential Clinical Importance

6.2.2.1. Laboratory values

To identify laboratory values of potential clinical importance, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v5.0 or higher) will be used to assign grades for laboratory parameters including clinical chemistry, hematology, liver function tests, thyroid function tests, pancreatic enzyme tests, QTc (Bazett's or Fridericia's) values, and vital signs (heart rate, blood pressure, temperature, pulse oximetry).

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern. The laboratory reference ranges will be provided on the

listings of laboratory data. Clinical laboratory test results outside of the reference range will be flagged in the listings.

To identify laboratory values of potential clinical importance, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v5.0 or higher) will be used to assign grades to the relevant laboratory parameters. NCI-CTCAE v5.0 can be found at http://ctep.cancer.gov/reporting/ctc.html.

For laboratory data which are not listed in the NCI-CTCAE v5.0 or higher, a summary of values outside the normal range will be provided.

6.2.2.2. ECG values

To identify QTc (Bazett's or Fridericia's) values of potential clinical importance, NCI-CTCAE v5.0 or higher will be used to assign grades (see adverse event 'Electrocardiogram QT corrected interval prolonged'). The eCRF collects either QTcB or QTcF. The clinical concern range for QRS Duration is approximately based on the limits determined by Ramirez, 2011.

The following criteria indicates electrocardiogram (ECG) values that are values of potential clinical importance:

ECG Parameter	Units	Potential Clinical Importance (PCI) Range
Absolute QTcF [QTcB] interval	Msec	≥450 to ≤480 (Grade 1) ≥481 to ≤500 (Grade 2) ≥501 (Grade 3)
Increase from baseline QTcF [QTcB]	Msec	Increase of ≥31 to ≤60 Increase of >60

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
QRS Duration	Msec	<70	>105

6.2.2.3. Vital Signs

To identify values of potential clinical importance, NCI-CTCAE v5.0 or higher will be used to indicate categories that align with the grades for 'Hypothermia', 'Fever', 'Sinus Bradycardia' / 'Sinus Tachycardia' and 'Hypoxia'.

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Heart Rate	bpm	<60	>100
Temperature	Degrees C	≤35	≥38
Pulse Oximetry	%	<88	N/A

To identify values of potential clinical importance for Increase from Baseline Systolic and Diastolic Blood Pressure, NCI-CTCAE v5.0 or higher will be used, aligning with the grades for 'Hypertension'.

Vital Sign Parameter	Units	Potential Clinical Importance (PCI) Range

Increase from baseline Systolic Blood Pressure	mmHg	≥120 to <140 (Grade 1) ≥140 to <160 (Grade 2) ≥160 (Grade 3)
Increase from baseline Diastolic Blood Pressure	mmHg	≥80 to <90 (Grade 1) ≥90 to <100 (Grade 2) ≥100 (Grade 3)

For Hypotension, decrease from baseline for diastolic and systolic blood pressure will be presented using the thresholds defined below.

Vital Sign Parameter	Units	Potential Clinical Importance (PCI) Range
Decrease from baseline Systolic Blood Pressure	mmHg	≥80 to <100 (Low) <80 (Very Low)
Decrease from baseline Diastolic Blood Pressure	mmHg	≥60 to <70 (Low) <60 (Very Low)

6.2.3. Study Phase

Assessments and events will be classified according to the time of occurrence relative to the study intervention period.

6.2.3.1. Study Phases for Disposition

Study Phase	Definition
Leukapheresis Phase	First Day of Leukapheresis ≤ Date < First Day of Lymphodepletion
Interventional Phase - (Lymphodepletion)	First Day of Lymphodepletion Date < 1st T-cell Infusion (Day 1)
Interventional Phase - (Post T-cell Infusion)	1st T-cell Infusion (Day 1) ≤ Date ≤ Start of Follow-up Phase (Date of Confirmed PD / Withdrawal from Interventional Phase)
Follow-up Phase	Start of Follow-up Phase (Date of Confirmed PD / Withdrawal from Interventional Phase) < Date

6.2.3.2. Study Phases for Concomitant Medication and Blood Product

Study Phase	Definition
Prior	If lymphodepletion start date is missing, i.e., for participants that did not receive lymphodepletion. Else if end date of medication is not missing and end date < lymphodepletion start date. Else if start date of blood product is not missing and start date < lymphodepletion start date.
Concomitant	Any medication or blood product that is not Prior.

NOTES:

- Please refer to Section 6.2.7: Reporting Standards for Missing Data for handling of missing and partial

dates for concomitant medication. Use the rules in this table if concomitant medication date is missing.

