

**INSTITUT DE RECHERCHES INTERNATIONALES SERVIER
(I.R.I.S.)**



<i>Document title</i>	STATISTICAL ANALYSIS PLAN (SAP)
<i>Full title</i>	A first in human Phase 1/2 open-label, multicentre, dose escalation and expansion study of PRS-344/S095012 in patients with solid tumors
<i>Short title</i>	A study of PRS-344/S095012 (PD-L1x4-1BB bispecific antibody) in patients with solid tumors
<i>Acronym</i>	
<i>Test drug code</i>	PRS-344/S095012
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CL1-95012-001 - Statistical Analysis Plan | VV-TMF-264628 | 1.0

CL195012001 - Statistical Analysis Plan - Final version 2.0

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Follow up of versions

Version	Release date (dd/mm/yyyy)	Key change(s) (*)	Protocol version associated	Rationale
1.0	12June2023	Not applicable	Version 6.0	Initial version
2.0	01July2025	<ul style="list-style-type: none"> • Updates implemented following CSR Dry-run 1. • Use of unscheduled lab data are clarified • Clarified that Cohort 7 where participants are treated with pre-treatment Obinutuzumab dose are analysed separately. • A general definition of 'On-treatment' period is added to Section 4.2. • Presentation of data for the participant who were enrolled but not treated. • The definition of Previous and Concomitant Medication is updated to be as per the records capture on the 	Version 9.0	<ul style="list-style-type: none"> • Clarification that the analysis sets are defined so that they can be applied regardless of whether the participants are in Phase 1 or Phase 2. • Text for imputation of partially missing and missing dates is changed to start with missing date, then missing date and month and finally missing full date. This can be easily applied but should not provide different results than the current version. • Analysis of PK and ADA data are detailed. • Further clarifications of analysis in general are done to make this version is consistent with the Stable TFL Shells Version 0.6 • PDs will not be confirmed as there are no independent review data or radigraphic assessment data to include in the current

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		<p>concomitant medication page of eCRF.</p> <ul style="list-style-type: none"> Added the decisions made at the sponsor meeting on 25Oct2024. Servier review comments incorporated. Remove Disease Control Rate, Time to response, Duration of response, Progression free survival and overall survival from secondary efficacy endpoints In study design, paragraph on phase 2 – Dose expansion was simplified In section 5.1.1, added reference to swimmer plot of tumor response and participants disposition during study duration Corrected calcium added in laboratory gradable parameters (instead of total calcium) 		<p>dry run. These data will not be available in future as the study is terminated.</p> <ul style="list-style-type: none"> The lack of instructions on how to use unscheduled lab data was identified during the programming. As per the Sponsor instructions, Cohort 7 participants will be analysed separately. A definition for ‘On-treatment’ period is required for vital signs. This keep consistency across all data categories. Required further clarifications on the presentation in tables and listings outputs when Obinutuzumab+ 36 mg treatment arm was separated. Several changes identified during the production of DryRun2. Update wording as per Protocol version 9 Secondary efficacy endpoints removed to align with the abbreviated CSR scope of work
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		<ul style="list-style-type: none">• When triplicate sinus rhythm is recorded, definition of the visit value was clarified• Clarification added on how concentrations below LLOQ are imputed		<ul style="list-style-type: none">• Design of Phase 2 – Dose expansion is not described anymore in SAP as phase 2 has been discontinued due to unfavorable benefit/risk balance• Only corrected calcium is gradable, not total calcium
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(*) Key changes as compared to the statistical analyses planned in the protocol for the first SAP signed version (1.0).

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List of abbreviations

ADA	Anti-drug antibody
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine (Amino)Transferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate (Amino)Transferase
ATC	Anatomical therapeutic
BLRM	Bayesian Logistic Regression Model
BMI	Body Mass Index
BOR	Best Overall Response
bpm	beats per minute (heart rate unit)
BSA	Body Surface Area
C1D1	Cycle 1 Day 1
C1D28	Cycle 1 Day 28
CBHM	Clustered Bayesian Hierarchical Model
CI	Confidence Interval
CK	Creatine Kinase
CPI	Checkpoint inhibitor
CR	Complete response
CSCC	Cutaneous squamous cell carcinoma
DBP	Diastolic Blood Pressure
DC	Disease control
DLT	Dose Limiting Toxicity
DLTES	Dose Limiting Toxicity Evaluable Set
DoR	Duration of Response
ECG	Electrocardiogram
e-CRF	electronic-Case Report Form
ECOG	Eastern Cooperative Oncology Group
ES	Enrolled Set
FIH	First-in-Human
FU	Follow-up
GGT	Gamma-Glutamyl Transferase (Gamma-Glutamyl Transpeptidase)
HR	Heart Rate
I.R.I.S.	Institut de Recherches Internationales Servier
ICH	International Council for Harmonization
IGS	Immunogenicity Set
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IPD	Important protocol deviation
IU	International Unit
kg	kilogram
L	Litre
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal laboratory reference range
Max	Maximum
MAD	Maximum Administered Dose

MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
Min	Minimum
mL	millilitre
mmHg	millimetre of mercury
MTD	Maximum Tolerated Dose
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-L1	Programmed death- ligand 1 (receptor)
PFS	Progression-free survival
PK	Pharmacokinetics
PKS	Pharmacokinetic Set
PR	Partial response
Q2W	Every two weeks
Q3W	Every three weeks
QTcF	QT interval corrected using Fridericia formula
RBC	Red Blood Cells
RDI	Relative dose intensity
RES	Response Evaluable Set
RECIST 1.1	Response Evaluation Criteria in Solid Tumors v 1.1
RP2D	Recommended Phase 2 dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
StD	Standard deviation
SAE	Serious Adverse Event
SOC	System Organ Class
TLG	Tables, Listings and Graphs
TMB	Tumor mutational burden
TS	Treated Set
TTR	Time to Response
ULN	Upper Limit of Normal laboratory reference range
WBC	White Blood Cells
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) Version 2.0 details the planned analyses to be performed, in accordance with the main characteristics of the study protocol CL1-95012-001 version 9.0 dated 22Jan2024.

Note: The previous versions of the protocols allow combination therapy with chemotherapy (e.g., Irinotecan) but all study participants have been treated with monotherapy of PRS-344/S095012.

The templates for Tables, Listings and Graphs (TLG) are described in a separate document.

This SAP will cover high level summaries of pharmacokinetic and immunogenicity data. Additional analyses will be performed under the responsibility of the Servier Quantitative Pharmacology department in Institut de Recherches Internationales Servier (I.R.I.S.) and will be reported separately.

