



Statistical Analysis Plan

NCT Number: NCT05220098

Title: A Phase 1/2, First-in-Human, Open-Label, Dose-Escalation Study of TAK-280 in Patients With Unresectable Locally Advanced or Metastatic Cancer

Study Number: TAK-280-1501

Document Version and Date: Version 2.0, 09 Jun 2023

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Phase: 1/2

Version: 2.0

Date: 09-June-2023

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Based on:

Protocol Version: 3.0

Protocol Date: 19-May-2023

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REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
Original version	02-Feb-2022	Not Applicable
Amendment 1		To make SAP consistent with Amendment 3 of the protocol

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LIST OF IN-TEXT FIGURES

Not applicable.

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ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
AUC	area under the concentration-time curve
AUC _{0-last}	area under the concentration-time curve from time 0 to time of the last quantifiable concentration
AUC _{0-inf}	area under the concentration-time curve from time 0 to infinity
BOIN	Bayesian Optimal Interval
CL	total clearance
C _{max}	maximum observed plasma concentration
eCRF	electronic case report form
CR	complete response
CRS	Cytokine release syndrome
ctDNA	circulating tumor DNA
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
██████████	██
IHC	immunohistochemistry
iRECIST	Immunotherapy Response Evaluation Criteria in Solid Tumors
IV	intravenous
██████████	██
MedDRA	Medical Dictionary for Regulatory Activities
mCRPC	Metastatic castration-resistant prostate cancer
MTD	maximum tolerated dose
NAb	neutralizing antibody
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
██████████	██
ORR	overall response rate
OS	overall survival
PCWG3	Prostate Cancer Working Group 3
PD	progressive disease
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PSA	prostate-specific antigen
Q1w	once weekly
RECIST	Response Evaluation Criteria in Solid Tumors

RDE	Recommended dose for expansion
RP2D	recommended phase 2 dose
SAP	statistical analysis plan
SI	Standardized international
$t_{1/2}$	terminal phase half-life
$t_{\max}$	time of first occurrence of maximum observed concentration

World Health Organization

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1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objectives

The primary objective of this study is:

- To characterize the safety, tolerability, and DLTs of TAK-280 to determine the maximum tolerated dose (MTD) (if any) and recommended phase 2 dose (RP2D).

1.1.2 Secondary Objectives

The secondary objectives of the study are:

- To characterize the PK of TAK-280.
- To evaluate the preliminary antitumor activity of TAK-280 per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
- To evaluate the potential immunogenicity of TAK-280.

1.1.3 Exploratory Objectives

The exploratory objectives of the study are:

- To explore the relationships between PK, pharmacodynamics, safety, and TAK-280 antitumor activity.
- To evaluate circulating tumor DNA (ctDNA) before versus during treatment and to evaluate its correlation with TAK-280 antitumor activity.
- To evaluate relationships between baseline biomarkers including, but not limited to B7-H3 and PD-L1 expression in tumor biopsy specimens and TAK-280 antitumor activity.
- To evaluate qualitatively cleaved collagen from pretreatment and on-treatment plasma samples.
- To evaluate changes in target expression, immune cell infiltration, and activation markers in baseline (pretreatment) versus on-treatment tumor biopsy specimens (eg, changes in tumor infiltration lymphocytes [TILs]) to support dose selection.
- To evaluate the dose-response impact on tumor T-cell infiltration following TAK-280 administration.
- To evaluate the preliminary antitumor activity of TAK-280 per Immunotherapy Response Evaluation Criteria in Solid Tumors (iRECIST) (Seymour, et al., 2017).

1.2 Endpoints

1.2.1 Primary Endpoint(s)

The primary endpoint is:

- Incidence of DLTs and other toxicities during the dose-escalation phase.

Safety endpoints will be evaluated according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 for non-CRS toxicities and American Society for Transplantation and Cellular Therapy (ASTCT) CRS consensus grading (Lee et al. 2019) for CRS/IRR toxicities.

1.2.2 Secondary Endpoint(s)

The secondary endpoints are:

- PK parameters, including, but not limited to the following: maximum observed plasma concentration (C_{max}), area under the concentration-time curve (AUC), time of first occurrence of maximum observed plasma concentration (t_{max}), terminal disposition phase half-life ($t_{1/2}$), total clearance, and volume of distribution at steady state after intravenous administration for total TAK-280.
- Response assessments by the investigator for both dose escalation and cohort expansion using RECIST V1.1 (Eisenhauer et al. 2009). Patients with mCRPC that has metastasized to the bone will also be evaluated by using Prostate Cancer Working Group 3 criteria (Scher et al. 2016).
- Confirmed overall response rate (ORR) (complete [CR] + partial responses [PR]).
- Duration of response (DOR), defined as the time from the date of first documentation of a PR or better to the date of first documentation of progressive disease (PD) or death due to any cause, whichever occurs first, for patients with a confirmed response (PR or better).
- PFS, defined as the time from the date of the first dose of TAK-280 to the date of first documentation of PD or death due to any cause, whichever occurs first.
- OS, defined as the time from the date of the first dose of TAK-280 until death due to any cause.
- Disease control rate, defined as the percentage of patients who achieve PR or CR or stable disease (SD), with a duration of ≥ 2 consecutive scans.
- PSA response, defined as PSA reduction from baseline $\geq 50\%$ and confirmed at least 3 weeks later (patients with mCRPC only).
- Duration of PSA response, defined as the time from first PSA response to first documented PSA progression (patients with mCRPC only).

- Time to PSA progression, defined as the time from the date of the first dose of TAK-280 to the date that an increase of 25% or more and absolute increase of 2 ng/mL or more from the nadir are documented (patients with mCRPC only).
- The percentage of patients with PSA reductions of $\geq 50\%$ at 6 months (patients with mCRPC only).
- Immunogenicity Characterization (presence, titer, and impact of ADA and neutralizing antibody ([NAb], as appropriate).

1.2.3 Exploratory Endpoint(s)

The exploratory endpoints are:

- PD-L1 expression by standard IHC.
- Cleaved collagen levels in plasma.
- Tumor infiltration of different immune cell populations, including but not limited to, CD4 and CD8 T cells, natural killer (NK) cells.
- Evaluation of ctDNA levels.
- Evaluation of cytokine levels.
- B7-H3 expression in tumor tissue by IHC.
- PK parameters for total prodrug TAK-280.
- Response assessments by the investigator for both dose escalation and cohort expansion using iRECIST (Seymour, et al., 2017).

2.0 STUDY DESIGN

Study TAK-280-1501 is a phase 1/2, open-label, dose-escalation and cohort-expansion study designed to characterize the safety, tolerability, PK, pharmacodynamics, immunogenicity, and preliminary antitumor activity of TAK-280 administered by intravenous infusion QW in patients with unresectable, locally advanced or metastatic cancer who have experienced treatment failure or are intolerant to standard therapies.

The study consists of a dose-escalation phase to determine the 2 recommended doses for expansion (RDEs) of TAK-280 to be used during cohort expansion, followed by an open-label, cohort-expansion phase to further define the efficacy, safety and tolerability, PK, and pharmacodynamics of TAK-280 as a single agent, and determine the RP2D of TAK-280 in patients with mCRPC, [REDACTED]. Approximately 142 to 182 patients will be evaluated in this study.