6.2.3.3. Phases of COVID-19 Pandemic Measures

Pandemic measures began in different countries at different times. A dataset containing the date when pandemic measures began, as determined by the GSK country Issue Management Teams (IMT), and available within the HARP reporting environment (arcomn folder), will be used to determine the start date of pandemic measures within each country. A copy of this dataset will be taken at the time of database freeze (DBF).

Adverse events will be summarised according to whether the onset date was before or after the start of the COVID-19 pandemic measures. If the AE onset date is missing, then the AE will be assumed to be After pandemic measures phase.

Pandemic Measures Phase	Definition
Before	AE onset date < pandemic measures start date
After	Pandemic measures start date ≤ AE onset date

6.2.3.4. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent (T-cell Phase)	• If AE onset date is equal to T-cell infusion start date (AE start date = T-cell infusion start date): 1. If missing AE onset time and missing T-cell infusion time 2. If non-missing AE onset time and missing T-cell infusion time 3. If missing AE onset time and non-missing T-cell infusion time: a. If AE end date and time are non-missing: ▪ If AE end date = T-cell infusion start date and AE end time is on or after T-cell infusion start time (AE End Time >= T-cell infusion start time) b. If AE end date is non-missing and is after T-cell infusion start date c. If AE end date and/or time is missing 4. If non-missing AE onset time and non-missing T-cell infusion time: a. If AE onset time >= T-cell infusion time • Else if AE onset date is not equal to T-cell infusion start date (AE start Date ≠ T-cell infusion start date) and AE onset date is after T-cell infusion start date (AE Start Date ≥ T-cell Infusion Start Date), OR if AE onset date is before T-cell infusion start date, but the AE increases in grade after T-cell infusion (with respect to maximum grade of the AE before T-cell infusion. • . • If AE onset date is missing and AE end date is either missing or on or after T-cell infusion start date. ○ If T-cell infusion date is missing i.e., the patient did not receive T-cell infusion, then the AE will not be classified as Treatment Emergent.
Lymphodepletion Emergent (Lymphodepletion Phase)	• If AE onset date is equal to Lymphodepletion start date (AE Start Date = Lymphodepletion Start Date): 1. If missing AE onset time and missing Lymphodepletion start time 2. If non-missing AE onset time and missing Lymphodepletion start

Flag	Definition
	time 3. If missing AE onset time and non-missing Lymphodepletion start time: a. If AE end date and time are non-missing: ▪ If AE end date = Lymphodepletion start date and AE end time is on or after Lymphodepletion start time (AE End Time >= Lymphodepletion Start Time) b. If AE end date is non-missing and is after Lymphodepletion start date c. If AE end date and/or time is missing 4. If non-missing AE onset time and non-missing Lymphodepletion start time: a. If AE Onset Time >= Lymphodepletion Start Time • Else if AE onset date is not equal to Lymphodepletion start date (AE start Date ≠ Lymphodepletion start date) and: ○ AE onset date is after Lymphodepletion start date and before T-cell infusion start date (Lymphodepletion Start Date < AE Start Date < T-cell Infusion Start Date), OR ○ AE onset date is after Lymphodepletion start date and T-cell infusion date is missing i.e., the participant did not receive the T-cell infusion, OR ○ AE onset date is before Lymphodepletion start date and before T-cell infusion start date, but the AE increases in grade after Lymphodepletion start date (with respect to maximum grade of the AE before Lymphodepletion). • If AE onset date is missing and AE end date is either missing or after lymphodepletion start date. ○ If lymphodepletion date is missing i.e., the participant did not receive lymphodepletion, then the AE cannot be classified as Lymphodepletion Emergent.

Flag	Definition
Pre-Lymphodepletion Emergent (Pre-Lymphodepletion Phase)	• If AE onset date is equal to lymphodepletion start date (AE Start Date = Lymphodepletion Start Date) 1. If missing AE onset time and non-missing Lymphodepletion start time: a. If AE end date and time are non-missing: ▪ If AE end date = Lymphodepletion start date and AE end time is before the Lymphodepletion start time (AE End Time < Lymphodepletion Start Time) 2. If non-missing AE onset time and non-missing Lymphodepletion start time: a. If AE Onset Time < Lymphodepletion Start Time • Else if AE onset date is not equal to Lymphodepletion start date (AE start Date ≠ Lymphodepletion start date) and: ○ AE onset date is before Lymphodepletion start date (AE Start Date < Lymphodepletion Start Date), OR ○ Lymphodepletion start date and T-cell infusion start date is missing i.e., the participant did not receive Lymphodepletion or T-cell infusion. • If AE onset date is missing and the AE end date is before the Lymphodepletion start date. • If both the AE onset and end date are missing.