The Bayesian Logistic Regression Model (BLRM) for the selection of maximum tolerated dose (MTD) is not covered in this document. All relevant details can be found in protocol Appendix 6.

1.1. Study Objectives and Endpoints

1.1.1. Phase 1 (PRS-344/S095012 - Dose escalation)

Primary Objectives	Objectives	Endpoints
	<ul style="list-style-type: none">- To evaluate the safety and tolerability profile of single-agent PRS-344/S095012- To determine the MTD or MAD and RP2D of PRS-344/S095012	<ul style="list-style-type: none">- Incidence of DLTs- Incidence and severity of adverse events (AEs)- Discontinuation of study treatment due to an AE- Laboratory, electrocardiogram (ECG) and vital sign measurements- Incidence of DLTs
Secondary Objectives	Objectives	Endpoints
	<ul style="list-style-type: none">- To characterize the PK of PRS-344/S095012	<ul style="list-style-type: none">- Serum PK parameters of PRS-344/S095012
	<ul style="list-style-type: none">- To evaluate the immunogenicity of PRS-344/S095012	<ul style="list-style-type: none">- Detection of ADA against PRS-344/S095012 and their titration when applicable
	<ul style="list-style-type: none">- To assess the preliminary anti-tumor activity of PRS-344/S095012 as per the investigator, according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.	<ul style="list-style-type: none">- Objective Response (OR): Defined as Complete Response (CR) plus Partial Response (PR)

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Exploratory Objectives	Objectives	Endpoints
	- To evaluate the intra-tumor pharmacodynamics of PRS-344/S095012 through the analysis of pre- and on-treatment tumor biopsies	- PD-L1, CD8, and 4-1BB expression in the tumor microenvironment by immunohistochemistry (IHC) - Immune cell subsets and activation status (such as but not limited to expression of Ki67 and Granzyme in CD8 T cells) by IHC - And/or gene expression profiling in the tumor such as but not limited to IFN γ gene signature
	- To characterize treatment-induced pharmacodynamic effects in peripheral blood	- Immuno-phenotyping of T cell subsets and their activation (such as, but not limited to, CD4, CD8, regulatory T cells, naive and memory subsets, Ki67) and changes by flow cytometry. - Cytokine levels - Soluble 4-1BB level
	- To analyze potential predictive biomarkers of response from tumor and blood samples	- PD-L1, 4-1BB, and CD8 expression in the tumor - And/or tumor mutational burden (TMB), in the tumor and/or blood, microsatellite instability (MSI) status, specific mutations in the tumor (or in the blood if feasible, with an optional sample) - And/or gene expression profiling in the tumor and/or blood
	- To assess any potential PK/pharmacodynamic relationship through a population modelling approach that may support the selection of the RP2D and schedule of administration	- PK and pharmacodynamic parameters in PK/pharmacodynamic models and simulation outcomes to support RP2D and schedule of administration.

1.1.2. Phase 2 (PRS-344/S095012 - Disease-specific cohorts)

Primary Objectives	Objective	Endpoint
	- To evaluate the potential anti-tumor activity and efficacy of PRS-344/S095012, as per central assessment according to RECIST v1.1 criteria based on appropriate clinical standards for the specified tumor type.	- Arms 1 and 2: OR as per central assessment according to RECIST v1.1 criteria - Arm 3: OR as per central assessment and composite response criteria (digital medical photography and/or imaging as per RECIST v1.1)
Secondary Objectives	Objectives	Endpoints
	- To further describe the efficacy	- All arms: OR as per investigator assessment - Disease Control (DC) - DoR - PFS - OS - TTR (Time to Response)
	- To further characterize the safety and tolerability of PRS-344/S095012	- AEs, serious adverse event (SAEs) - Laboratory, ECG, vital signs
	- To further characterize the PK profile of PRS-344/S095012	- Serum concentrations of PRS-344/S095012
	- To further characterize immunogenicity of PRS-344/S095012	- Detection of ADA against PRS-344/S095012 and their titration when applicable

Exploratory Objectives	Objectives	Endpoints
	<ul style="list-style-type: none"> - To evaluate potential predictive biomarkers of response from tumor and/or blood samples 	<ul style="list-style-type: none"> - PD-L1, and potentially other markers like 4-1BB, and CD8 expression in the tumor - And/or TMB in the tumor and/or blood, MSI status, specific mutations in the tumor (or in the blood if feasible, with an optional sample) - And/or gene expression profiling in the tumor and/or blood
	<ul style="list-style-type: none"> - To evaluate pharmacodynamic changes in the tumor and blood samples 	<ul style="list-style-type: none"> - Immune cell quantity and phenotype characterization in the blood and in the tumor - And/or cytokine levels - And/or soluble 4-1BB levels

1.2. Study design

This is a first-in-human (FIH), Phase 1/2, multicenter, open-label, dose escalation and dose expansion study designed to determine the safety and anti-tumour activity of PRS-344/S095012 in participants with advanced and/or metastatic solid tumors.

PRS-344/S095012 will be administered as SA through IV infusion every two weeks (Q2W), initially. The dose of PRS-344/S095012 will be determined during end of cohort meetings, based on safety data and available PK data. A Q3W administration schedule may be evaluated in new cohorts, if necessary or appropriate and agreed upon during an end of cohort meeting. The starting dose will be a flat dose of 12 mg dosed Q2W. The DLT observation period will be 28 days (Cycle 1) for the Q2W schedule and 21 days for the Q3W schedule.

Phase 1 - Dose escalation (parts A and B): The Phase 1 part of the study consists of dose escalation conducted in 2 parts (Part A and Part B). Part A is an accelerated dose escalation following a 1+3 design. Part B is a dose escalation in multiple participant cohorts, guided by a Bayesian Logistic regression model (BLRM) (Neuenschwander et al., 2008, Babb et al., 1998). Approximately 45 participants will be enrolled for dose escalation. For part A, one to four evaluable participants will be enrolled per dose level.

Phase 1 will evaluate the safety and tolerability of PRS-344/S095012 in participants for which standard treatment options are not available, no longer effective, or not tolerated.

In phase 1, backfilling will be allowed (i.e. the possibility to enrol additional participants in prior cohorts as long as an acceptable safety profile has been observed in the cohort being backfilled). Approximately 30 additional participants may be enrolled as many as 5 previously evaluated dose levels, in order to further characterize their safety, PK or PD.

In addition, approximately 10-12 participants will be treated with PRS-344/S095012 preceded by obinutuzumab administration. Obinutuzumab will be administered as single dose or a single dose split over 2 consecutive days, administered fourteen to seven days before the first dose of PRS-344/S095012, as per investigator's judgment.

