Statistical Analysis Plan Amendment 1

Study ID: 209012 Substudy 1

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

NCT ID for sub-study: NCT06048705

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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

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

Study Number: 209012

Compound Number: GSK3901961

Abbreviated Title: Master Protocol of Autologous Enhanced T-Cell in Advanced Tumors

Substudy 1: GSK3901961 in previously treated advanced (metastatic or unresectable) synovial sarcoma / myxoid/round cell liposarcoma, and previously treated metastatic non-small cell lung cancer

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s)

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Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP v1	17 May 2022	209012/Amendment 3 (20-Dec-2021)	Not Applicable	Original version
SAP Amendment 1	03 Apr 2023	209012/Amendment 4 (27-May-2022)	In addition to minor typographical and formatting changes, the following updates have been made in relation to the reduction in scope of original planned analyses as a result of substudy termination: • Removal of references to summaries based on RP2D or the Evaluable Analysis Set (throughout document). • Clarification on the presentation of the safety and efficacy analyses (Section 4.1.1) • Removal of subgroup analyses (Section 4.6.1) • Clarification that the protocol-planned Interim and Primary	Reduction in scope of original planned analyses as a result of substudy termination.

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			analyses will not be conducted (Section 4.7). • Removal of Exploratory CCI endpoint description. Instead details are described in the core SAP. (Section 4.4)	

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to describe the planned analyses to be included in the CSR for Substudy 1 (GSK3901961) 209012. The core SAP covers the majority of the analyses for this substudy. However, additional details that are specific to this substudy are provided below.

As described in Core SAP Amendment 2, due to early termination of all substudies only a subset of the previously planned analyses are now required. The following key changes to previously planned analyses are relevant to this document: 1) since the substudy was 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). 2) The Interim and Primary analyses described in Substudy 1 Protocol Amendment 4 Section 10.5 will not be conducted, only the Final Analysis will be undertaken. 3) No subgroup analyses will be undertaken as a result of recruiting fewer participants than the planned target sample size.

1.1. Objectives, Estimands and Endpoints

The full list of objectives and endpoints below is the list given in the Substudy 1 Protocol Amendment 4.

As of Substudy 1 SAP Amendment 1: Due to early termination of this substudy, only a subset of the exploratory endpoints will be analysed.

1.1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the safety, tolerability and determine recommended phase 2 dose (RP2D) of GSK3901961 in HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 positive participants with: - NY-ESO-1 and/or LAGE-1a positive previously treated metastatic Non-Small Cell Lung Cancer (NSCLC) (Cohort 1) - NY-ESO-1 and/or LAGE-1a positive, previously treated, advanced (metastatic or unresectable) Synovial Sarcoma (SS) / Myxoid/Round Cell Liposarcoma (MRCLS) (Cohort 2)	• 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 anti-tumor activity of GSK3901961 in HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 positive participants with:	• Overall Response Rate (ORR) (investigator assessed according to RECIST v1.1)