NOTES:

- Time of study treatment dosing and start[/stop] time of AEs should be considered, if collected.
- T-cell infusion start date is in reference to the 1st T-cell infusion throughout these derivations.
- AEs to be used in the derivation is the overall AE event unless the AE grade changes across AE phases (as defined in Table 7) in this case the derivation is based on the AE segment (that had the grade change) of the same overall AE.

6.2.4. Study Day and Reference Dates

The reference date is the study intervention start date (1st T-cell infusion date) and will be used to calculate study day.

The study day is calculated as below:

- *Assessment Date = Missing → Study Day = Missing*
- *Assessment Date < Reference Date → Study Day = Assessment Date – Ref Date*
- *Assessment Date ≥ Reference Date → Study Day = Assessment Date – Ref Date + 1*

6.2.5. Assessment Window

No assessment windows will be applied.

For data summaries by visit, scheduled visits with nominal visit description as well as the worst case post baseline will be displayed. Unscheduled visits will not be displayed or slotted into a visit window but will be included in the derivation of worst case post-baseline assessment. All unscheduled visits will be displayed in the listing.

6.2.6. Multiple measurements at One Analysis Time Point

When multiple assessments are taken at one analysis time point, the mean of the measurements will be calculated first, and summary statistics will be based on the calculated mean. This will apply to both baseline and post-baseline assessments.

For character variables, if multiple assessments on different days are reported for the same scheduled assessment, then the worst case assessment for that scheduled assessment will be analysed.

For laboratory tests on a study day, if more than one assessment is taken on the same day from the same type of lab, the worst case will be used.

Participants having both High and Low values for normal ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of “Any visit post-baseline” row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.

6.2.7. Handling of Partial Dates

Imputed partial dates may not be used to derive study day, duration, or elapsed time variables. In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset. Refer to the OPS for more details on partial dates.

Imputed dates will not be displayed in listings. However, where necessary, display macros may impute dates as temporary variables for the purpose of sorting data in listings only. In addition, partial dates may be imputed for ‘slotting’ data to study time periods or for specific analysis purposes as outlined below.

The partial date imputation will follow ADaM conventions. The ADaM approach is to populate the numeric date variables with the imputed date and add a flag variable to the dataset that indicates the level of imputation.

The flag variable can contain the values: blank, 'D', 'M', 'Y'.

blank: indicates that no imputation was done

D='Day': indicates that the day portion of the date is imputed

M='Month': indicates that the month and day portions of the date are imputed

Y='Year': indicates that the entire date (year, month, and day) is imputed

Example of date variables:

XYZD_ - character date variable

XYZDT - numeric date variable

XYZDTFL - flag variable

Details on imputing partial dates for specific datasets are outlined below

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>Adverse Events</td><td>

Imputations in the adverse events dataset are used for slotting events to the appropriate study time periods and for sorting in data listings.
This includes identifying an AESI as first or last occurrence.
Partial dates for AE recorded in the CRF will be imputed using the following conventions:

<table>
<tr><td>Missing AE start day</td><td>

If lymphodepletion start date is missing (i.e., participant did not start lymphodepletion), then set AE start date = 1st of month.
Else if lymphodepletion start date is not missing and T-cell infusion date is missing (i.e., participant did not have T-cell infusion)

If month and year of AE start date = month and year of lymphodepletion start date, then

If AE stop date contains a full date and AE stop date is earlier than lymphodepletion start date, then set AE start date= 1st of month.
Else set AE start date = lymphodepletion start date.

Else set AE start date =1st of the month

Else if lymphodepletion start date is not missing and T-cell infusion date is not missing

If month and year of AE start date = month and year of both T-cell infusion start date and lymphodepletion start date, then

If AE stop date contains a full date and stop date is earlier than lymphodepletion start date, then set AE start date=1st of the month
Else if AE stop date contains a full date and stop date is earlier than T-cell start date but later than lymphodepletion start date, then set AE start date=Lymphodepletion start date
Else set AE start date=T-cell infusion start date

If month and year of AE start date = month of only T-cell infusion start date, then

If AE stop date contains a full date and AE stop date is earlier than T-cell infusion, then set AE start date=1st of the month
Else set AE start date=T-cell infusion start date