Intra-patient dose escalation may be considered under certain conditions.

Phase 2 – Dose expansion: This phase was discontinued because of an unfavorable benefit/risk balance, and no statistical analysis will be conducted on it. Design of phase 2 dose expansion is fully described in protocol [Section 6.1](#).

Figure 1. CL1-95012-001 Study Design

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Phase 1						Phase 2	
Part A		Part B				Arm 1 : Cervical cancer, CPI naive	
C1: 12mg	C2: 36mg	C3: 60mg	C4: 180mg	C5: 500mg	C6: 1000mg	Arm 2: Cervical cancer, CPI relapsed/refractory	
						Arm 3: non-melanoma skin cancer / CSCC – CPI relapsed/refractory	

Dose levels are provisional and will be guided by the BLRM recommendation and cumulative safety data observed. C = Cohort; CPI = checkpoint inhibitors, CSCC: cutaneous squamous cell carcinoma.

1.2.1. Study plan

The study will be divided into the following periods for each participant:

Screening Period:

Phase 1 participants will be assessed for inclusion/exclusion criteria between Day -21 to Day -1 and Screening assessments and evaluations performed before the first study dose. These assessments are performed at similar timepoints for participants consented for Phase 2.

A fresh baseline biopsy is mandatory for both Phase 1 (including backfill) participants and Phase 2 participants unless archival tumor tissue less, than 9 months old for Phase 1 and 6 months old for Phase 2, is available. If the participant has received any anti-cancer treatment since the biopsy was taken a fresh biopsy is mandatory.

Treatment Period:

Participants will be allocated to different dose levels in dedicated cohorts in Phase 1 or to dedicated arms in Phase 2 and will receive doses of PRS-344/S095012 administered by IV infusion on Day 1 and Day 15 of each cycle, (*i.e.*, every two weeks - Q2W). A treatment cycle will initially consist of 28 days. Every 3 weeks (Q3W) administration of study treatment schedule may be evaluated. Further details are provided in protocol [Section 6.3.1](#). The current SAP describes the analysis of Q2W only.

Treatment is planned to be provided until disease progression. Treatment may be administered beyond progression according to the criteria described in protocol [Section 9.2.1](#). However, participants may be discontinued from treatment with the study treatment earlier according to the criteria described in protocol [Section 6.6.3](#).

End of Treatment:

End of treatment corresponds to the 3-month safety follow-up visit as described in below section.

1-month Safety FU visit

Participants will be evaluated 30 days after the last investigational medicinal product (IMP) administration. During this visit, participant safety will be evaluated through physical examination, vital signs, ECG and laboratory assessments as specified in the study schedule in order to assess any ongoing AEs.

Long-term Safety FU visits

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Participants will be evaluated 60 and 90 days after the last IMP administration. During this visit, participant safety will be evaluated through physical examination, vital signs, ECG and laboratory assessments as specified in Table 9 of the protocol, in order to assess any ongoing AEs. Disease status and survival (12 weeks after last IMP intake) will be documented during the 90-day visit. New information will be documented in the AE page. Any participant who develops immune-related toxicity will receive an appropriate assessment and/or performed the adequate test(s) to treat the event(s). In case of unresolved AE, the participants will be continuously followed until resolution or stabilization, or until the end of the study whatever comes first. SAEs related to the IMP (PRS-344/S095012) will be reported without time limit.

Disease Status and Survival FU visits

Disease Status and survival must be followed every 12 weeks (+/- 14 days). Disease status will be monitored through radiologic/photographic assessments up to progressive disease (PD) or if the participant receives another treatment for the cancer disease. Participants Survival will be followed via phone calls or contact with physician. Refer to Protocol [Section 6.2.3](#).

End of Study:

The end of the study is defined as the last participant's last visit, which includes the long-term safety FU visit, 90 days after the last dose of IMP or the date of the last contact attempt if the last participant is declared lost to follow-up (FU).

Antitumor activity measurements

The antitumor activity of the treatment will be assessed by RECIST version 1.1 or WHO criteria for externally visible skin tumors (only arm 3 in Phase 2) every 8 weeks initially.

In Phase 1, tumor responses will be assessed locally by the investigator. In Phase 2, tumor responses will be assessed locally by the investigator and confirmed by a central assessment.

After 50 weeks of treatment, antitumor activity will be assessed every 12 weeks until discontinuation of treatment. Imaging/photography should be done at the time the decision is made to stop the treatment (+/- 14 days). After discontinuation of treatment for any reasons other than PD, tumor assessments are to be performed by imaging/photography at every 12 weeks (+/- 14 days) until PD, initiation of another treatment for the participant's cancer, loss to follow-up, end of study, withdrawal of consent, or death (whichever comes first).

Survival follow-up may be done remotely by using various wired and wireless telecommunication technologies, including but not limited to phone, internet and shared electronic medical records, and will continue until death, withdrawal of consent, or closure of study.

For participants who progressed, treatment may continue beyond progression. A confirmation scan will be conducted at least four weeks after the initial scan indicating progression to confirm progression.

Antitumor activity of PRS-344/S095012 will be assessed using OR, DC, DoR, PFS, OS and TTR.

1.2.2. Type of randomization

Not applicable

1.3. Determination of sample size

Phase 1 - Dose escalation (parts A and B): The number of participants will depend on the number of dose cohorts that will be enrolled before reaching the MTD. It is expected that approximately 45 participants will be enrolled for dose escalation. The size and design of the dose escalation phase of the study is consistent with standard phase 1 accelerated dose escalation designs and multiple-participant cohort dose escalation based on the BLRM with the objective of determining the MTD/RP2D. For part A, one to four evaluable participants will be enrolled per dose level.

Thirty additional participants may be enrolled to backfill cohorts as mentioned in [Section 1.2](#).

In addition, approximately 10-12 participants will be treated with PRS-344/S095012 preceded by obinutuzumab administration, with the objective of having safety, PK, PD and ADA data over 2 cycles of treatment for 5-6 participants (as mentioned in Section 4.3.2.2). The sample size is driven by having reasonable Wilson score intervals (at 80% confidence level) so that the following conclusions can be made when the target ADA prevention rate is 80%.

Scenario	Conclusion
No patients developed ADA	Target achieved.
1 patient developed ADA	Enrol additional patients to decide.
≥2 patients developed ADA	Target missed.

The Wilson score interval across various scenarios are included in the table below.