2.1 Dose Escalation Phase

The purpose of the dose-escalation phase is to generate data to characterize the initial safety and tolerability profile of TAK-280 and determine the 2 RDEs to be administered to patients during the cohort-expansion phase.

- Single-Patient Dose Cohorts

Dose escalation will begin with a single patient cohort at each of the first 2 dose levels, [REDACTED].

- BOIN Design 3-Patient Cohorts

Then the cohort size will be converted to at least 3 patients for all subsequent dose levels of [REDACTED] following BOIN design (Liu & Yuan, 2015).

1. Treat the first cohort of at least 3 patients.
2. Assign a dose to the next cohort of patients as follows:
 - a) If the observed DLT rate at the current dose is ≤ 0.236 , escalate the dose to the next higher dose level.
 - b) If the observed DLT rate at the current dose is ≥ 0.359 , de-escalate the dose to the next lower dose level.
 - c) Otherwise, stay at the current dose level.
3. Repeat Step 2 until
 - 1) the maximum sample size of 27 DLT-evaluable patients is reached.
 - 2) the lowest dose is eliminated.
 - 3) at least 9 patients are evaluable at the current dose and the current dose would be the recommended dose for the next cohort based on BOIN design.

Intermediate dose levels other than the preplanned dose levels due to the cap of maximum dose increment and alternative dosing regimens will be explored selectively during the dose escalation phase of the study on the basis of the cumulative safety data and on agreement between the investigators and the sponsor. Cohort size other than 3 may also be considered.

A total of approximately 15 backfill patients may be enrolled during the dose-escalation phase at a dose level not exceeding the MTD for further evaluation of safety, PK, pharmacodynamics, and preliminary anti-tumor activity of TAK-280 after discussion between the investigators and sponsor. The backfill patients are not counted into the maximum sample size by BOIN design.

2.2 Cohort Expansion Phase

The purpose of the cohort-expansion phase is to provide additional information on the safety and tolerability of TAK-280 at the selected RDEs, contributing to the determination of the RP2D, to obtain additional data on the PK, pharmacodynamics, and immunogenicity of TAK-280, and to

assess the preliminary antitumor activity of TAK-280 in patients with mCRPC, [REDACTED]
[REDACTED]

At the end of the dose-escalation phase, 2 RDEs (a low and high dose) will be selected based on safety and tolerability, PK, pharmacodynamic, and efficacy data. The cohort-expansion phase will be conducted in [REDACTED] indications: [REDACTED], mCRPC, [REDACTED]. One of the [REDACTED] indications will be selected as the indication for randomization. Patients from the selected indication will be randomized 1:1 to receive either TAK-280 high RDE or low RDE. TAK-280 will be evaluated in the remaining [REDACTED] indications at the high RDE.

[REDACTED]
[REDACTED]
[REDACTED] Based on safety and tolerability, PK, pharmacodynamic, and efficacy analyses across indications [REDACTED] at the end of the expansion cohorts, a cohort using the low RDE (up to approximately 40 total patients) or 1:1 randomization of patients to high RDE and low RDE may also be initiated in the remaining [REDACTED] indications to further determine the RP2D.

2.3 [REDACTED]

2.4 Survival Follow-up Period

All patients will attend an EOT visit 30 days (+10 days) after the last dose of study drug or before the start of subsequent systemic anticancer therapy, whichever occurs first. All patients will be followed for survival every 12 weeks for 48 weeks by methods that include, but are not limited to, telephone, email, mail, or retrieval from online or other databases (eg, Social Security indexes). Patients will be followed until death, withdrawal of consent, lost to follow-up, or the follow-up has continued for a total of 48 weeks after the last dose of study drug, whichever occurs first.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

Not applicable.

4.0 SAMPLE-SIZE DETERMINATION

Approximately 142 to 182 total patients will be evaluated in this study.

The sample size (number of treated patients) for the dose-escalation phase will be approximately 42 patients, including approximately 27 DLT-evaluable patients and approximately 15 backfill patients. The total sample size of the cohort-expansion phase is estimated to be approximately 100 to 140 patients. A Bayesian predictive probability design was used [REDACTED]
[REDACTED] within each tumor histology. Because it is unknown which

cohorts will continue enrolling to the predefined full expansion cohort, enrollment may be stopped early.

5.0 ANALYSIS SETS

5.1 DLT evaluable analysis set

All patients in the dose-escalation phase who have received at least 3 doses of TAK-280 () or have had a DLT within the DLT-evaluation period. The DLT analysis set will be used to guide dose escalation decisions and to determine the MTD.

5.2 Safety analysis Set

All patients who received at least 1 dose of TAK-280. This population will be used for safety analyses, some efficacy analysis, and to determine the RDEs for the cohort-expansion phase.

5.3 Response evaluable analysis set

All patients with at least 1 dose of TAK-280 received and measurable disease at baseline, who had at least 1 postinfusion radiographic tumor assessment, or treatment discontinuation due to adverse event, clinical progression or death before first postinfusion radiographic tumor assessment.

5.4 PSA response analysis set

All patients with mCRPC who received at least 1 dose of TAK-280 and with a baseline elevation of PSA, who have at least 1 postinfusion PSA value, or treatment discontinuation due to adverse event, clinical progression or death before postinfusion PSA sample is collected.

5.5 PK analysis set

All patients who received at least 1 dose of TAK-280 and have sufficient PK data to reliably estimate 1 or more PK parameters. This population will be used for PK analyses.

5.6 Immunogenicity analysis set

All patients who received at least 1 dose of TAK-280 and had a baseline immunogenicity sample and at least 1 postbaseline immunogenicity sample for assessment.

5.7 Pharmacodynamic analysis set

All patients who received at least 1 dose of TAK-280 and had baseline and at least 1 postbaseline pharmacodynamic assessment.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. Standard deviation will be displayed to two levels of precision greater than the data collected. Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

Safety and efficacy summaries will be provided by dose level and schedule in the Dose Escalation Phase, and by tumor type and RDE in the Cohort Expansion Phase.

In descriptive summaries for safety, outliers (i.e., extreme relative to the majority of the data) will not be altered or removed from the summary. A row denoted “Missing” will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of patients treated with that dose level and schedule (Dose Escalation Phase), or with that tumor type and RDE (Cohort Expansion Phase) within the analysis set of interest, unless otherwise specified.

Data will be displayed in all listings sorted by dose level and schedule (Dose Escalation Phase), or by tumor type and RDE (Cohort Expansion Phase).

The study day will be calculated as assessment date - first dose date + 1 if the assessment date is on or after the first dose date; it will be calculated as assessment date – first dose date if the assessment occurs prior to the first dose administration.

All data are summarized based on the visit name collected on the electronic Case Report Form (eCRF) page.

6.1.1 Handling of Treatment Misallocations

Not applicable.

6.1.2 Analysis Approach for Continuous Variables

Continuous data will be described using descriptive statistics (i.e., N, mean, standard deviation, median, minimum, and maximum) unless stated otherwise in the section specific to an endpoint.

6.1.3 Analysis Approach for Binary Variables

Binary variables will be described using the patient count and percentage in each category unless stated otherwise in the section specific to an endpoint.

6.1.4 Analysis Approach for Time-to-Event Variables

Time-to-event data will be described using Kaplan-Meier methodology using 25th, 50th (median), and 75th percentiles with associated two-sided 95% confidence intervals as well as the survival probabilities at specified timepoints, unless otherwise specified.