If month and year of AE start date = month and

</td></tr>
</table>
</td></tr>
</table>

Element	Reporting Detail	
		year of only lymphodepletion start date, then ▪ If AE stop date contains a full date and AE stop date is earlier than lymphodepletion, then set AE start date=1st of the month ▪ Else set AE start date=lymphodepletion start date o Else set AE start date =1st of the month
	Missing AE start day and month	• If lymphodepletion start date is missing (i.e., participant did not start lymphodepletion), then set start date = January 1st • Else if lymphodepletion start date is not missing and T-cell infusion date is missing (i.e., participant did not have T-cell infusion) o If year of start date = year of lymphodepletion start date, then ▪ If stop date contains a full date and stop date is earlier than lymphodepletion start date, then set start date= January 1st ▪ Else set start date = lymphodepletion start date. o Else set start date =January 1st • Else if lymphodepletion start date is not missing and T-cell infusion date is not missing o If year of start date = year of both T-cell infusion start date and lymphodepletion start date, then ▪ If stop date contains a full date and stop date is earlier than lymphodepletion start date, then set start date=January 1st ▪ Else if stop date contains a full date and stop date is earlier than T-cell start date but later than lymphodepletion start date, then set start date=Lymphodepletion start date ▪ Else set start date=T-cell infusion start date o If year of start date = year of only T-cell infusion start date, then ▪ If stop date contains a full date and stop date is earlier than T-cell infusion, then set start date=January 1st ▪ Else set start date=T-cell infusion start date o If year of start date = year of only

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>lymphodepletion start date, then
▪ If stop date contains a full date and stop date is earlier lymphodepletion, then set start date=January 1st
▪ Else set start date=lymphodepletion start date
o Else set start date =January 1st</td></tr>
<tr><td>Missing AE stop day</td><td>Last day of the month will be used.</td></tr>
<tr><td>Missing AE stop day and month</td><td>No Imputation</td></tr>
<tr><td>Completely missing AE start/end date</td><td>No imputation. Consequently, time to onset and duration of such events will be missing.</td></tr>
</table>
</td></tr>
<tr><td>Concomitant Medications (CM)/ Medical History (MH)</td><td>
• These imputation rules will be used for classifying a medication as prior or concomitant
• Completely missing start dates will not be imputed
• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
<table>
<tr><td>Missing CM/MH start day</td><td>• If lymphodepletion start date is missing (i.e., participant did not receive lymphodepletion), then set CM/MH start date = 1st of month.
• Else if lymphodepletion start date is not missing:
o If month and year of CM/MH start date = month and year of lymphodepletion start date, then
▪ If CM/MH stop date contains a full date and stop date is earlier than lymphodepletion start date, then set CM/MH start date= 1st of month.
▪ Else set CM/MH start date = lymphodepletion start date.
o Else set CM/MH start date=1st of the month.</td></tr>
<tr><td>Missing CM/MH start day and month</td><td>• If lymphodepletion start date is missing (i.e., participant did not receive lymphodepletion), then set CM/MH start date = January 1st.
• Else if lymphodepletion start date is not missing:
o If year of CM/MH start date = year of lymphodepletion start date, then</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>

If CM/MH stop date contains a full date and stop date is earlier than lymphodepletion start date, then set CM/MH start date = January 1st.
Else set CM/MH start date = lymphodepletion start date.

Else set CM/MH start date=January 1st

</td></tr>
<tr><td>Missing CM/MH end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year)</td></tr>
<tr><td>Missing CM/MH end day and month</td><td>Earliest of (Dec 31st, date of last contact) will be used</td></tr>
<tr><td>Completely missing CM/MH start/end date</td><td>No imputation</td></tr>
</table>
</td></tr>
<tr><td>Surgical Procedures/ Radiotherapy</td><td>

No Imputation for completely missing dates
If partial date contains a year only set to January 1st.
If partial date contains a month and year set to the 1st of the month

</td></tr>
<tr><td>New On-Study Anti-Cancer Therapy/ Radiotherapy/ Surgical Procedures for Efficacy Evaluation (e.g., response rate, time to event)</td><td>
Start dates for on-study anti-cancer therapy, radiotherapy (where applicable), and surgical procedures (where applicable) will be imputed in order to define event and censoring rules for progression-free survival, response rate, or duration of response (i.e., start date for new anti-cancer therapy). Dates will only be imputed when a month and year are available, but the day is missing. The following rules will be used to impute the date when partial start dates are present on anti-cancer therapy, radiotherapy, and/or surgical procedures dataset[s]:

Completely missing start dates will remain missing, with no imputation applied
Partial start dates will be imputed using the following convention:
If both month and day are missing, no imputation will be applied
If only day is missing:

If the month of partial date is the same as the month of last dosing date, minimum of (T-cell infusion date + 1, last day of the month) will be used for the day
If the month of partial date is the same as the month of last disease assessment and the last disease assessment is PD, minimum of (last date of disease assessment + 1, last day of the month) will be used for the day
If both conditions above are met, the later date will be used for the day
Otherwise, a ‘01’ will be used for the day

Completely or partial missing end dates will remain missing, with no imputation applied;

</td></tr>
</table>

- T-cell infusion start date is in reference to the 1st T-cell infusion throughout these derivations.

6.2.8. Example Scenarios of Assignments of Confirmed Best Overall Response per iRECIST

Table 8 Derivation of iBOR when Confirmation is Required

Overall Response first timepoint	Overall Response subsequent timepoint	Best Overall Response
iCR	iCR	iCR
iCR	iPR	iSD provided minimum criteria for iSD duration met, otherwise, iUPD
iCR	iSD	iSD provided minimum criteria for iSD duration met, otherwise, iUPD
iCR	iUPD	iSD provided minimum criteria for iSD duration met, otherwise, iUPD
iCR	NE	iSD provided minimum criteria for iSD duration met, otherwise, NE
iPR	iCR	iPR
iPR	iPR	iPR
iPR	iSD	iSD provided minimum criteria for iSD duration met, otherwise, NE Note: if after iSD there is an iPR (i.e. iPR-iSD-iPR) then iBOR is iPR.
iPR	iUPD	iSD provided minimum criteria for iSD duration met, otherwise, iUPD
iPR	NE	iSD provided minimum criteria for iSD duration met, otherwise, NE
iSD	iCR	iSD provided minimum criteria for iSD duration met, otherwise, NE
iSD	iPR	iSD provided minimum criteria for iSD duration met, otherwise, NE Note: if prior to iSD there is a iPR (i.e. iPR-iSD-iPR) then iBOR is iPR.
iSD	iSD	iSD provided minimum criteria for iSD duration met, otherwise, NE
iSD	iUPD	iSD provided minimum criteria for iSD duration met, otherwise, iUPD
iSD	NE	iSD provided minimum criteria for iSD duration met, otherwise, NE
iUPD	iUPD	iUPD
iUPD	iCPD	iCPD
iUPD	NE	iUPD
NE	NE	NE

Note: For patients with non-target disease only at baseline, only iCR or non-iCR/non-iUPD can be assigned at each timepoint response but is not shown in the table for ease of presentation.

6.3. Appendix 3 Combined list and Focused list

6.3.1. Combined Preferred Terms

The combined terms for MedDRA Version 25.1 are listed below. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional combined terms, therefore the list of combined preferred terms will be based on the safety review team agreements in place at the time of reporting.

List of Preferred Terms to Be Combined	
The following synonyms will be combined under the PT as shown below. The combined term will be used when reporting AE data in tables by PT. Synonymous terms will be combined regardless of body system.	
Combined Term	**MedDRA Preferred Term (MedDRA 25.1)**
Anaemia/Red blood cell count decreased	Anaemia
	Red blood cell count decreased
Cytokine Release Syndrome (CRS)	Cytokine Release Syndrome
	Cytokine Storm
Acute GvHD - Skin	Acute graft versus host disease in skin
Acute GvHD - Gut (Liver and Intestine)	Acute graft versus host disease in liver
	Acute graft versus host disease in intestine
Acute GvHD - Other (Lung, Bone Marrow, not specified)	Acute graft versus host disease
	Acute graft versus host disease oral
Chronic GvHD - Skin	Chronic graft versus host disease in skin
Chronic GvHD - Gut (Liver and Intestine)	Chronic graft versus host disease in liver
	Chronic graft versus host disease in intestine
Chronic GvHD Other - (Lung, Bone Marrow, not specified)	Chronic graft versus host disease
	Chronic graft versus host disease in eye
	Chronic graft versus host disease oral
	Chronic graft versus host disease in lung
Unspecified GvHD - Skin	Graft versus host disease in skin
Unspecified GvHD - Gut (Liver and Intestine)	Graft versus host disease in liver
	Graft versus host disease in gastrointestinal tract
Unspecified GvHD - Other (Lung, Bone Marrow, not specified)	Graft versus host disease
	Graft versus host disease in eye