ADA Prevention (n/N)	80% Wilson Score Interval	ADA Prevention (n/N)	80% Wilson Score Interval
3/5	(0.33, 0.82)	3/6	(0.27, 0.73)
4/5	(0.51, 0.94)	4/6	(0.41, 0.85)
5/5	(0.75, 1)	5/6	(0.57, 0.95)
		6/6	(0.79, 1)

Phase 2 – Dose expansion: Approximately 108 participants will be enrolled in arms 1 to 3, with approximately 36 participants in each arm..

The planned sample size is considered adequate for controlling the chance of falsely claiming efficacy at <15% in each arm, i.e., when the underlying ORR is futile. It also provides reasonable accuracy in claiming efficacy when the underlying ORR reflects an efficacious treatment effect..

2. STATISTICAL HYPOTHESES AND MULTIPLICITY HANDLING

2.1. Statistical hypotheses

No formal statistical hypotheses are planned for Phase 1 dose escalation (FIH) or Phase 2 dose expansion parts of the study.

2.2. Multiplicity handling

Not applicable for either Phase 1 or Phase II part of the study.

3. ANALYSIS SETS / TREATMENT ARMS

3.1. Analysis sets

In the SAP, the analysis sets are defined regardless of the study phase and when they are applied to Phase 1 or Phase 2 analysis, the corresponding participants population from each phase will only be included.

Enrolled Set (ES): All screened participants who are eligible to take part in a study according to all inclusion/exclusion criteria. Participants will be analysed according to their planned treatment.

Treated Set (TS): All participants who received at least one dose of IMP (PRS-344/S095012). Participants will be analysed according to the actual treatment they receive.

Response Evaluable Set (RES): All participants in the TS who have measurable disease at baseline and meet any of the following conditions: 1) at least one post-baseline disease assessment; 2) documented clinical progression; 3) death. Participants will be analysed according to the actual treatment they receive.

DLT evaluable Set (DLTES): All participants who have received at least 80% of the required Cycle 1 PRS-344/S095012 dose, and completed the DLT observation period or who experienced a DLT. Participants will be analysed according to the actual treatment they receive.

Pharmacokinetic Set (PKS): All participants who received at least one dose of IMP, for whom at least one reportable post-dose PK concentration available. Participants will be analysed according to the actual treatment they receive.

Immunogenicity Set (IGS): All participants who received at least one dose of IMP and have baseline and at least one post-baseline (pre-infusion) immunogenicity assessment. Participants will be analysed according to the actual treatment they receive.

3.2. Treatment arms

Table 3.2-1 Phase 1 planned treatment arms for Q2W:

Dose level	Treatment arm
1	PRS-344/S095012 12 mg (Q2W)
2	PRS-344/S095012 36 mg (Q2W)
3	PRS-344/S095012 60 mg (Q2W)
4	PRS-344/S095012 80 mg (Q2W)
5	Obinutuzumab + PRS-344/S095012 36 mg (Q2W)

In Phase 2, in each disease-specific expansion cohorts, participants will receive the PRS-344/S095012 RP2D dose as monotherapy Q2W.

Table 3.2-2 Phase 2 Planned treatment arms for Q2W	
Dose level	Treatment arm
1	PRS-344/S095012 RP2D mg Q2W

4. GENERAL STATISTICAL CONSIDERATIONS

4.1. Descriptive statistics

- Categorical data are summarised with the number of observed values (n) and percentage (%) derived using non-missing values for each category level. Only for the pre-specified categorical data, a 'Missing' level will be considered in the summary tables.
- Unless otherwise stated, percentages will be calculated out of the total number of participants in the analysis set for the corresponding treatment arm. Overall summary (i.e., data from Part A and Part B combined) will be produced for baseline summaries only.
- For categorical data, percentages will be rounded to 1 decimal place.
- Continuous data will be summarised using number of observed values (n), mean, standard deviation (StD), median, minimum (min) and maximum (max).
- For continuous data, mean and median will be rounded to 1 additional decimal place compared to the original (raw/derived) data. The standard deviation will be rounded to 2 additional decimal places compared to the original (raw/derived) data. Minimum and maximum will be displayed with the same accuracy as the original data. If original data have 2 or more decimal places, associated statistics will be limited to a maximum of 3 decimal places.

For survival data, number of participants in the analysis set, number and percentage of participants experiencing an event overall and by event type and number of participants with censored data overall and by reason for censoring will be presented in summary tables. Kaplan-Meier estimate of median event-free survival and 95% confidence intervals (CIs) will be provided for planned survival analyses.

Median event-free survival (95% CI) and number of participants at risk will be presented in any Kaplan-Meier graphs produced.

4.2. General definitions

- The following study periods are defined in detail in [Section 1.2](#). Study plan:
 - Screening Period,
 - Treatment Period and End of Treatment Period
 - 1-Month Safety FU, Long-term Safety FU and Disease Status and Survival FU
 - End of Study.

- Baseline is defined as the last available observation prior to the first administration of study treatment. Scheduled and unscheduled assessments will be considered to assess baseline observation. Both date and time or timepoint (if available) of assessment will be considered to identify baseline assessments. If no time or timepoint is collected, schedule of assessments may be used to identify the baseline if the assessment and first administration of study treatment are on the same day. For participants enrolled but not treated, the last available observation from screening period will be used as baseline.
- On-treatment period is defined as time from the first dose date to 90 days after the last dose date of study treatment. Imputation of dates

Fully or partially missing start dates or end dates of AEs, all non-study medications will be imputed for the summary tables as detailed below.

Fully or partially missing start date of radiotherapy and surgery for the studied disease and medical history of the studied disease will be imputed for the summary tables as detailed below.

- For missing or partial start dates of AEs and all non-study medications, and for missing or partial date of radiotherapy and surgery for the studied disease and medical history of the studied disease the following will be applied:
 - a. If day is missing, impute as the 1st of the month unless month and year are the same as month and year of the first dose of S095012 then impute as first dose date.
 - b. If both day and month are missing, impute as '01 January' unless year is the same as first dose date then impute first dose date
 - c. If date is completely missing, impute the first dose date unless the end date suggests it must have started prior to this in which case impute the 1st January of the same year as the end date

For AEs and non-study medications, if end date is complete date and imputed start date is greater than end date, then start date is imputed to end date.

- For AE missing end dates, the following will be applied if AE outcome is 'recovered' or 'recovered with sequelae':
 - a. If day is missing, impute as the last day of the month unless month and year are same than date of AE last information then impute by date of AE last information.
 - b. If month is missing, impute as 'December' unless the year is same than date of AE last information then, impute by date of AE last information.
 - c. If date is completely missing, impute by date of AE last information.

AE last information is defined as the maximum between onset date, dates of change of severity and action taken, and dates of the seriousness criteria (death, hospitalisation or prolongation of hospitalisation, medically important, life-threatening, disability/incapacity or congenital anomaly.)