6.2 Disposition of Patients

The analyses will be performed using *Safety Analysis Set*.

6.2.1 Patient Disposition

The number and percentage of on study treatment patients, patients who have discontinued study treatment, the reasons for discontinuation of study treatment, patient who participate in survival follow-up, who are on study, who have discontinued from the study, and the reasons for discontinuation of study will be summarized.

Patient disposition data will also be presented in a data listing.

Patients who failed at screening and the reason for screen failure will also be presented in a data listing.

6.2.2 Protocol Deviations

Protocol deviations will be recorded within the PPD Clinical Trial Management System (CTMS) and undergo cross-functional team review prior to database lock. The Study Deviations Rules Document contains all potential protocol deviations, classified by CTMS subtype. In addition, protocol deviation classification (e.g. significant vs. not significant) as determined by Takeda prior to database lock will be documented in CTMS.

All significant protocol deviations and activity subtype will be summarized.

All protocol deviations will also be presented in a data listing.

6.2.3 Missed Visits due to COVID-19

Information about missed visits or assessments due to COVID-19 will be recorded on a dedicated page in eCRF. The number and percentage of patients with at least one missed visits or assessments due to COVID-10, visit impact, reason for missing data, and impacted assessments will be summarized.

Missed visits or assessments due to COVID-19 will also be presented in a data listing.

6.3 Demographic and Other Baseline Characteristics

The analyses will be performed using *Safety Analysis Set*.

6.3.1 Demographics

Age, sex, ethnicity, race and race sub-categories, childbearing potential (female patients only), ECOG performance status at baseline, baseline height, baseline weight, baseline BMI, baseline

systolic blood pressure, baseline diastolic blood pressure, baseline pulse rate, baseline respiratory rate, baseline oxygen saturation, baseline temperature, and other parameters as appropriate will be summarized. Categories for missing data will be presented as needed.

Demographic and baseline characteristics will also be presented in a data listing.

6.3.2 Tobacco and Alcohol Usage

Usage, amount of usage, and number of smoking years for cigarettes, cigars, pipes, vaping, and tobacco, as well as usage, amount of usage, and number of drinking years for alcohol will be summarized.

Tobacco and alcohol usage data will also be presented in a data listing.

6.3.3 Disease Characteristics

Initial diagnosis, time since diagnosis (years), anatomic stage at initial diagnosis, anatomic stage at study entry, histologic type, EGFR mutation status for non-small cell lung cancer, ALK aberration status for non-small cell lung cancer, HPV status for HNSCC or cervical cancer, BRAF mutation status for CRC, KRAS mutation status for CRC, microsatellite instability overall status for CRC, BRCA status for TNBC, ovarian cancer, pancreatic ductal adenocarcinoma, or prostate cancer, BRAF mutation status for SCC, and PD-L1 status for all tumors will be summarized for both safety analysis set and response evaluable set.

Disease characteristics will also be presented in a data listing.

Time since diagnosis in years will be derived as (Date of informed consent signature – Date of diagnosis + 1) / 365.25.

6.3.4 Medical History

Medical history will be coded using the latest version of MedDRA.

General medical history, defined as any medical condition within 28 days of the first dose of TAK-280. A patient with multiple occurrences of medical history with a SOC will be counted only once in that SOC. A patient with multiple occurrences of medical history with a PT will be counted only once within that PT. Patient medical history will be summarized overall and for each SOC and PT.

Patient medical history will also be presented in a data listing.

6.4 Medication History and Concomitant Medications

The analyses will be performed using *Safety Analysis Set*.

6.4.1 Prior Medications

- Prior anti-cancer therapy related to the disease under study

The number and percentage of patients who received at least one line of therapies, lines of prior therapy, treatment intent, treatment setting, reason for discontinuation, best overall response, associated with radiation will be summarized.

Prior anti-cancer therapy related to the disease under study will also be presented in the Prior and Concomitant anti-cancer therapy data listing and flagged.

- Prior surgeries or procedures related to the disease under study

Prior surgeries or procedures related to the disease under study will be coded using the latest version of MedDRA dictionary.

The type of surgery or procedure will be summarized overall and for each system organ class and preferred terms.

Prior surgeries or procedures related to the disease under study will also be presented in the Prior and Concomitant Surgeries or Procedures data listing and flagged.

- Prior radiotherapy related to the disease under study

Radiation therapy type, anatomical location, treatment intent, treatment setting, and best overall response will be summarized.

Prior radiotherapy related to the disease under study will also be presented in the Prior and Concomitant Radiotherapy data listing and flagged.

See Section 9.2.4 for data handling rules for missing or partial dates.

6.4.2 Concomitant Medications

- Concomitant medications

Concomitant medications will be coded using the latest version of WHO Drug Dictionary.

The number and percentages of patients with at least one concomitant medication will be summarized overall and by Anatomical Therapeutic Chemical (ATC) level 4 term and PT. Concomitant medications will be sorted in descending order by ATC level 4 term based on counts in the overall column; PTs will be sorted alphabetically within each ATC level 4 term.

Concomitant medications will also be presented in the Prior and Concomitant Medications data listing. Of note, if a medication starts prior to the first dose of study treatment and has a stop date after the first dose of study treatment or is ongoing, will be flagged as both prior and concomitant.

- Anti-cancer therapy

The number and percentage of patients who received at least one line of therapies, lines of therapy, treatment intent, treatment setting, reason for discontinuation, best overall response, associated with radiation will be summarized.

Anti-cancer therapy will also be presented in the anti-cancer therapy data listing.

- Concomitant procedures

Concomitant procedures will be coded using the latest version of MedDRA dictionary, defined as procedures which are used concurrently and overlapping with the duration of current study treatment.

The concomitant procedures will be summarized overall and for each system organ class and preferred terms.

The concomitant procedures will also be presented in the Prior and Concomitant Surgeries or Procedures data listing.

- Concomitant radiotherapy

Concomitant radiotherapies are defined as radiotherapies which are used concurrently and overlapping with the duration of current study treatment.

Concomitant radiation therapy type, anatomical location, treatment intent, treatment setting, and best overall response will be summarized.

Concomitant radiotherapies will also be presented in the Prior and Concomitant Radiotherapy data listing. If a radiotherapy starts prior to the first dose of study treatment and has a stop date after the first dose of study treatment or is ongoing, will be flagged as both prior and concomitant.

See Section 9.2.4 for data handling rules for missing or partial dates.

6.5 Efficacy Analysis

Efficacy endpoints will be derived for all patients enrolled into the study (both in Dose Escalation and Cohort Expansion Phases) and listed as appropriate.

Efficacy analyses will include only patients treated with the dose level/schedule selected for the Dose Escalation Phase and with tumor type and RDE eligible for the Cohort Expansion Phase.

6.5.1 Primary Endpoint(s) Analysis

Not applicable. Efficacy is not the primary endpoint for this study.

6.5.2 Secondary Endpoint(s) Analysis

Secondary efficacy endpoints include ORR, DOR, PFS, OS, DCR, PSA response, duration of PSA response, time to PSA progression, and the percentage of patients with prostate-specific antigen (PSA) reductions of $\geq 50\%$ at 6 months (for patients with mCRPC only).

No formal statistical tests will be performed for these secondary efficacy endpoints.

6.5.2.1 Derivation of Endpoint(s)

ORR is defined as the percentage of patients who achieve confirmed CR or PR (determined by the investigator) during the study.