List of Preferred Terms to Be Combined	
The following synonyms will be combined under the PT as shown below. The combined term will be used when reporting AE data in tables by PT. Synonymous terms will be combined regardless of body system.	
Combined Term	**MedDRA Preferred Term (MedDRA 25.1)**
	Graft versus host disease in lung
	Prophylaxis against graft versus host disease
	Transfusion associated graft versus host disease
	Engraftment syndrome
Leukopenia/White blood cell decreased	White blood cell count decreased
	Leukopenia
Lymphopenia/Lymphocyte count decreased	Lymphocyte count decreased
	Lymphopenia
	CD4 lymphocytes decreased
	CD8 lymphocytes decreased
Neutropenia/Neutrophil count decreased	Neutrophil count decreased
	Neutropenia
Rash/Rash maculo-papular	Rash maculo-papular
	Rash
	Rash erythematous
Thrombocytopenia/Platelet count decreased	Platelet count decreased
	Thrombocytopenia
Immune effector cell-associated neurotoxicity syndrome (ICANS)	Immune effector cell-associated neurotoxicity syndrome
	Encephalopathy
Tachycardia	Tachycardia
	Sinus tachycardia

6.3.2. Focused list

AE of Special Interest (AESI)	MedDRA Preferred Term (MedDRA 25.1)
Guillain-Barre syndrome (Focused list)	Demyelinating polyneuropathy
	Guillain-Barre syndrome
	Peripheral sensorimotor neuropathy
	Subacute inflammatory demyelinating polyneuropathy
	Zika virus associated Guillain Barre syndrome
Source: MedDRA preferred terms from Guillain-Barre syndrome SMQ	

Graft versus Host Disease (Focused list)	Acute graft versus host disease in skin
	Acute graft versus host disease in liver
	Acute graft versus host disease in intestine
	Acute graft versus host disease
	Acute graft versus host disease oral
	Chronic graft versus host disease
	Chronic graft versus host disease in skin
	Chronic graft versus host disease in liver
	Chronic graft versus host disease in eye
	Chronic graft versus host disease oral
	Chronic graft versus host disease in lung
	Graft versus host disease in skin
	Graft versus host disease in liver
	Graft versus host disease in gastrointestinal tract
	Graft versus host disease
	Graft versus host disease in eye
	Graft versus host disease in lung
	Prophylaxis against graft versus host disease
	Transfusion associated graft versus host disease
	Engraftment syndrome
Source: MedDRA preferred terms considered associated with graft versus host disease	
Cytokine Release Syndrome (Focused list)	Cytokine release syndrome
	Cytokine storm
Source: MedDRA preferred terms considered associated with Cytokine release syndrome	

Immune Effector-Cell Associated Neurotoxicity Syndrome (ICANS) (Focused list)	Encephalopathy
	Immune effector cell-associated neurotoxicity syndrome
Sources: MedDRA preferred terms from Noninfectious encephalitis SMQ and Noninfectious encephalopathy/delirium (SMQ)	

Hematopoietic Cytopenias (including Pancytopenia and Aplastic Anemia) (Focused List)	Febrile bone marrow aplasia
	Autoimmune aplastic anaemia
	Aplastic anaemia
	Pancytopenia
	Bone marrow failure
	Full blood count abnormal
	Full blood count decreased
	Cytopenia
	Haemoglobin abnormal
	Hypoplastic anaemia
	Red blood cell count abnormal
	Haematocrit decreased
	Normochromic anaemia
	Normochromic normocytic anaemia
	Normocytic anaemia

	Reticulocyte count decreased
	Reticulocytopenia
	Haematocrit abnormal
	Haemoglobin decreased
	Anaemia macrocytic
	Erythropoiesis abnormal
	Anaemia
	Erythropenia
	Microcytic anaemia
	Red blood cell count decreased
	Neutropenic sepsis
	Band neutrophil percentage decreased
	Febrile neutropenia
	Granulocytopenia
	Neutropenia
	Neutrophil count abnormal
	Neutrophil percentage decreased
	Neutrophil count decreased
	Plateletcrit abnormal
	Plateletcrit decreased
	Acquired amegakaryocytic thrombocytopenia
	Megakaryocytes decreased
	Platelet production decreased
	Platelet count abnormal
	Platelet count decreased
	Platelet disorder
	Thrombocytopenia
	White blood cell count decreased
	Leukopenia
	Lymphocyte count decreased
	Lymphopenia
	CD4 lymphocytes decreased *
	CD8 lymphocytes decreased *
Sources: MedDRA preferred terms from Hematopoietic cytopenias SMQ and * MedDRA preferred terms considered associated with hematopoietic cytopenia	