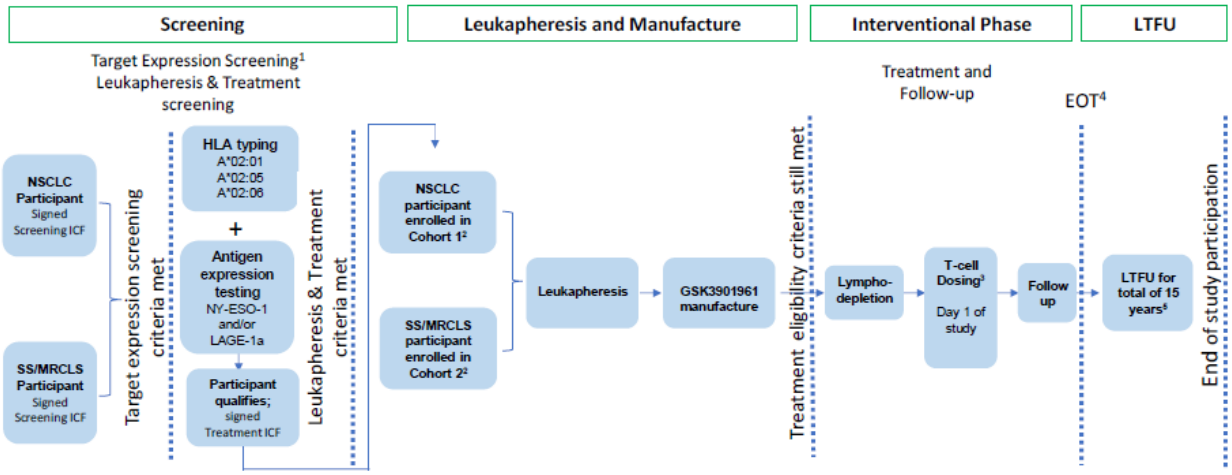
Objectives	Endpoints
- NY-ESO-1 and/or LAGE-1a positive previously treated metastatic NSCLC (Cohort 1) - NY-ESO-1 and/or LAGE-1a positive, previously treated, advanced (metastatic or unresectable) SS/MRCLS (Cohort 2)	• Duration of Response (DoR)
Secondary – Pharmacokinetics (PK)	
To characterize in vivo cellular PK profile (levels, expansion, persistence) of GSK3901961 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]	

Objectives	Endpoints
CCI	

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; CCI HLA = human leukocyte antigen; CCI ; MRCLS = myxoid/round cell liposarcoma; NSCLC = non-small cell lung cancer; NY-ESO-1 = New York esophageal antigen-1; ORR = overall response rate; CCI ; PFS = progression-free survival; CCI ; RECIST = Response Evaluation Criteria In Solid Tumors; RNA = ribonucleic acid; RP2D = recommended phase 2 dose; SAE = serious adverse event; SS = synovial sarcoma; Tmax = Time to Cmax; CCI CCI . † = PK and CCI exploratory endpoints not covered in this SAP, will be detailed in separate PK and CCI reporting and analysis plans. [1] = Exploratory efficacy endpoints that will not be analysed due to the early termination of the study.

1.2. Study Design

Overview of Study Design and Key Features



EOT = end of treatment (i.e., interventional) portion of the trial; HLA = human leukocyte antigen; ICF = informed consent form; LTFU = long-term follow-up; MRCLS = myxoid/round cell liposarcoma; NSCLC = non-small cell lung cancer; PD = progressive disease; RP2D = recommended phase 2 dose; SS = synovial sarcoma.

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

Dose Confirmation Phase

Cohort 1 in NSCLC and Cohort 2 in SS/MRCLS may be enrolled

- Progressive disease after SOC treatment
- For SS/MRCLS, no brain metastasis allowed
- For SS/MRCLS, disease confirmed by translocation
- Measurable disease
- Supportive chemotherapy permitted between screening and lymphodepletion

- N=6-15 total enrolled from either Cohort
- Split dose for sentinel participant (1 total)
- 2-week staggering for first 3 participants
- Potential Dose de-escalation
- Safety review after each 3 dosed participants

Cohort 2 in SS/MRCLS

- N=10 total evaluable participants @ RP2D
- Followed until PD or the end of interventional phase, whichever is sooner

LTFU for total of 15 years

LTFU for total of 15 years

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

Design Features	• This is a first time in human (FTIH) multi-cohort, non-randomized, open-label substudy to investigate GSK3901961 in previously treated participants with advanced (metastatic or unresectable) synovial sarcoma (SS) / myxoid/round cell liposarcoma (MRCLS) or previously treated metastatic NSCLC). NY-ESO-1 and/or LAGE-1a positive, previously treated, advanced (metastatic or unresectable) SS/MRCLS (Cohort 2).