DOR is the time from the date of first documentation of a PR or better to the date of first documentation of PD or death due to any cause, whichever occurs first, for patients with a confirmed response (PR or better). Patients who have a response without documentation of PD or death will be censored at the date of last response assessment that is SD or better. Documentation of PD will be measured based on RECIST v1.1.

PFS is defined as the time from the date of the first dose of TAK-280 to the date of first documentation of PD or death due to any cause, whichever occurs first. Patients without documentation of PD or death will be censored at the date of the last response assessment that is SD or better. Documentation of PD will be measured based on RECIST v1.1.

OS is defined as the time from the first dose of TAK-280 to the date of death due to any cause. A patient will be censored if, at any time of last contact, the patient was alive, or lost to follow-up, or unknown to have died.

DCR is defined as the percentage of patients who achieve PR or CR or SD, with a duration of ≥ 2 consecutive scans.

PSA response is defined as a reduction in baseline PSA level of $\geq 50\%$ maintained for at least 3 weeks for patients with mCRPC only.

Duration of PSA response is the time from the date of the first PSA response to the date of the first documented PSA progression for patients with mCRPC only.

Time to PSA progression is the time from the date of the first dose of TAK-280 to the date that an increase of 25% or more and absolute increase of 2 ng/mL or more from the nadir are documented for mCRPC patients only.

6.5.2.2 Main Analytical Approach

6.5.2.2.1 ORR

The analyses will be performed using *Safety Analysis Set* and *Response Evaluable Analysis Set*.

ORR will be summarized by frequencies and percentages, and point estimates with two-sided exact 95% CIs, based on RECIST v1.1 and PCWG3 for mCRPC patients that has metastasized to the bone.

BOR will be summarized by frequencies and percentages. See Section 9.2.3 definitions of BOR based on RECIST v1.1.

A swimmer plot will be provided: each patient's study treatment duration will be represented by a bar, with symbols to distinguish the status at the end of the bar (still on study treatment, discontinued study treatment due to PD or discontinued study treatment not due to PD) and all the tumor assessments overall responses up to the last available scan.

A waterfall plot for best percentage change from baseline in the sum of diameters will also be provided. The best percentage change from baseline is defined as the maximum decline in sum of diameters, observed up until date of subsequent anti-tumor therapy. Waterfall plots go from the

worst value, such as greatest progression of disease, on the left side of the plot, to the best value, i.e., most reduction of tumor, on the right side of the plot (Socinski, et al., 2008).

The overall response and BOR will also be presented in data listings.

6.5.2.2.2 DOR

The analyses will be performed using *Confirmed responders in the Safety Analysis Set* and *Confirmed responders in the Response Evaluable Analysis Set*.

The duration of response in weeks will be calculated as follows:

- For patients who have PD or died, duration of response = (Date of death/PD – Date of initial response + 1) / 7;
- For patients who are alive without documented PD, duration of response = (Date of last tumor assessment where response is SD or better – Date of initial response + 1) / 7.

Table 6.a below specifies the scenarios, censoring rules and date of event/censored that will be carried out for the analysis using RECIST v1.1.

Scenarios	Event/Censored	Event/Censoring Date
No post-baseline tumor assessments and no death	Censored	Date of first dose of study drug
Available tumor assessments after initial response, but not known to have progressed or died according to data in the database	Censored	Date of last tumor assessment that is SD or better
Death or PD after two or more consecutive missed tumor assessments (i.e. 126 days or more without assessments) with no prior evidence of disease progression	Censored	Date of last tumor assessment prior to the first missed assessment
Disease progression (one objective PD)	Event	Date of PD
Death due to any reason without PD	Event	Date of death
Start of any new-anti cancer therapy with no prior evidence of disease progression	Censored	Date of last tumor assessment prior to the start of new anti-cancer therapy

The number and percentages of patients with an event, the reasons leading to event, the number of patients censored, and the reasons leading to censoring will be summarized.

The 25th percentile, median, and 75th percentile of DOR in weeks along with the corresponding two-sided 95% CIs will be estimated by the KM method. The CIs will be calculated using method of Brookmeyer and Crowley (1982).

Corresponding plots of Kaplan-Meier curves of DOR will be presented.

The DOR will also be presented in data listings.

6.5.2.2.3 PFS

The analyses will be performed using *Safety Analysis Set*.

The PFS in weeks will be calculated as follows:

- For patients who have PD or died, $PFS = (\text{Date of death/PD} - \text{Date of first dose of TAK-280} + 1) / 7$;
- For patients who are alive without documentation of PD, $PFS = (\text{Date of last tumor assessment that is SD or better} - \text{Date of first dose of TAK-280} + 1) / 7$;

The number and percentages of patients with an event, the reasons leading to event, the number of patients censored, and the reasons leading to censoring will be summarized using the same censoring rules as DOR in Table 6.a.

The 25th percentile, median, and 75th percentile of PFS in weeks along with the corresponding two-sided 95% CIs will be estimated by the KM method. PFS rates at 8 weeks (2 cycles), 16 weeks (4 cycles), and 32 weeks (8 cycles) from the first dose of TAK-280 will be computed along with two-sided 95% CIs. The CIs will be calculated using method of Brookmeyer and Crowley (1982).

Corresponding plots of Kaplan-Meier curves of PFS will be presented.

The PFS will also be presented in data listings.

6.5.2.2.4 OS

The analyses will be performed using *Safety Analysis Set*.

The OS in weeks will be calculated as follows:

- For patients who have died: overall survival = $(\text{Date of death} - \text{Date of first dose of TAK-280} + 1) / 7$;
- For patients who are lost-to-follow-up or not known to have died: overall survival = $(\text{Last date known to be alive} - \text{Date of first dose of TAK-280} + 1) / 7$;

The number and percentages of patients with an event, the reasons leading to event, the number of patients censored, and the reasons leading to censoring will be summarized.

The 25th percentile, median, and 75th percentile of OS in weeks along with the corresponding two-sided 95% CIs will be estimated by the KM method. OS rates at 8 weeks (2 cycles), 16 weeks (4 cycles), and 32 weeks (8 cycles) from the first dose of TAK-280 will be computed along with two-sided 95% CIs. The CIs will be calculated using method of Brookmeyer and Crowley (1982).

Corresponding plots of Kaplan-Meier curves will be presented.

The OS will also be presented in data listings.

6.5.2.2.5 DCR

The analyses will be performed using *Safety Analysis Set* and *Response Evaluable Analysis Set*.

DCR will be summarized by frequencies and percentages, and point estimates with two-sided 95% exact binomial CIs, based on RECIST v1.1 and PCWG3 for mCRPC patients that has metastasized to the bone.

The DCR will also be presented in data listings.

6.5.2.2.6 PSA Response

The analyses will be performed using *PSA Response Analysis Set*.

The PSA response will be summarized by frequencies and percentages of patients with mCRPC who achieve PSA response, and point estimates with two-sided 95% exact binomial CIs. The frequencies and percentage of patients with mCRPC with PSA reductions of $\geq 50\%$ at 6 months will also be summarized, with point estimates with two-sided 95% exact binomial CIs.

The PSA response will also be presented in a data listing.

6.5.2.2.7 Duration of PSA Response

The analyses will be performed using *mCRPC patients who have PSA response*.