Pneumonitis (Focused list)	Acute interstial pneumonitis
	Alveolar lung disease
	Alveolar proteinosis
	Alveolitis
	Alveolitis necrotising
	Autoimmune lung disease
	Bronchiolitis
	Brochiolitis obliterans syndrome
	Chronic graft versus host disease in the lung
	Combined pulmonary fibrosis and emphysema
	Confirmed e-cigarette or vaping product use associated lung injury
	Diffuse alveolar damage
	Eosinophilia myalgia syndrome
	Eosinophilic granulomatosis with polyangiitis

	Eosinophilic pneumonia
	Eosinophilic pneumonia acute
	Eosinophilic pneumonia chronic
	Hypersensitivity pneumonitis
	Idiopathic interstitial pneumonia
	Idiopathic pneumonia syndrome
	Idiopathic pulmonary fibrosis
	Immune-mediated lung disease
	Interstitial lung disease
	Low lung compliance
	Lung infiltration
	Lung opacity
	Necrotising bronchiolitis
	Obliterative bronchiolitis
	Pleuroparenchymal fibroelastosis
	Pneumonitis
	Probable e-cigarette or vaping product use associated lung injury
	Progressive massive fibrosis
	Pulmonary fibrosis
	Pulmonary necrosis
	Pulmonary radiation injury
	Pulmonary septal thickening
	Pulmonary toxicity
	Pulmonary vasculitis
	Radiation alveolitis
	Radiation bronchitis
	Radiation fibrosis - lung
	Radiation pneumonitis
	Rheumatoid arthritis-associated interstitial lung disease
	Small airways disease
	Transfusion-related acute lung injury
Source: MedDRA preferred terms considered associated with pneumonitis	

6.4. Appendix 4 Modified Toxicity Probability Interval 2 (mTPI-2)

As of Core SAP Amendment 2: Note that all substudies were terminated prior to the determination of RP2D, and so there will be no RP2D recommended based on the mTPI-2.

This study will employ an mTPI-2 [Guo, 2017] design. mTPI-2 is implemented within a formal Bayesian decision framework and is extension of the modified toxicity probability interval method (mTPI) [Ji, 2010]. mTPI-2 was chosen over mTPI because it is more preventative against overdosing and non-intuitive decision making, resulting in an improved decision Table that uses the same estimation procedure for the maximum tolerated dose as mTPI. Additionally, mTPI-2 preserves the simple and transparent nature of mTPI with Bayesian statistical modifications.

The choice of this design is validated by simulation results found in Section 6.4.1.

The three dosing intervals are associated with three different dose-escalation decisions. The under-dosing interval corresponds to a dose re-escalation (R), overdosing corresponds to a dose de-escalation (D), and proper dosing corresponds to staying at the current dose (S), found in

Table 9. In addition, decision U means that the current dose level is unacceptable because of high toxicity and should be excluded from the trial. Similar to mTPI, mTPI-2 employs a simple beta-binomial hierarchic model. Decision rules are based on calculating the unit probability mass (UPM) of three classifications of intervals corresponding to under dosing, proper dosing, and overdosing in terms of toxicity. We assume the target toxicity is defined as pT. The unit interval (0,1) is divided into equal length subintervals of size (e1+e2), such that the proper dosing interval is (pT – e1, pT + e2), the under-dosing intervals are all intervals contained in (0, pT – e1), and the overdosing intervals are all intervals contained in (pT + e2, 1), where e1 and e2 are small fractions to account for the uncertainty around the true target toxicity. If the proper dosing interval has the highest UPM, it is chosen as the winning model and the dosing decision is to stay at the current dose. If any interval contained in the under-dosing interval has the highest UPM, it will be chosen as the winning model and the decision is to escalate the next cohort to a higher dose. If any interval contained in the over-dosing interval has the highest UPM, it will be chosen as the winning model and the decision is to deescalate the next cohort to a lower dose. Guo et al. [Guo, 2017] shows that the decision based on the UPM is optimal in that it minimizes a subsequent expected loss. Under the mTPI-2 design, a trial is terminated when either the lowest dose is above the maximum tolerated dose (MTD) or a prespecified maximum sample size is reached. For this study, pT, the target toxicity level is 0.3, the uncertainty values are set at e1=e2=0.05, the stopping rule threshold for excessive toxicity is 0.95 and the prior probability of toxicity at each dose is distributed as Beta(1,1).