Overview of Study Design and Key Features	
	• This substudy will consist of two phases: Dose Confirmation Phase and Dose Expansion Phase. Enrolment into this substudy will consist of two phases: Dose Confirmation Phase and Dose Expansion Phase. It is anticipated that this substudy will include approximately 29 participants. • **Dose Confirmation Phase (n=6-15)** o NSCLC or SS/MRCLS participants may be enrolled within this phase, based on competitive enrolment. o The primary objective of the dose confirmation phase is to identify the RP2D of GSK3901961. RP2D will be determined as the maximum tolerated dose (MTD) or lower that provides adequate biologic activity with superior tolerability. The MTD is defined as the dose that maximizes the probability of target toxicity of 30% while controlling the probability of excessive or unacceptable toxicity. o To find the RP2D, a modified toxicity probability interval 2 (mTPI-2) design will be implemented. Participants will be recruited and treated in blocks of three. The design aims to identify a dose with a true underlying toxicity rate of 30%, with a range of 25% to 35%. o The dose will be re-escalated/de-escalated based on all available data. The DLT information on all participants enrolled in the trial is used to update the estimated dose toxicity relationship and provide supportive information in addition to the mTPI-2 design in the next re-escalation/de-escalation decision. o Dose Selection Committee (DSC) will meet after the DLT period in every 3 participants to enable dose decision until the final dose selection is achieved (6 to 15 participants). o The final determination of RP2D will be based on the mTPI-2 recommended dose, as defined as $\geq$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. • **Dose Expansion Phase (n=20)** o After RP2D has been determined, each cohort will enroll additional participants to ensure n=10 participants have become evaluable at the RP2D in each cohort. o The definition of an evaluable participant is provided in the core SAP, Section 3.0. • For each individual participant, the study will consist of the following: 1) Screening, 2) Leukapheresis and manufacture, 3) Interventional Phase (Lymphodepletion, Treatment and Follow-up), 4) Long-term follow-up (LTFU). • Participants will undergo stepwise enrolment on the study followed by treatment according to defined phases within this substudy which will include: Part 1: Screening ▪ Target expression screening for the presence of HLA- A*02:01, HLA-A*02:05 and/or HLA-A*02:06 positivity and tumour expression of NY-ESO-1 and/or LAGE-1a, ▪ Leukapheresis screening phase to determine eligibility for undergoing leukapheresis beginning up to 28 days prior to leukapheresis Part 2: Leukapheresis and Manufacture ▪ Eligible participants will be entered into one of the two study cohorts (NSCLC or SS/MRCLS) then will undergo Leukapheresis procedure to obtain cells for manufacture of autologous NY-ESO-1 TCR bearing T-cells,

Overview of Study Design and Key Features	
	▪ Leukapheresis procedure requires that the participant has completed prior line of therapy and had radiographic or clinical evidence of disease progression. ▪ Note: Leukapheresis may have been performed under another GSK sponsored protocol or substudy of this protocol. Part 3: Interventional Phase (Lymphodepletion, Treatment, and Follow-up) - Treatment fitness assessment and eligibility confirmation, ▪ Interventional phase including Lymphodepletion from Days -7 to -4, GSK3901961 intravenous (IV) infusion on Day 1 and follow-up until the end of study (as defined in Protocol Section 5.3 of this Substudy), ▪ Note: TCR engineered T-cell 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 GSK3901961 infusion.
Study Intervention	• **Leukapheresis** o Participants will undergo leukapheresis to obtain starting material for the manufacture of GSK3901961. • **Bridging therapy and/or standard of care intermediate anti-cancer therapy** o Bridging or standard of care systemic chemotherapy, experimental therapy and/or local therapy (e.g., radiotherapy, cryoablation, surgical resection) may be administered between Target Expression Screening and Leukapheresis. o Systemic chemotherapy may be administered between Leukapheresis and the start of Lymphodepletion, if a participant has progressive disease and cannot be treatment-free. o Mandatory washout periods prior to Leukapheresis or Lymphodepletion are required. • **Lymphodepletion** o When the GSK3901961 has been manufactured, has fulfilled release criteria, and is available for infusion at the site, lymphodepleting regimen can be administered. The lymphodepleting regimen consists of fludarabine 30mg/m^2/day x 4 days (Day -7 to -4) and cyclophosphamide 900mg/m^2/day x 3 days (Day -6 to -4). This regimen is adjusted for participants >60 years of age, as specified in Table 11 of the substudy Protocol. Lymphodepletion regimen dose modification may also occur as described in Section 7.1.3 of the substudy Protocol. • **Dose Confirmation Phase** o The starting dose will be the RP2D of GSK3377794 (lete-cel); that is, the initial group of 3 participants will receive a dose in the range of 1×10^9 - 8×10^9 transduced T cells. o If DLTs are reported that require dose de-escalation according to the mTPI-2 model, then a lower dose range of 0.1×10^9 - 0.8×10^9 transduced T cells will be explored, with the possibility to re-escalate if the model supports such action. Alternative doses may be investigated if warranted by the emerging safety profile. o Split dosing and staggered treatment: The first study participant receiving GSK3901961 (SS/MRCLS or NSCLC) will receive the total assigned dose (1×10^9 - 8×10^9 transduced T cells) as 2 separate infusions, 7 days apart, in aliquots of ~30% (first infusion) and ~70% (second infusion) of the total manufactured dose, respectively. If no DLTs are reported for the participant receiving split dosing during the stagger period, then all subsequent