Duration of PSA response in weeks will be calculated as follows:

- For patients who have PSA progression or died, duration of PSA response = (Date of death/first documented PSA progression – Date of first PSA response + 1) / 7;
- For patients who are alive without documented PSA progression, duration of PSA response = (Date of last PSA assessment – Date of first PSA response + 1) / 7.

The number and percentages of mCRPC patients with an event and the number of patients censored will be summarized.

The 25th percentile, median, and 75th percentile of duration of PSA response in weeks along with the corresponding two-sided 95% CIs will be estimated by the KM method. The CIs will be calculated using method of Brookmeyer and Crowley (1982).

Corresponding plots of Kaplan-Meier curves of duration of PSA response will be presented.

The duration of PSA response will also be presented in a data listing.

6.5.2.2.8 Time to PSA Progression

The analyses will be performed using *Safety Analysis Set*.

Time to PSA progression in weeks will be calculated as follows:

- For patients who have PSA progression or died, time to PSA progression = (Date of death/PSA progression – Date of first dose of TAK-280 + 1) / 7;
- For patients who are alive without documented PSA progression, duration of PSA response = (Date of last PSA assessment – Date of first dose of TAK-280 + 1) / 7.

The number and percentages of mCRPC patients with an event and the number of patients censored will be summarized.

The 25th percentile, median, and 75th percentile of time to PSA progression in weeks along with the corresponding two-sided 95% CIs will be estimated by the KM method. The CIs will be calculated using method of Brookmeyer and Crowley (1982).

Corresponding plots of Kaplan-Meier curves of time to PSA progression will be presented.

The time to PSA progression will also be presented in a data listing.

6.5.2.3 Sensitivity Analysis

ORR will be summarized by frequencies and percentages, and point estimates with two-sided 95% exact binomial CIs, based on iRECIST and PCWG3 for mCRPC patients that has metastasized to the bone. The analytical methods are the same as 6.5.2.1.1.

6.5.2.4 Supplementary Analysis

PFS is defined as the time from the date of the first dose of TAK-280 to the date of first documentation of PD, or death due to any cause, or start of any new anti-cancer therapy, whichever occurs first. Patients without documentation of PD or death or any new anti-cancer therapy will be censored at the date of the last response assessment that is SD or better.

Documentation of PD will be measured using both RECIST v1.1.

The PFS in weeks will be calculated as follows:

- For patients who have PD or died or start any new anti-cancer therapy, PFS = (Date of death/PD/new anti-cancer therapy – Date of first dose of study drug + 1) / 7;
- For patients who are alive without documented PD or new anti-cancer therapy, PFS = (Date of last tumor assessment that is SD or better – Date of first dose of study drug + 1) / 7.

The analytical methods are the same as 6.5.2.2.3.

6.5.3 Exploratory Endpoint(s) Analysis

The exploratory efficacy endpoint is the response assessments by the investigator for both dose escalation and cohort expansion using iRECIST (Seymour, et al., 2017).

6.5.3.1 ORR

Documentation of PD will be measured using iRECIST. See Section 9.2.3 definitions of BOR based on iRECIST.

The analytical methods are the same as 6.5.2.2.1.

Table 6.b below specifies the scenarios, censoring rules and date of event/censored that will be carried out for the analysis using iRECIST.

Scenarios	Event/Censored	Event/Censoring Date
No post-baseline tumor assessments and no death	Censored	Date of first dose of study drug
Available post-baseline tumor assessments, but not known to have progressed (i.e. confirmed PD) or died according to data in the database -No unconfirmed PD in any post-baseline tumor assessments -One unconfirmed PD followed by at least one subsequent tumor assessment with an overall response of SD, PR or CR (i.e. PD not confirmed)	Censored	Date of last tumor assessment
Death or confirmed PD after two or more consecutive missed tumor assessments (i.e. 126 days or more without assessments) with no prior evidence of disease progression	Censored	Date of last tumor assessment before first missed assessment
Disease progression: - Two scans proving PD or - one scan proving PD and no subsequent adequate tumor assessment (i.e missing or NE as overall response)	Event	Earliest Date of PD
Death due to any reason without PD	Event	Date of death
Start of any new-anti cancer therapy with no prior evidence of disease progression	Censored	Date of last tumor assessment prior to the start of new anti-cancer therapy

6.5.3.2 PFS

Documentation of PD will be measured using iRECIST and same censoring rules as DOR in Table 6.b. The analytical methods are the same as 6.5.2.2.3 and 6.5.2.4.

6.5.3.3 DCR

DCR will be summarized by frequencies and percentages, and point estimates with two-sided 95% exact binomial CIs, based on iRECIST and PCWG3 for mCRPC patients that has metastasized to the bone. The analytical methods are the same as 6.5.2.2.5.

6.6 Safety Analysis

6.6.1 DLTs

The analyses will be performed using *DLT evaluable analysis set*.

The frequencies and percentages of DLTs overall and by SOC and PT will be summarized for each dose level in the Dose Escalation Phase.

All DLTs will also be presented in a data listing.

6.6.2 Adverse Events

6.6.2.1 Definition of TEAE

TEAEs are defined as follows:

- Any immune-related AEs that occurred or worsened after administration of the first dose of study drug and through 90 days after the last dose date, or the initiation of new anticancer therapy, whichever occurs first.
- Any other non-immune-related AEs that occurred or worsened after administration of the first dose of study drug and through 30 days after the last dose date, or the initiation of new anticancer therapy, whichever occurs first.

Events that existed before the first administration of study drug and then increased in severity during or after the first administration of study drug will also be considered treatment emergent. Such events will be captured on the eCRF as new events, with the onset date as the date of the increase in severity.

Only TEAEs will be summarized in tables. Adverse events prior to treatment (e.g., due to study-related procedure) will only be listed. Refer to 6.6.2.7 for details.

6.6.2.2 Severity of Adverse Events

Adverse events will be coded using the MedDRA dictionary Version 24.0 or later (based on version at time of database lock). Severity will be evaluated according to CTCAE 5.0 for non-CRS toxicities and ASTCT consensus grading (Lee et al. 2019) for CRS toxicities.

Toxicity grades range from 1 to 5 where 1 = “Mild”, 2 = “Moderate”, 3 = “Severe”, 4 = “Life-threatening” and 5 = “Fatal”.

TEAEs with a missing severity will be summarized in tables as Grade 3 but will be presented in the data listings with a missing severity. If a patient reported multiple occurrences of the same TEAE, only the most severe will be presented.

6.6.2.3 Relationship of Adverse Events to Study Drug

The investigator will provide an assessment of the relationship of the event to the study drug. The possible classifications are 'Related', and 'Not related'.

TEAEs with a missing relationship will be summarized in tables as 'Related', but will be presented in the data listing with a missing relationship.

6.6.2.4 Serious Adverse Events

Serious TEAEs and drug-related serious TEAEs will be selected based on data reported in the eCRF page of Serious Adverse Events, and will be summarized as detailed in Section 6.6.2.7.

6.6.2.5 Adverse Events Leading to Dose Modifications

Dose modifications include dose reduction, drug interruption, drug withdrawn, dose delayed, drug infusion interruption. TEAEs leading to dose modifications will be selected based on data reported in the AE eCRF page of Action Taken with Study Treatment and will be summarized as detailed in Section 6.6.2.7.