- For partial end dates of all non-study medications, the following will be applied:
 - a. If day is missing, impute as the last day of the month unless month and year are same as death date. In such case, impute to death date.
 - b. If both day and month are missing, impute as '31 December' unless year is same as death date. In such case, impute to death date.
 - c. If date is completely missing, no imputation except if participant died. In such case, impute to death date.
- For partial start date of subsequent anti-cancer therapy the following will be applied if only day is missing:
 - d. If month and year are after the month and year of max(Date of Last Exposure to Treatment ; End of Treatment Date), then impute with the 1st of the month
 - e. If month and year are the same as max(Date of Last Exposure to Treatment ; End of Treatment Date), then impute with max(Date of Last Exposure to Treatment ; End of Treatment Date)+1
- For partial date of diagnosis, date of last line of therapy and date of last relapse, if only day is missing, if month and year are prior ICF month and year then impute with the 1st of the month in time from diagnosis to enrollment, treatment free interval and duration from last relapse derivations.
- For partial date of death, if only day is missing then impute with the 1st of the month in time to event derivations

The imputed dates will be used for the summary tables and these dates will be presented as reported in the data listings.

4.3. Other statistical considerations

- Summary of data will be presented by Part A and Part B and dose levels within these parts for Phase 1 and by disease-specific arms for Phase 2. Baseline characteristics (including disease characteristics and participants characteristics) and safety analyses will include an overall summary of Phase 1 as well as Phase 2.
- Data will be listed, similarly, by Part A and Part B and dose levels within these parts for Phase 1 and by disease-specific arms for Phase 2.
- The following titles will be used for Phase 1 study parts and Phase 2 arms for summary tables and listings:
 - Dose levels: PRS-344/S095012 XX mg.

- Disease-specific arms: ‘Arm 1: CC CPI naïve’, ‘Arm 2: CC CPI R/R’ and ‘Arm 3: CSCC CPI R/R’.

Backfill Participants: Backfill participants, if any, at the time of the database lock will be included in the corresponding treatment arm within Part A or Part B.

All data analyses will be performed using SAS® Version 9.4.

5. STATISTICAL ANALYSIS

The statistical analysis of the study data will be presented in tables and figures and all reported study data, that are considered as supportive of study objectives, will be listed in ‘raw’ or ‘derived’ form.

The data for both phases will be presented in one listing unless otherwise indicated. Separate summary tables are presented for Phase 1 and Phase 2, if data are available. All tables are supported by one or more ‘source’ listings and these listings will be indicated in the shells of the tables.

If figures are produced, the estimates in figures should also be presented in tables.

5.1. Study participants

5.1.1. Disposition

Analyses of disposition of study participants will be based on the ES. The following will be summarized:

- Participants disposition at the end of treatment and reason for discontinuation
- Participants disposition at the end of study and reason from discontinuation from study
- Number of participants treated at least once in each of the cycle
- Number of participants who progressed after coming off study
- Number of participants who started a new cancer treatment at follow up

The size of each analysis set, and reasons for exclusion will be described. These summaries will be provided for each dose level of Phase 1 and disease-specific arms of Phase 2 and overall.

A swimmer plot of tumor response and participants disposition during study duration will be created.

Disposition at the end of treatment / study and associated reason for discontinuation will be listed. Analysis sets and reason for exclusion from analysis sets will also be presented in a listing.

5.1.2. Protocol deviations

Analyses of protocol deviations will be based on the ES.

Important protocol deviations (IPD) before or at inclusion, as well as after inclusion, will be summarized by sub-category and coded term.

Protocol deviation term, coded term, sub-category (based on International Council for Harmonization (ICH) E3 guideline and ICH E3 Q&A) and visit as in SDTM domain for protocol deviations will be listed.

5.1.3. Demographic data and baseline characteristics

Demographic data and baseline characteristics will be described based on the ES.

5.1.3.1. Demographics and physical measurements

The following demographic characteristics and physical measurements recorded at Baseline will be summarized:

- Demographic characteristics
 - Sex: Male, Female
 - Age (years): summary statistics
 - Age group:
 - <65 years, ≥65 years
- Physical measurements
 - Height (cm)
 - Weight (kg)
 - Body mass index (BMI) (kg/m²)
 - Body surface area (BSA) (m²)
 - Pregnancy test (Total females, Positive, Negative, Not done)
 - ECOG (0, 1, 2, 3, 4)
 - Royal Marsden score

Notes: Race and ethnic origin were not collected for this study.

5.1.3.2. Baseline characteristics

Baseline disease and participants characteristics will be summarised on the ES.

The following baseline disease characteristics will be summarized:

- Stage at diagnosis (I, Ia, Ib, II, IIa, IIb, III, IIIa, IIIb, IIIc, IV, IVa and IVb)
- Site of primary tumor
- Primary diagnosis
- Current tumor status (In relapse only, Metastasis only, In relapse and metastasis)
 - In relapse (Yes, No)
 - Metastasis (Yes, No)
- PD-L1 status (Positive, Negative, Not done)
- Time from diagnosis to enrollment (months)
- Duration of disease category (≤ 1 month, > 1 to ≤ 2 months, > 2 to ≤ 4 months, > 4 months)
- Treatment free interval (≤ 1 month, > 1 month to ≤ 2 months, > 2 months)

- Duration from last relapse (≤ 1 month, >1 to ≤ 4 months, > 4 months)

The derivations are:

- [1] Time from diagnosis to enrollment (months) = (date ICF signed – date the disease investigated was diagnosed + 1) / (365.25/12).
- [2] Treatment free interval (months) = (date ICF signed – date of the end of last line of therapy + 1) / (365.25/12).
- [3] Duration from last relapse (months) = (date ICF signed – date of the last relapse + 1) / (365.25/12). Derived for those participants who experienced a relapse.

Site of primary tumor and primary diagnosis may be reviewed and categorized by clinical team for the baseline disease characteristics summary.

Summaries of the details of biopsy and site of metastasis listed below may also be presented when data are available.

- Tumor biopsy performed (Fresh Archived)
- Site of tumor biopsy (primary tumor, metastasis)
- Site of metastasis (Lung, Liver, Bone, Brain etc.)

5.1.3.3. Relevant medical and surgical history

Medical and surgical history other than for the solid tumors will be summarized by System Organ Class (SOC) and PT according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary in participants of the ES.

5.1.3.4. Previous treatment for solid tumors

Previous medications are defined as treatments reported and completed prior to date of first dose. An overall summary of previous treatment and procedures for solid tumors. A summary of previous treatments for solid tumors by medication class and standardised medication name will be presented.