Overview of Study Design and Key Features	
	participants treated with the particular investigational agent will receive the full dose as a single i.e., one-time, infusion. If DLTs are reported for the participants receiving split doses, additional participants may be treated with a split dose regimen at the discretion of the sponsor in consultation with the participating Investigators and the DSC. At each dose level, dose administration in the first 3 participants will be staggered. The initiation of lymphodepleting regimen in the 2nd and 3rd (across SS/MRCLS and NSCLC) participant will be separated by a minimum of 2 weeks from the complete GSK3901961 dose administered to the 1st participant. • **Dose Expansion Phase** o Each cohort will enroll additional participants to ensure n=10 participants have become evaluable at the RP2D in each cohort. Each cohort with enrol additional participants enrolled to ensure n=10 participants dosed at the RP2D of GSK3901961 have become evaluable at the RP2D in each cohort.
Study Intervention Assignment	• This is a non-randomized, single arm open-label substudy. It is planned that all participants will receive GSK3901961.
Interim Analysis	• **Dose Confirmation Phase** o During the dose confirmation phase, no formal interim analysis is planned. All available data (including safety laboratory data, CCI [redacted] (if applicable), PK data (if applicable) and the safety profile) will be reviewed during the DSC meetings to inform dose escalation decisions. The mTPI-2 design will be utilised to guide dose re-escalation/de-escalation and RP2D decisions. • **Dose Expansion Phase** o An interim analysis will be performed for each cohort after 10 participants in the cohort are evaluable at the RP2D. These analyses may be performed earlier with fewer than 10 evaluable participants at the RP2D if it is clear from the accumulated data what the decision at 10 evaluable participants treated at RP2D would be. In the event that an early futility decision is made for ORR then enrollment to the cohort will be closed. • **Primary Analysis** o The primary analysis for each cohort will be performed after enrollment to the cohort is complete and all the enrolled participants in the cohort that will receive T cell infusion have done so and of those: ▪ at least 80% of those dosed at the RP2D have confirmed disease progression or died, or ▪ were withdrawn or lost to follow-up from the substudy; and ▪ all the remaining infused participants (including any treated at doses other than the RP2D) have completed at least 2 post baseline disease assessments since infusion. o If the primary analysis for a cohort is expected to occur within 9 months of the final analyses for the cohort, then the primary analysis may be omitted and only the final analyses carried out.
Time & Events	• For the schedule of activities refer to Section 2 of the substudy Protocol.