6.6.2.6 Death or Treatment-related Death

Fatal TEAEs will be selected based on data reported in the eCRF page of Adverse Events (Outcome of Adverse Event = "Fatal"). All deaths, deaths within 30 days of treatment discontinuation, deaths related to disease under study as primary cause, and death between last dose date and death will be summarized.

6.6.2.7 Incidence of Adverse Events

AE data will be descriptively summarized by dose level/schedule in the Dose Escalation Phase and by tumor type and RDE in the Cohort Expansion Phase using *Safety Analysis Set*.

An overall summary table will display the number and percentage of patients who experience at least one event of any TEAE.

In addition, the following summary tables will display the number and percentage of patients by MedDRA System Organ Class (SOC) and preferred term (PT) (and CTCAE severity, when specified). Patients with multiple occurrences of events of the same preferred term and SOC will be counted once for each preferred term or SOC (at the highest severity and closest relationship to study drug, as applicable). All percentages will be calculated out of the number of patients in the Safety analysis set. These tables will be ordered in descending order of overall SOC incidence and overall PT incidence within each SOC:

- All TEAEs;

- All TEAEs by maximum CTCAE severity grade;
- All TEAEs CTCAE severity Grade 3 and 4;
- All TEAEs CTCAE severity Grade 5;
- Drug-related TEAEs;
- Drug-related TEAEs by maximum CTCAE severity grade;
- Drug-related TEAEs CTCAE severity Grade 3 and 4;
- Drug-related TEAEs CTCAE severity Grade 5;
- Serious TEAEs;
- Serious TEAEs by maximum CTCAE severity grade;
- Serious TEAEs CTCAE severity Grade 3 and 4;
- Drug-related Serious TEAEs;
- Drug-related Serious TEAEs by maximum CTCAE severity grade;
- Drug-related Serious TEAEs CTCAE severity Grade 3 and 4;
- TEAEs leading to dose reduction;
- TEAEs leading to drug interruption;
- TEAEs leading to dose withdrawn;
- TEAEs leading to dose delay;
- TEAEs leading to drug infusion interruption;
- TEAEs leading to death or treatment-related death;
- All deaths.

The following summary tables will display the number and percentage of patients by PT only and will be ordered in descending order of PT:

- All TEAEs;
- Drug-related TEAEs;
- Serious TEAEs;
- Drug-related Serious TEAEs.

The following data will also be presented in data listings:

- Serious TEAEs;
- TEAEs leading to dose reduction;
- TEAEs leading to drug interruption;

- TEAEs leading to dose withdrawn;
- TEAEs leading to dose delay;
- TEAEs leading to drug infusion interruption;
- TEAEs leading to death or treatment-related death;
- All deaths.
- All AEs;
- AEs leading to dose reduction;
- AEs leading to drug interruption;
- AEs leading to dose withdrawn;
- AEs leading to dose delay;
- AEs leading to drug infusion interruption;

6.6.2.8 CRS

CRS data will be descriptively summarized by dose level/schedule in the Dose Escalation Phase and by tumor type and RDE in the Cohort Expansion Phase using *Safety Analysis Set*.

An overall summary table will display the number and percentage of patients who experience each of the following:

- Any Treatment-Emergent CRS adverse events;
- DLT of CRS;
- CRS leading to dose reduction;
- CRS leading to drug interruption;
- CRS leading to dose withdrawn;
- CRS leading to dose delay;
- CRS leading to infusion interruption;
- The Maximum ASTCT grade of CRS;
- Outcome of the last CRS
- CRS signs and symptoms by SOC and PT;
- Grade 3 or above CRS signs and symptoms by SOC and PT;
- Time to onset of CRS event with respect to each lead-in dose and full dose in hours, defined as start time of the earliest signs and symptoms of CRS onset – stop time of each infusion immediately before each CRS event;

- Time to resolution of CRS event in hours, defined as stop time of the latest signs and symptoms of CRS resolution – start time of the earliest signs and symptoms of CRS onset.

In addition, CRS by Grade vs. time profile and the Tocilizumab usage in patients in safety population with any Treatment-Emergent CRS adverse events will be summarized.

The summary statistics of the time to onset of CRS event with respect to each lead-in dose and full dose in hours will be displayed with mean, median, minimum, and maximum by dose level/schedule in the Dose Escalation Phase only.

The Treatment-Emergent CRS adverse events, and use of anti-cytokine agents for patients in safety population with any Treatment-Emergent CRS adverse events (including drug name, dose, the administration time, the administration time relative to respective study drug dosing, and the grade of CRS incidence) will also be presented in data listings.

A Sanky plot of CRS events will be generated by dose day for each dosing regimen. The following categories will be displayed with different textures: no CRS, grade 1 CRS without tocilizumab, grade 1 CRS with tocilizumab, grade 2 CRS without tocilizumab, grade 2 CRS with tocilizumab, grade 3 CRS and above without tocilizumab, grade 3 and above CRS with tocilizumab, and no dose administrated.

6.6.3 Clinical Laboratory Evaluation

The analyses will be performed using *Safety analysis set*.

Clinical laboratory tests for pregnancy, hematology, comprehensive chemistry panel, special chemistry, coagulation, endocrine, and urinalysis (collectively referred to as “safety” labs) will be performed locally. All continuous safety laboratory values will be converted to Standardized International (SI) unites of measure.

The actual values of safety laboratory parameters and changes from baseline for each parameter will be summarized by cycle, day, and scheduled timepoints. Shift tables for safety laboratory parameters will be generated for changes in CTCAE 5.0 grades from baseline to worst postbaseline value. Separate shift tables will be generated for safety laboratory parameters with bi-directional toxicity grading with “high” conditions depending on the maximum post-baseline value and the “low” conditions depending on the minimum post-baseline value. In addition, the number and percentage of patients meeting the following concomitant criteria will be summarized:

- $AST > 3 \times \text{upper limit normal (ULN)}$
- $ALT > 3 \times \text{ULN}$
- Concurrent elevation of total bilirubin $> 2 \times \text{ULN}$
- $AST \text{ and/or } ALT > 3 \times \text{ULN}$ and concurrent elevation of total bilirubin $> 2 \times \text{ULN}$ (suggest a possible event meeting the Hy’s law criteria)

All safety laboratory test results will also be presented in data listings. The safety laboratory test results which are classified as out-of-range will be presented in a separate listing. A listing of

liver function tests, including flags to identify $AST > 3 \times ULN$, $ALT > 3 \times ULN$, concurrent elevation of total bilirubin $> 2 \times ULN$, and results meeting Hy's law criteria will also be presented. A listing of pregnancy test results will also be presented.

Mean laboratory values over time will be plotted for key laboratory parameters. Scatter plots of baseline values versus worst postbaseline values will be generated for key laboratory parameters.

6.6.4 Extent of Exposure and Compliance

The analyses will be performed using *Safety Analysis Set*.

6.6.4.1 Extent of Exposure

The following exposure variables will be summarized descriptively.

- Study treatment duration (weeks): $(\text{date of last dose} - \text{date of first dose} + 1) / 7$.
- Number of treated cycles: Total number of complete or partial treatment cycles the patient received.
- Number of infusions: Total number of TAK-280 infusions administered, even partially.
- Total cumulative dose (μg): The sum of actual doses (μg) received across all cycles.
- Duration of infusion (minutes): Stop time of infusion – start time of infusion; when infusions have been interrupted, the duration of the infusion will be computed as $(\text{interruption time} - \text{start time of infusion}) + (\text{stop time of infusion} - \text{infusion resume time})$.