Previous therapies will be summarized for participants in the ES.

Number and percentage of participants with at least one previous surgery, radiotherapy, drug treatment, immune therapy including anti-PD(L)1 checkpoint inhibitor and combination of previous therapies will also be presented. Combination of previous therapy considered are:

- No previous therapy
- Surgery only
- Radiotherapy only
- Drug treatment only
- Surgery + radiotherapy
- Surgery + drug treatment
- Radiotherapy + drug treatment
- Surgery + radiotherapy + drug treatment

Number of drug treatment lines (e.g., 1, 2, 3, 4-7 and ≥ 7) will also be presented.

Previous radiotherapies and surgeries will be listed.

5.1.3.5. Other previous treatments

Previous treatments participants received for diseases other than the solid tumors (recorded under 'General Treatments') will be described for participants in the ES. They will be summarised by medication class and standardised medication name.

5.2. Treatments of participants

Treatment of participants will be described on the TS by treatment arms.

5.2.1. Extent of exposure and treatment compliance

For the presentation of exposure data, the following endpoints are derived using non-zero dose levels of the study treatment (PRS-344/S095012).

- Treatment duration (months): (last dose date - first dose date + 1) / (365.25/12)
- Duration of exposure (months): (last dose date - first dose date + 14) / (365.25/12)
- Duration of exposure (cycles): number of cycles where participants receive at least one dose of PRS-344/S095012
- Cumulative dose (mg): sum of the actual doses administered.
- Actual dose intensity (mg/cycle): actual cumulative dose (mg) within a cycle, calculated as cumulative dose (mg) / number of cycles with non-zero dose received.
- Relative dose intensity (RDI) (%): $100 \times \text{Actual dose intensity (mg/cycle)} / \text{Planned dose intensity (mg/cycle)}$, where planned dose intensity (mg/cycle) is defined as: planned cumulative dose (mg) within a cycle, calculated as planned dose level (mg) $\times 2$. Planned dose intensity will not be summarized in table as it will be the same for all participants assigned to a same treatment group.

These exposure endpoints are summarised using descriptive statistics.

In addition:

- Duration of exposure (months) will be summarized for categories (>0 to ≤ 1 , >1 to ≤ 2 , >2 to ≤ 3 , 3 to ≤ 6 , >6 to ≤ 9 , >9 to ≤ 12 , and >12 months).
- Duration of exposure (cycle) to study treatment will be summarized for categories (1, 2, 3-6, 7-10, >10).
- RDI will be summarized for categories ($<90\%$, 90% - 110% , $>110\%$).

Study treatment compliance will be described using the number of dose interruptions (1, 2, 3, >3), number of dose delays (1, 2, 3, >3), number of dose omissions (1, 2, 3, >3) and number of dose reduction (1, 2, 3, >3).

5.2.2. Concomitant treatments

Concomitant treatments are defined as non-study medications that started during the on-treatment period or before the start of the study treatment and ended or remain ongoing during the on-treatment period. All concomitant treatments will be described for each treatment arm/arm, and overall, in the TS, by medication class and standardised medication name.

Similarly, concomitant procedures are described for each treatment arm/arm, and overall, in the TS by system organ class and preferred term.

Concomitant treatments and procedures will also be listed in participants data listings.

5.3. Efficacy analyses

Tumor response in Phase 1 is evaluated as per RECIST 1.1 ([Eisenhauer et al, 2009](#)) in participants by the investigator and the efficacy analyses are based on the tumor assessment by investigator.

5.3.1. Primary efficacy analysis

Not applicable for Phase 1. All efficacy analyses performed for Phase 1 are secondary efficacy analysis which are detailed in section “[Secondary efficacy analysis](#)”.

Phase 2 was discontinued because of an unfavorable benefit/risk balance, so primary efficacy analysis for phase 2 was not developed in this document.

5.3.2. Secondary efficacy analysis

5.3.2.1. Objective response rate

Objective response rate (ORR) is analysed on the TS and a supportive analysis is performed on the RES.

ORR is defined as the proportion of participants with a best overall response of confirmed CR or confirmed PR (See [Section 5.3.2.2](#)) before the first documentation of PD, and prior to the initiation of subsequent anticancer therapy. Participants who met these criteria are considered as responders.

Participants who do not have a post-baseline tumor assessment due to early progression, who receive subsequent anticancer therapy prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders and will be censored for survival analysis of endpoints.

ORR by treatment arm will be estimated along with the 2-sided 95% CI using the Wilson score method.

5.3.2.2. Best overall response

Best overall response (BOR) is analysed on the TS.

BOR will be based on all post-baseline disease assessments until the first documentation of PD, and prior to the initiation of subsequent anticancer therapy. BOR will be summarized by the number and percentage of participants in the following categories: CR, PR, SD, PD and non-evaluable (NE). Definitions of the response categories are the following:

- CR: at least two CRs at least 4 weeks apart.
- PR: at least two PRs or better (PR followed by PR or PR followed by CR) at least 4 weeks apart, and not qualifying for a CR.
- SD: at least one SD assessment (or better) ≥ 43 days (assuming a 8-week scan interval with a 14-day visit window) after start of study treatment, and not qualifying for CR or PR.
- PD: documentation of PD after start of study treatment (and not qualifying for CR, PR, SD).
- NE: all other cases.

If CR is pending confirmation and is designated at an assessment followed by 1 or more NE assessments, CR may be confirmed thereafter. Similarly, if a PR is pending confirmation and is designated at an assessment followed by 1 or more NE and/or SD assessments, PR may be confirmed thereafter.

Note: Date of confirmed and unconfirmed response is the date the response first recorded regardless of whether they are confirmed following the second assessment after 4 weeks.

5.3.2.3. Tumor shrinkage from baseline

Tumor shrinkage is analysed on the TS.

Tumor shrinkage is recorded as sum of longest diameter (SOD) for non-nodal lesion and short axis for nodal lesion. The percent change from baseline in target lesions will be summarised.

It will be derived as:

- $((\text{SOD of target lesions at week X} - \text{sum of target lesions at baseline}) / \text{sum of target lesions at baseline}) \times 100$

The maximum shrinkage in target lesions from baseline will be derived across all post-baseline disease assessments until PD, excluding assessments after start of subsequent anticancer therapy. This summary will consider unscheduled visits if they exists.

A waterfall plot showing the best percent change from baseline in the SOD of target lesions will be provided. Only those participants with baseline and at least one post-baseline disease assessment will be included.