2. STATISTICAL HYPOTHESES

The primary aim is to determine the recommended phase 2 dose, safety profiles and pharmacology of GSK3901961. Descriptive methods will be used in analyses of the data from this substudy. No inferential statistical hypothesis testing will be conducted.

The assumptions for the secondary endpoint of ORR, as defined in the core SAP Section 4.3.1.1.1, underlying the design are detailed below:

NSCLC (Cohort 1):
The null hypothesis for the secondary endpoint ORR is: p=10%

The alternative hypothesis is: p=30%

SS/MRCLS (Cohort 2):
The null hypothesis for the secondary endpoint ORR is: p=40%

The alternative hypothesis is: p=60%

2.1. Multiplicity Adjustment

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

3. ANALYSIS SETS

Refer to Section 3 of the core SAP.

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

As of Substudy 1 SAP Amendment 1: Substudy terminated prior to enrolment of any Cohort 1 (NSCLC) participants. As such, analyses will be limited to Cohort 2 (SS/MRCLS).

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 subjects (n), mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

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

Cohort 2 includes participants with both Synovial Sarcoma (SS) and Myxoid/Round Cell Liposarcoma (MRCLS) tumor types. In general, participants of both SS/MRCLS will be summarised together but will be distinguished separately in the listings.

For safety, data will be summarised by cohort and phase. In general, safety data will be displayed by actual dose received (total number of transduced T-cells) using the following columns: 0.1-0.8 x 10^9 vs. 1-8 x 10^9 (mITT population tables). Please refer to Table 1 in the core SAP for the applicable tables that are to be displayed by the planned dose. The planned dose tables will use the following columns: DL-1 for (0.1-0.8 x 10^9) and DL1 (for 1-8 x 10^9). For tables on the ITT population, an additional column of “No treatment” will be included consisting of those who did not receive lymphodepletion chemotherapy and T-cell infusion.

For efficacy, data will be summarised by phase. The planned analyses will only include the efficacy data from the cohort of interest for the analyses. Data will be displayed by actual dose received (total number of transduced T-cells) using the following columns: 0.1-0.8 x 10^9 vs. 1-8 x 10^9 (mITT population tables only)

Details of the planned displays are provided in the core and Substudy 1 Output and Programming Specification (OPS) documents and are based on GSK data standards and statistical principles.

4.1.2. Baseline Definition

Refer to Section 4.1.2. of the core SAP.

4.2. Primary Endpoint(s) Analyses

Refer to Section 4.2. of the core SAP.

4.3. Secondary Endpoint(s) Analyses

Refer to Section 4.3 of the core SAP.

4.4. Exploratory Endpoint(s) Analyses

Refer to Section 4.4 of the core SAP.

4.5. Safety Analyses

Refer to Section 4.5 of the core SAP.

4.6. Other Analyses

4.6.1. Subgroup analyses

Due to early termination of this substudy, subgroup analyses will not be conducted.

4.7. Interim Analyses

As of Substudy 1 SAP Amendment 1: 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. Dose Confirmation Phase

As of Substudy 1 SAP Amendment 1: Note that this substudy was terminated prior to the determination of RP2D, and so there will be no RP2D recommended based on the mTPI-2.

For the dose confirmation phase there are no formal interim analyses planned.

All available safety and tolerability data including safety laboratory data, CCI [redacted], and PK data (if applicable) and the safety profile observed will be reviewed during the DSC meetings to inform dose escalation decisions and support the RP2D decision. The DSC meetings will occur after the DLT period (28 days after last IP dose) in every 3 participants to enable dose decision until the final dose selection is achieved.

The DLT information on all participants enrolled in the trial is used to update the estimated dose toxicity relationship and provide supportive information in addition to the mTPI-2 (Section 4.7.1.1) in the next re-escalation/de-escalation decision; the mTPI-2 approach is expected to be used as the primary criteria for dose escalation.

The final determination of RP2D will be based on the mTPI-2 (Section 4.7.1.1) 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 Pharmacodynamics data generated from all participants.