Individual and overall exposure data will also be presented in a data listing.

6.6.4.2 Treatment Compliance and Modifications

The following compliance variables will be summarized descriptively.

- Dose intensity ($\mu\text{g/kg/weeks}$): $[\text{Total cumulative dose received } (\mu\text{g}) / \text{Baseline weight } (\text{kg})] / \text{Study treatment duration (weeks)}$.
- Expected dose intensity ($\mu\text{g/kg/weeks}$): $[\text{initial planned dose for each infusion } (\mu\text{g/kg}) \times \text{planned number of infusions at each cycle} \times \text{planned number of cycles}] / \text{planned study treatment duration (weeks)}$.

- Relative dose intensity (%): $((\text{Dose intensity}) / (\text{expected dose intensity})) \times 100$.
- Average dose per infusion ($\mu\text{g/infusion}$): $\text{Total cumulative dose } (\mu\text{g}) / (\text{number of infusions})$.

A dose is missed when the administration at site does not occur. A dose modification (e.g. dose delay, dose interruption during infusion, dose reduction, dose discontinuation) can occur per different protocol reasons. The numbers and percentages of patients with missed dose, dose

reduced, drug interrupted, drug withdrawn, dose delayed, and drug infusion interruption will be summarized along with their reason for dose adjustment.

6.6.5 Vital Signs

The analyses will be performed using *Safety Analysis Set*.

Vital signs include height, weight, temperature, pulse rate, systolic and diastolic blood pressure, respiratory rate and oxygen saturation.

The vital signs actual values and mean changes from baseline will be summarized using a shift table by cycle, day, and scheduled timepoints.

Vital signs actual values will also be presented in a data listing.

6.6.6 ECOG Performance Score

The analyses will be performed using *Safety Analysis Set*.

ECOG performance scores and change from baseline will be summarized using a shift table by cycle, day, and scheduled timepoints.

6.6.7 ECGs

The analyses will be performed using *Safety Analysis Set*.

ECG parameters include heart rate, PR interval, RR interval, QRS duration, QT interval, QTcB interval, and QTcF interval. For triplicate ECGs, the average of the available results for each parameter will be considered for summaries.

ECG parameters and mean change from baseline will be summarized using a shift table by cycle, day, and scheduled timepoints. ECG abnormalities will be summarized by cycle, day, and scheduled timepoints. The numbers and percentages of patients with QTcF < 450 msec, between 450 and 480 msec (inclusive), > 480 msec and < 500 msec and ≥ 500 msec will also be provided by cycle, day, and scheduled timepoints.

An ECG outlier analysis with numbers and percentages of patients with the following conditions will also be provided:

- Heart rate < 60 beats/min
- Heart rate < 50 beats/min
- Heart rate < 50 beats/min and concomitant $\geq 25\%$ reduction from baseline (i.e., bradycardic patient)
- Heart rate > 100 beats/min and concomitant $\geq 25\%$ increase from baseline (i.e., tachycardiac patient)
- Post-baseline QT interval > 500 msec with baseline QT interval ≤ 500 msec
- Post-baseline QTcF interval > 500 msec with baseline QTcF interval ≤ 500 msec

- Post-baseline QTcF interval > 480 msec with baseline QTcF interval ≤ 480
- Post-baseline QTcF interval > 450 msec with baseline QTcF interval ≤ 450
- Patients with QTcF maximum change from baseline
 - no increase
 - $>0 - < 30$ msec
 - $\geq 30 - \leq 60$ msec
 - > 60 msec
- Patients with QTcB maximum change from baseline
 - no increase
 - $>0 - < 30$ msec
 - $\geq 30 - \leq 60$ msec
 - > 60 msec

For triplicate ECGs, the above thresholds are checked for average values (not for the three single measurements).

ECG parameters will also be presented in a data listing.

6.7 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

6.7.1 Pharmacokinetic Analysis

6.7.1.1 PK Noncompartmental Analysis

The analyses will be performed using *PK Analysis Set*.

PK parameters will be estimated using noncompartmental methods from individual concentration-time profiles for each patient in the PK population. The following PK parameters will be determined for total, cleaved, and intact TAK-280, as the data permit:

- $C_{\max}$
- $t_{\max}$
- $AUC_{0-\text{last}}$
- $AUC_{0-\text{inf}}$
- $t_{1/2}$
- CL
- V_{ss}

PK parameters will be summarized using descriptive statistics, including n, arithmetic and geometric mean, median, standard deviation, percentage coefficient of variation (%CV), geometric (%CV), minimum, and maximum, by cycle and day. A separate table will be generated by cycle, day, and ADA status.

TAK-280 concentration-time data will be summarized using descriptive statistics, including n, NALQ, arithmetic and geometric mean, median, standard deviation, percentage coefficient of variation (%CV), geometric (%CV), minimum, and maximum, by cycle, day, and scheduled timepoint. A separate table will be generated by cycle, day, and ADA status.

PK parameters and concentration-time data will also be presented in data listings.

Individual and mean concentration-time profiles will be plotted by cycle, day, and scheduled timepoint, by dose level in the dose escalation phase and by cohort in the cohort expansion phase. Scatterplots of each PK parameter versus dose level will be generated.

6.7.1.2 PK Sampling Intended for Population PK Analysis

The plan for population PK analysis will be defined separately and the results reported separately.

6.7.2 Pharmacodynamic Analysis

The plan for pharmacodynamic analysis will be defined separately and the results reported separately.

6.7.3 Biomarker Analysis

The plan for biomarker analysis will be defined separately and the results reported separately.

6.8 Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis

Not applicable.

6.9 Other Analyses

6.9.1 Immunogenicity Analyses

The analyses will be performed using *Immunogenicity Analysis Set*.

The numbers and percentages of patients who have no detectable ADA at baseline and become positive in this assay, who have no detectable ADA at baseline and remain negative without detectable ADA, and who have detectable ADA at baseline and remain positive, and who have detectable ADA at baseline and become negative will be summarized. NAb titers will be assessed, if applicable.

The ADA and NAb data will also be presented in a data listing.

6.10

[REDACTED]

6.11 Data Monitoring Committee/Internal Review Committee/ [Other Data Review Committees]

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

7.0 References

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8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

Not applicable.

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9.0 APPENDIX

9.1 Changes from the Previous Version of the SAP

Change Number	Sections Affected by Change	Description of Each Change	Rationale
1	1.1 Objectives	Primary objectives, secondary objectives, and exploratory objectives updated.	Update according to protocol amendment 3
2	1.2 Endpoints	Primary endpoints, secondary endpoints, and exploratory endpoints updated.	Update according to protocol amendment 3
3	2.0 Study design	Cohort expansion phase study design updated.	Update according to protocol amendment 3
4	4.0 Sample size determination	Sample size updated for both dose-escalation and cohort-expansion phases updated.	Update according to protocol amendment 3
5	5.0 Analysis sets	5.1 DLT evaluable analysis set definition updated 5.3 Response evaluable analysis set added 5.4 PSA response analysis set added 5.6 Immunogenicity analysis set added	Update according to protocol amendment 3
6	6.1 General considerations	Safety and efficacy summaries in cohort expansion phase will be provided “by RDE” added.	Update according to protocol amendment 3
7	6.5.2 Secondary Endpoint(s) Analysis	The analyses of DCR, PSA response, duration of PSA response, time to PSA progression added. Analysis of ORR and DOR updated to be based on RECIST v1.1. Sensitivity analysis of ORR updated to be based on iRECIST.	Update according to protocol amendment 3
8	6.5.3 Exploratory Endpoint(s) Analysis	The analyses of ORR, PFS, and DCR added	Update according to protocol amendment 3
9	6.6.2.8 CRS	The analyses of CRS events added	Update according to protocol amendment 3
10	6.10 [REDACTED]	[REDACTED]	Update according to protocol amendment 3
11	9.2.4 Handling of missing or partial dates	Handling of missing start and stop time of CRS signs and symptoms and missing death dates added.	To assist the analysis of CRS events and deaths

9.2 Data Handling Conventions

9.2.1 Definition of Baseline

Baseline is defined as the last non-missing evaluation prior to or on the date that the first dose of the study drug is taken.