5.3.2.4. Sensitivity analyses

Not applicable

5.3.2.5. Supplementary analyses

Not applicable

5.3.2.6. Subgroup analysis

Not applicable

5.4. Safety analysis

The full study safety analysis (i.e., AEs, laboratory data, vital signs and ECG analyses) will be performed on the TS.

5.4.1. Adverse Events**5.4.1.1. Dose Limiting Toxicity**

The DLT analysis will be performed on the DLTES.

Dose Limiting Toxicity (DLT) is defined in protocol. Number and percentage (%) of participants with at least one DLT during the DLT evaluation period (Cycle 1 Day 1 [C1D1] to Cycle 1 Day 28 [C1D28]) will be presented by treatment arm for Part A and Part B of Phase 1.

DLT will also be summarized by PT.

Details of DLTs will be provided in a listing.

5.4.1.2. Adverse Events

Treatment-emergent AEs (TEAEs) are AEs with the onset date within the on-treatment period (i.e., on or after the first dose of study treatment and on or before 90 days after the last dose) of study treatment or worsening from baseline during on-treatment period. If AEs that are worsened during the on-treatment period is reported as a new AE, the definition of TEAE doesn't have to include worsening of AEs. All TEAE will be coded using the latest version of MedDRA dictionary and summaries will be provided by SOC and/or PT, severity, seriousness, and relationship to study treatment. Severity is based on CTCAE grades according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0. An AE is considered as 'Severe' if the CTCAE Grade ≥ 3 .

Each participant will be counted only once within each SOC or PT. If a participant has reported multiple TEAEs under the same PT within a SOC for the same summary period, only the TEAE assessed as PRS-344/S095012 related or with the worst severity, as applicable, will be included in the summaries of relationship and severity, respectively. If a participant has TEAEs with missing and non-missing grades, worst case scenario is considered, and the maximum of the non-missing grades will be included for the summary tables. Missing CTCAE grades will not be imputed in the listings.

The following will be summarized:

- TEAEs by SOC and PT
- TEAEs by SOC, PT, and worst CTCAE grade
- Grade ≥ 3 TEAEs by PT.

- PRS-344/S095012 related TEAEs, by SOC and PT
- PRS-344/S095012 related TEAEs, by SOC, PT, and worst CTCAE grade
- Grade ≥ 3 TEAEs, by SOC and PT
- PRS-344/S095012 related Grade ≥ 3 TEAEs, by SOC and PT
- Serious TEAEs, by SOC and PT
- PRS-344/S095012 related Serious TEAEs, by SOC and PT
- TEAEs leading to treatment discontinuation by SOC and PT
- PRS-344/S095012 related TEAEs leading to treatment discontinuation by SOC and PT
- TEAEs leading to death, by SOC and PT
- PRS-344/S095012 related TEAEs leading to death, by SOC and PT
- TEAEs leading to treatment interruptions by SOC and PT
- TEAEs leading to treatment delays by SOC and PT
- TEAEs leading to treatment reductions by SOC and PT
- COVID-19 infection related TEAEs (if related data available)
- Most common TEAEs by PT; will include TEAEs (any grade) with overall frequency $\geq 10\%$. These thresholds may be changed based on the observed data without an amendment to this SAP.
- PRS-344/S095012 related Grade ≥ 3 hepatic toxicity TEAE by PT

Hepatic toxicity TEAE are defined as TEAE with SOC equal to "Hepatobiliary disorders" or with High Level Term in "Hepatobiliary function diagnostic procedures", "Hepatic failure and associated disorders", "Hepatic enzymes and function abnormalities".

5.4.2. Death

Deaths will be analysed on TS.

The number and percentage of participants who died, along with the cause of death, will be summarised on TS using the data on death in the clinical database.

These summaries will be presented for the following categories:

- On-treatment death: Deaths on or after the first dose of study treatment and on or before 90 days after the last dose of study treatment
- Post-treatment death: Deaths more than 90 days after the last dose of study treatment
- Overall: All deaths (on-treatment + post-treatment)

Any partial date of death will be imputed with the same rules as partial start dates of AE (refer to [section 4.2](#)) in the derivation of On-treatment / Post-treatment death flags.

In addition, deaths reported in the eCRF that are related to COVID-19 may be summarized, if relevant information is available.

A listing of all deaths in the study will be presented on ES.

5.4.3. Clinical and laboratory evaluation

All clinical and laboratory values for haematology, clinical chemistry, coagulation, thyroid and adrenal function tests and change from baseline of these values will be summarised by presenting descriptive statistics. For the laboratory data summaries over time unscheduled visits are not considered. Baseline, all on-treatment scheduled visits and scheduled follow up visits (Safety follow up, Safety follow up 60 days and Safety follow up 90 days) will be included in summary tables.

Value by grade at baseline and worst/last grade on treatment according to the grade at baseline will be provided for gradable parameters. These summaries will consider unscheduled visits if they exists.

Details of gradable and non-gradable parameters are given in [Table 5.4.3-1](#) and [Table 5.4.3-2](#).

Table 5.4.3-1 Gradable parameters

	Parameter	CTCAE Term (High direction)	CTCAE Term (Low direction)
Blood biochemistry	ALanine (Amino)Transferase (ALT)	Alanine transaminase (ALT) increased *	NA
	Albumin	NA	Hypoalbuminemia
	Alkaline phosphatase (ALP)	Alkaline phosphatase (ALP) increased *	NA
	Amylase	Serum amylase increased	NA
	ASpartate (Amino)Transferase (AST)	Aspartate transaminase (AST) increased *	NA
	Bilirubin (total)	Blood bilirubin increased *	NA
	GGT	Gamma glutamyl transferase (GGT) increased *	NA
	Corrected Calcium [a]	Hypercalcemia	Hypocalcemia
	Creatinine (serum)	Creatinine increased *	NA
	Creatinine Kinase (CK)	CPK increased	NA
	Glucose	Hyperglycemia	Hypoglycaemia
	Lipase	Lipase increased	NA
	Magnesium	Hypermagnesemia	Hypomagnesemia
	Potassium	Hyperkalaemia	Hypokalaemia
	Sodium	Hypernatremia	Hyponatremia
Blood haematology	Hemoglobin	Hemoglobin increased *	Anaemia

	Lymphocytes	Absolute lymphocytes count increased	Absolute lymphocytes count decreased
	Neutrophils	NA	Absolute neutrophils count decreased
	White blood cells	Leukocytosis	White blood cell (WBC) decreased
	Platelets	NA	Platelet count decreased
Blood coagulation	Activated Partial thromboplastin time (aPTT)	Activated partial thromboplastin time prolonged	NA
	Prothrombin International Normalized Ratio (INR)	Prothrombin International normalised ratio (INR) increased	NA

*: Parameter with grade dependent on baseline value (no grade can be computed at baseline)

[a] Corrected calcium is derived based on Total calcium and albumin from the same date and visit of the same subject. Corrected calcium (mmol/L) = measured total calcium (mmol/L) + 0.02 * [40 – serum albumin (g/L)]. Since corrected calcium should not be lower than total calcium, if albumin is higher than 40 g/L, then corrected calcium = calcium. If albumin is missing, then corrected calcium cannot be calculated.