4.7.1.1. Modified Toxicity Probability Interval 2 (mTPI-2) Design

As of Substudy 1 SAP Amendment 1: Note that this substudy was terminated prior to the determination of RP2D, and so there will be no RP2D recommended based on the mTPI-2.

The dose confirmation phase of this study is based on mTPI-2 [Guo, 2017] design. mTPI-2 is implemented within a formal Bayesian decision framework. The mTPI-2 design for this study assumes the underlying toxicity rate for maximum tolerated dose of GSK3901961 falls within the range from 25% to 35% and is centred at 30%. 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 monitoring rules guiding dose escalation are provided in Table 1. Columns provide the numbers of participants treated at the current dose level, and rows provide the corresponding numbers of participants experiencing DLTs. The entries of the table are dose-finding decisions (i.e., R, S, and D) representing re-escalating the dose, staying at the same dose, and de-escalating the dose. In addition, decision U means that the current dose level is unacceptable because of high toxicity and should be excluded from the trial. For example, when one of three participants experiences toxicity, the decision can be located at row 1 and column 3, which is S –to stay at the current dose level. Consequently, the next block of participants will be treated at the same dose level currently being used. If zero of three participants experience toxicity, the decision is at row 0 and column 3, which is R –to re-escalate. Thus, the next block of participants will be treated at the higher dose level, if available. If three of three participants experience toxicity, the decision is to de-escalate to the lower dose level and exclude the current dose from the trial, because the toxicity level is unacceptable.

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 1 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

Target toxicity level=30%
e1=e2=0.05

4.7.2. Dose Expansion Phase

As of Substudy 1 SAP Amendment 1: Note that this substudy was terminated prior to the determination of RP2D. Hence this section of text is no longer applicable.

An interim analysis for futility will be performed for each cohort after 10 participants in the cohort are evaluable at the RP2D. Evaluable subjects who received RP2D in the dose confirmation phase will be included in the 10 participants. The endpoint assessed for futility is the Overall Response Rate (ORR), defined as the proportion of participants with an investigator-assessed confirmed complete response (CR) or confirmed partial response (PR) per RECIST v1.1.

These interim analyses may be performed earlier with fewer than 10 evaluable participants at the RP2D if it is clear from the accumulated data what the decision at 10 evaluable participants treated at RP2D would be.

Futility rules are provided in Table 2 and justification for these rules is provided in Section 5. Note that these rules are for guidance only and futility decisions will be made based on the totality of the data. In the event that an early futility decision is made then enrollment to the cohort will be closed.

- In Cohort 1 (NSCLC), if we observe 1 or fewer responders out of 10 evaluable participants, the posterior probability that the ORR is less than 30% is >96%. Therefore, for example, if no responders are observed in the first 9 evaluable participants at the RP2D, an early interim analysis for that cohort may be conducted.
- In Cohort 2 (SS/MRCLS), if we observe 4 or fewer responders out of 10 evaluable subjects, the posterior probability that the ORR is less than 60% is >90%. Therefore, for example, if no responders are observed in the first 6 evaluable participants at the RP2D, an early interim analysis for that cohort may be conducted.

Table 2 Interim Analysis Futility Rules

	Interim Analysis		Early Interim Analysis	
Cohort	Number of participants evaluable at RP2D	Stop for futility if number of responders is:	Number of participants evaluable at RP2D	Stop for futility if number of responders is:
Cohort 1: NSCLC	10	≤1	9	0
Cohort 2: SS/MRCLS	10	≤4	6	0

Abbreviations: RP2D = Recommended Phase 2 Dose.
Criteria are for guidance only. Final decisions will be based on a review of the totality of the data.

4.7.3. Primary Analysis

As of Substudy 1 SAP Amendment 1: 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.

Refer to Section 4.7.2 in the core SAP and Section 10.5.1.1 in the Substudy 1 Protocol.

4.7.4. Final Analysis

Refer to Section 4.7.3 in the core SAP.