9.2.2 Definition of Visit Study Days

Study Day 1 is defined as the date on which a subject is administered their first dose of the study drug (excluding test dose if any). The study day will be calculated as assessment date - first dose date + 1 if the assessment date is on or after the first dose date; it will be calculated as assessment date – first dose date if the assessment occurs prior to the first dose administration.

9.2.3 Definition of Best Overall Response

The best overall response is the best timepoint response recorded from TAK-280 infusion until the last disease assessment before a new anticancer treatment has started or the first disease progression, whichever occurs first and is defined as ‘better’ in the order of CR, PR, SD, PD, and NE. The parameters assessed based on the objective responses include ORR, DOR, DCR (defined as percentage of patients who achieve PR or CR or SD, with a duration of ≥ 2 consecutive scans), PFS, and OS. The BOR is determined once all the data for the patient are known (Eisenhauer, et al., 2009; Seymour, et al., 2017). Table 9.a provides the BOR interpretation.

Table 9.a Best Overall Response When Confirmation of CR, PR and PD Are Required

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD
CR	SD	SD
CR	PD	SD
CR	NE	SD
PR	CR	PR ^a
PR	PR	PR
PR	SD	SD ^b
PR	PD	SD
PR	NE	SD
PD	CR	SD ^c
PD	PR	SD ^d
PD	SD	SD
PD	PD	Confirmed PD
PD	NE	Unconfirmed PD
NE	NE	NE

BOR: best overall response; CR: complete response; NE: not evaluable; PD: progressive disease; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors; SD: stable disease
Red text represents change from RECIST v1.1 (Eisenhauer, et al., 2009).

^a. If the CR is confirmed on the next assessment, the BOR becomes a CR.

^b. If a patient has assessments that are PR, SD, then PR later without an intervening visit of PD, BOR becomes a PR.

^c. This will become a CR if a later visit > 4 weeks results in an assessment of CR with no responses of PD from an intervening visit.

^d. Will become a PR if a later visit > 4 weeks results in an assessment of PR with no responses of PD from an intervening visit.

9.2.4 Handling of Missing or Partial Dates

Missing or partial dates will be handled as follows:

- For time since histological or cytological diagnosis and time since diagnosis of metastatic disease, partial dates for histological or cytological diagnosis and diagnosis of metastatic disease, will be imputed as follows:
 - No imputation will be done if the year is missing.
 - If the year is before informed consent date, then missing days will be imputed as the first day of the month and missing months will be imputed as July.
 - If the year is the current year of informed consent date, then missing days will be imputed as the first day of the month and missing months will be imputed as January.

- For cancer related surgeries, partial dates will be imputed as follows: missing day of the month will be imputed as the first of the month and missing month will be imputed as January. No imputation will be done if the year is missing.
- For radiotherapies, partial dates will be imputed as follows:
 - For partially missing start dates, missing day of the month will be imputed as the first of the month and missing month will be imputed as January. No imputation will be done if the year is missing.
 - For partially missing stop dates, missing day of the month will be imputed as the last day of the month and missing month will be imputed as December and at least 1 day after the start date of the therapy. No imputation will be done if the year is missing.
- For Prior or Concomitant Medications: Partial start or stop dates (where UN and UNK indicate unknown day and month respectively) will be imputed as follows:
 - Start dates:
 - UN-MMM-YYYY: Impute missing day as 01, so that medications are assigned to prior and concomitant if there's any doubt.
 - DD-UNK-YYYY/UN-UNK-YYYY: If the year is before the year of first dose of study treatment, assume 01-JUL-YYYY of the collected year. If the year is after the year of first dose of study treatment, assume 01-JAN-YYYY of the collected year. If the year is the same as the year of first dose of study treatment and the stop date (after any imputation) is missing or is on or after the first dose of study treatment, then assume 01-JAN-YYYY, so that medications are assigned to prior and concomitant. If the year is the same as the year of first dose of study treatment and the stop date (after any imputation) is prior to the first dose of study treatment, then assume the stop date for the start date.
 - Stop dates:
 - UN-MMM-YYYY: Assume the last day of the month.
 - DD-UNK-YYYY/UN-UNK-YYYY: Assume 31-DEC-YYYY.
 - In case of the death/study termination of the patients and the imputed stop date is after the date of death/study termination, the stop date will be imputed as the date of death/date of study termination.
 - Completely missing dates will not be imputed.
- For Adverse Events (missing month is not expected; missing day is allowed): Partial start or stop dates will be imputed as follows:
 - Partial start dates UN-MMM-YYYY (where UN indicates unknown day):

- If the month and year are different from the month and year of the first dose of study drug, or the year is the same as the year of the first dose of study drug, but the month is different, it will be imputed as 01-MMM-YYYY.
- If the month and year are the same as the first dose of study drug and the end date (after any imputation) is missing or is on or after the first dose of study drug, then it will be imputed as the date of the first dose of study drug.
- If the month and year are the same as the first dose of study drug and the end date (after any imputation) is prior to the first dose of study drug, then it will be imputed as 01-MMM-YYYY.
- Partial end dates UN-MMM-YYYY (where UN indicates unknown day):
 - UN will be imputed as the last day of the month.
 - In case of death/study termination of the patient and if the imputed end date is after the date of death/study termination, the end date will be imputed as the date of death/date of study termination.
- For CRS signs and symptoms (missing day will be imputed as above for adverse events):
Missing start or stop time will be imputed as follows:
 - Start time:
 - If the date part (after any imputation) is the same as the date part of one of the infusion date, it will be imputed as the start time of that infusion.
 - Otherwise, it will be imputed as 'T00:00'.
 - Stop time:
 - Missing stop time will be imputed as 'T23:59'.
- For death dates:
 - For partially missing death dates, missing day of the month will be imputed as the first day of the month and missing month will be imputed as January. No imputation will be done if the date is completely missing, and the imputed death dates will only be used for the overall survival analysis.
 - In case of the imputed death date is after the patient's last known alive date, the imputed death date will then be set as the patient's last known alive date.

9.3 Analysis Software

PK parameters will be estimated using WinNonlin software. All other analyses will be conducted using SAS® Version 9.4 or higher (SAS® Institute, Inc., Cary, North Carolina, United States).

Signature Page for TAK-280-1501 SAP Amend1_06092023

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Approval	Statistics 14-Jun-2023 23:32:05 GMT+0000
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Document Number: TDN-000184088 v1.0

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