The final determination of RP2D will be based on the mTPI-2 recommended dose, as defined as ≥6 participants treated at this dose and an observed toxicity rate closest to the targeted toxicity rate at 30% after isotonic regression, in addition to considering the clinical response rate and available PK and PD data generated from all participants.

Table 9 DLT de-escalation/re-escalation rules

Number of participants with Dose Limiting Toxicities (DLTs) at the current dose	3	6	9	12	15
0	R	R	R	R	R
1	S	R	R	R	R
2	D	S	R	R	R
3	U	D	S	S	R
4		U	D	S	S
5		U	U	D	S
6		U	U	D	D
7			U	U	D
8			U	U	U
9			U	U	U
10				U	U
11				U	U
12				U	U
13					U
14					U
15					U

R=Re-escalate to the higher dose if applicable OR Stay at the current dose otherwise

S=Stay at the current dose
D=De-escalate to the lower dose if applicable OR Stay at the current dose otherwise
U=The current dose is unacceptably toxic; de-escalate to the lower dose if applicable.

Target toxicity level=30%
e1=e2=0.05

6.4.1. mTPI-2 Simulation Results

Simulations on the mTPI-2 design were conducted assuming either a 10% or 20% toxicity rate for the low dose ($0.1 \times 10^9 – 0.8 \times 10^9$ transduced T-cells) and a 10%, 20%, 30%, or 40% toxicity rate for the high dose ($1 \times 10^9 – 8 \times 10^9$ transduced T-cells). 10000 simulations were conducted per scenario. The maximum tolerated dose is defined as the dose with DLT rate of 30%. The simulation results are shown in the tables below which demonstrates that mTPI-2 is a robust study design under all scenarios.

Table 10 shows the results of the simulation study. Based on the preclinical evidence and observed GSK3337794 toxicity data, we assume the moderate (20%) or borderline (30%) high dose toxicities are the most likely scenarios for GSK3901961 & GSK3845097. For these scenarios, highlighted in bold, we see that average observed toxicity rate is very close to the true underlying rate for the high dose and lower than the true underlying rate for the low dose. The average number of participants who experienced DLTs at the high dose is less than 2 out of an average of 8 participants when there is a borderline toxicity rate and less than 2 out of an average of 7 participants if there is a moderate toxicity rate. These results support our claim that the chosen design will be protective against overdosing. Additionally, the maximum tolerated dose is chosen >91% of the time when there is a moderate toxicity rate in the high dose and >76% of the time when there is a borderline toxicity rate in the high dose, which shows that the design is robust in correctly choosing the correct MTD under different underlying dose-DLT rate models.

Table 10 Design Simulation Results

True DLT rates	Low: 0.1 High: 0.1	**Low: 0.1 High: 0.2**	**Low: 0.1 High: 0.3**	Low: 0.1 High: 0.4	**Low: 0.2 High: 0.2**	**Low: 0.2 High: 0.3**	Low: 0.2 High: 0.4
Average Observed Toxicity Rate							
Low Dose	0.07	**0.09**	**0.09**	0.09	**0.17**	**0.18**	0.18
High Dose	0.10	**0.20**	**0.30**	0.42	**0.20**	**0.31**	0.43
Average Number of DLTs							
Low Dose	0.02	**0.08**	**0.17**	0.30	**0.17**	**0.37**	0.62
High Dose	0.60	**1.23**	**1.90**	2.55	**1.21**	**1.82**	2.42
Average Sample Size							
Low Dose	0.15	**0.76**	**1.74**	2.94	**0.86**	**1.88**	3.14
High Dose	6.02	**6.13**	**6.30**	6.36	**6.04**	**6.07**	6.03
Total Dosed	6.17	**6.89**	**8.04**	9.29	**6.90**	**7.95**	9.17

True DLT rates	Low: 0.1 High: 0.1	**Low: 0.1 High: 0.2**	**Low: 0.1 High: 0.3**	Low: 0.1 High: 0.4	**Low: 0.2 High: 0.2**	**Low: 0.2 High: 0.3**	Low: 0.2 High: 0.4
Percent picked as Maximum Tolerated Dose (MTD)							
No Dose	0.00	**0.00**	**0.00**	0.00	**0.01**	**0.02**	0.02
Low Dose	0.01	**0.07**	**0.21**	0.42	**0.09**	**0.22**	0.42
High Dose	0.99	**0.93**	**0.79**	0.58	**0.91**	**0.76**	0.55

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