4.8. Changes to Protocol Defined Analyses

Any changes from the originally planned statistical analysis specified in protocol amendment 4 (Dated: 27-May-2022) are described in the Core SAP Section 4.8.

5. SAMPLE SIZE DETERMINATION

The Dose Confirmation phase would need 6-15 participants to establish RP2D (see mTPI-2 simulation results in core SAP Section 6.4.1). Thus, the total expected maximal number of participants is 15 in the Dose Confirmation phase. The RP2D will be established irrespective of cohorts, by combining participants from both cohorts.

Once the RP2D has been established, each cohort of the substudy will expand to up to n=10 evaluable participants each treated at that dose (includes participants from the Dose Confirmation Phase who were treated at RP2D).

NSCLC (Cohort 1)
The null hypothesis is that the true ORR is 10% and the alternative hypothesis is that the true ORR is 30%. This cohort size was chosen to allow for early stopping of further development due to futility if the posterior probability that the ORR is less than 30% is >96%. This is equivalent to observing 1 or fewer responders out of 10 treated participants. It was assumed that the prior distribution for the response rate follows an uninformative Beta(a=0.01, b=0.09) distribution. Additionally, if the true ORR is 10%, the probability of observing 1 or fewer responders out of 10 treated participants is 74% and if the true ORR is 30% the probability of observing 1 or fewer responders out of 10 treated participants is 15%.

SS/MRCLS (Cohort 2)
The null hypothesis is that the true ORR is 40% and the alternative hypothesis is that the true ORR is 60%. This cohort size was chosen to allow for early stopping of further development due to futility if the posterior probability that the ORR is less than 60% is >90%. This is equivalent to observing 4 or fewer responders out of 10 treated participants. It was assumed that the prior distribution for the response rate follows an uninformative Beta(a=0.02, b=0.08) distribution. Additionally, if the true ORR is 40%, the probability of observing 4 or fewer responders out of 10 treated participants is 63% and if the true ORR is 60% the probability of observing 4 or fewer responders out of 10 treated participants is 17%.

These decision rules are for guidance only and the final decision to stop for futility will be determined based on the totality of the data.

If supported by safety and efficacy results, additional participants may be enrolled to confirm the safety and efficacy via a protocol amendment or as part of a separate protocol.

- For Cohort 1, two or more confirmed responses (CR or PR) out of 10 evaluable participants treated at RP2D may provide sufficient efficacy evidence to enroll additional participants.
- For Cohort 2, five or more confirmed responses (CR or PR) out of 10 evaluable participants treated at RP2D may provide sufficient efficacy evidence to expand and enroll additional participants.

6. SUPPORTING DOCUMENTATION

Refer to Section 6 of the core SAP. Any differences or additional analyses are specified below.

6.1. Appendix 1 Study Population Analyses

6.1.1. Demographic and Baseline Characteristics

Disease characteristics at initial diagnosis and screening will be analysed as per Section 6.1.2 in the core SAP. Presentations will also include the specific disease characteristics related to SS, MRCLS and NSCLC that are entered on separate corresponding eCRF pages. For SS this will include the extent of the disease at screening (local unresectable or metastatic), SYT-SSX translocation (SYT-SSX1, SYT-SSX2, SYT-SSX4, not applicable or other) and histology type (monophasic, biphasic, not available, or other). For MRCLS this will include the extent of disease at screening (local unresectable or metastatic), specific translocation (FUS-DDIT3, EWSR1-DDIT3, not applicable or other) and percent round cell. For NSCLC, the presentations will also include histology of primary tumor type at initial diagnosis (adenocarcinoma, squamous cell carcinoma, large cell carcinoma or other) and histology grade at initial diagnosis (grade cannot be assessed, well differentiated, moderately differentiated, poorly differentiated or undifferentiated).

7. REFERENCES

Guo Wang SJ, Yang S, Lynn H, Ji Y. A Bayesian interval dose-finding design addressing Ockham's razor: mTPI-2. Contemp Clin Trials. 2017; 58:23-33.