Table 5.4.3-2 Non Gradable parameters

	Parameter	Worst Highest	Worst lowest
Blood biochemistry	Blood urea nitrogen (blood)	High blood urea nitrogen	NA
	Total calcium	Hypercalcemia	Hypocalcemia
	Bicarbonate	High bicarbonate	Low bicarbonate
	Chloride	High chloride	Low chloride
	Lactate dehydrogenase (LDH)	High LDH	NA
	Protein (total)	High proteins	Low total proteins
	Urea	High urea	NA
	Uric acid	High uric acid	NA
	Creatinine clearance	NA	Low creatinine clearance
	Bilirubin (direct)	High bilirubin	NA
Blood haematology	Basophils	NA	Low Basophil
	Eosinophils	High eosinophil	NA
	Haematocrit	High haematocrit	Low haematocrit
	Monocytes	High monocytes	NA
	Red blood cell count	High RBC	Low RBC

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	White blood cell count	High WBC	NA
Blood coagulation	Prothrombin time	NA	Low Prothrombin Time
Blood hormonology	Anti-thyroglobulin antibodies	High anti-thyroglobulin antibodies	Low anti-thyroglobulin antibodies
	TSH	High TSH	Low TSH
	T3 free	High T3	Low T3
	T4 free	High T4	Low T4
	ACTH	High ACTH	Low ACTH

In addition, haematology, clinical chemistry, coagulation, urine biochemistry, thyroid and adrenal function parameters data will be presented in listings.

5.4.4. Vital signs, clinical examination and other observations related to safety

5.4.4.1. Vital signs and clinical examination

Vital signs and clinical examination data (weight, Respiratory rate, systolic blood pressure [SBP], diastolic blood pressure [DBP], heart rate [HR]) and their change from baseline at on-treatment post-baseline visits will be summarised. For summaries over time, unscheduled visits are not considered.

Summaries will be produced for the following categories:

- SBP: (< 90 , ≥ 90 to < 140 , ≥ 140 mmHg),
- DBP: (< 60 , ≥ 60 to < 90 , ≥ 90 mmHg)
- HR: (< 60 , ≥ 60 to < 100 , ≥ 100 breaths/min)
- Respiratory rate (< 12 , ≥ 12 to < 20 , ≥ 20 breaths/min)

In addition, the worst (highest and lowest) absolute value and the last value under treatment will be summarised. This summary will consider unscheduled visits if they exist.

All vital signs will be presented in a listing.

5.4.4.2. Electrocardiogram

Absolute values of ECG data (Sinus rhythm, PR interval, QT interval, RR interval, heart rate and QT interval corrected using Fridericia formula [QTcF]) and their change from baseline at on-treatment post-baseline visits will be summarised. For summaries over time, unscheduled visits are not considered.

If triplicates are recorded, visit value will be derived as follows and the visit value will be listed and used as input to summary tables:

- For continuous data, the visit value will be the average of the triplicates.
- For sinus rhythm, the visit value will be the worst case.

QTcF will be described using the maximum absolute prolongation and maximum change from baseline at each on-treatment post-baseline visit. For post-baseline visits, each replicate will be considered as a separate record for identifying maximum QTcF. For baseline summary, baseline average of the triplicates will be used.

The following threshold defined in ICH E14 for QTcF will be used:

- Absolute values describing maximum prolongation: ≤ 450 , > 450 to ≤ 480 , > 480 to ≤ 500 and > 500 ms
- Change from baseline: ≤ 30 , > 30 to ≤ 60 and > 60 ms

Participants data listing for ECG data will include the on-treatment maximum absolute prolongation and maximum change from baseline in QTcF at each visit.

5.4.4.3. Quality of Life

Not applicable

5.5. Pharmacokinetics Analysis

Pharmacokinetic (PK) analysis will be performed on the PKs.

Serum drug concentration will be summarised for each protocol planned sampling time within cycles. For cycle 1 and 2, concentrations below the lower limit of quantification (LLOQ) which occurred prior to analysis visit maximum concentration (Cmax) will be imputed by 0, and concentrations below the LLOQ which occurred after the analysis visit Cmax will not be included in summary statistics. For all subsequent cycles, values reported as LLOQ will not be included in the summary statistics.

Summary statistics will also include the number of participants with serum drug concentration below the LLOQ. Unscheduled results won't be included in these summaries.

Serum concentration results will be presented in listing.

PK parameters will not be presented for Phase 1.

5.6. Immunogenicity Analysis

Immunogenicity analysis will be performed on the IGS.

Immunogenicity data summaries will include the following summaries of ADA status, titer and epitope towards 4-1BB and anti-PD-L1 per treatment arm.

ADA positive status definitions:

- ADA Prevalence (%) = (Number of participants with at least one positive ADA titer results in the study (n1)/ Number of participants with at least one ADA titer results in the study(n2)) x 100.
- Treatment-induced ADA positive = ADA negative at baseline and post-baseline ADA positive.

ADA results:

- ADA positive at any time in study
 - ADA Prevalence = At least one ADA titer in the study/ ADA positive at any time in study
- Treatment induced ADA positive
- ADA positive at baseline
- First post-baseline ADA positive titer

For each of the above categories a quantitative summary of positive ADA results will be presented.

If a participant has more than one positive ADA result, for the positive ADA summary the largest ADA result will be used.

4-1BB and Anti-PD-L1 results:

- 4-1 BB positive at any time in study
- Summary of positive ADA for positive 4-1BB results

- Anti-PD-L1 positive at any time in study
- Summary of positive ADA for positive Anti-PD-L1 results

If a participant has more than one positive 4-1BB or Anti-PD-L1 results, for the positive ADA summary the largest ADA result will be used.

6. INTERIM ANALYSES

Not applicable.

7. CHANGES TO PROTOCOL PLANNED ANALYSIS

No changes are made to the protocol planned analyses.

8. REFERENCES

1. Babb J, Rogatko A, Zacks S. Cancer phase I clinical trials: efficient dose escalation with overdose control. *Stat Med* 1998; 17(10):1103–20.
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9. APPENDICES

No Appendices.