



Clinical Study Protocol

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: Amendment 4, 22 Feb 2024

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PROTOCOL

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

Phase 1/2, First-in-Human Study of TAK-280 in Patients With Unresectable Locally Advanced or Metastatic Cancer

Sponsor: Takeda Development Center Americas, Inc
95 Hayden Avenue
Lexington, MA 02421

Study Number: TAK-280-1501 (ClinicalTrials.gov; NCT05220098)

PIND Number 162135

EU CT Number: 2023-504012-16

Compound: TAK-280

Date: 22 February 2024 **Amendment Number** 4

Amendment History:

Date	Amendment No.	Amendment Type	Region
22 February 2024	4	Substantial	Global
19 December 2023	3 GB v1	Nonsubstantial	Great Britain
19 May 2023	3	Substantial	Global
08 March 2023	2	Substantial	Global
23 November 2021	1	Substantial	Global
18 October 2021	Initial protocol	Not applicable	Global

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1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Serious adverse event (SAE) and pregnancy reporting information is presented in Section 10.0, as is information on reporting product complaints.

Takeda Development Center–sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each patient.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

The names and contact information for the medical monitor and responsible medical officer are in the study manual.

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1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic signatures may be found on the last page of this document.

_____, MD
_____, Oncology Clinical Sciences

Date

_____, PhD
_____, Oncology Biostatistics

Date

_____, PhD
_____, Oncology Quantitative
Clinical Pharmacology

Date

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, prescribing information, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study participants in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- ICH, E6 GCP: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section 10.0 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the investigator ([Appendix C](#)).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in [Appendix D](#) of this protocol.

Signature of Investigator

Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

1.3 Protocol Amendment 4 Summary of Changes

Protocol Amendment 4 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 4.

The primary purpose of this amendment is to allow the enrollment of patients with other tumor types with high B7 homolog 3 protein (B7-H3) protein expression. In addition, this amendment removes the analysis of cleaved collagen from the protocol, updates eligibility criteria to include patients with [REDACTED] who have received 4 prior therapies for locally advanced or metastatic cancer, adds mandatory requirement of tumor biopsy in patients enrolled in backfill, removes criterion that tumor biopsies are required for patients only at specific study sites during the cohort-expansion phase, removes the starting dose cohort level of [REDACTED] for tumor biopsies in the dose-escalation phase, removes limitations of pathologies in patients enrolled in backfill, adds a requirement that submission of an amendment to regulatory authorities is needed to restart recruitment after a halt in enrollment for study stopping rules, adds clarifying language to the dose-escalation rules, removes the requirement of post-treatment biopsy in patients with no baseline sample, updates the contraception requirements, and allows for treatment continuation beyond 14 treatment cycles.

In addition, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are applied throughout the document for clarification and administrative purposes.

Protocol Amendment 4			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	Section Number and Title	Description of Each Change and Rationale	
	Location	Description	Rationale
1.	Section 2.0 STUDY SUMMARY, Study Design, Dose-Escalation Phase, Cohort-Expansion Phase, and Main Criteria for Inclusion Section 6.1 Overview of Study Design Section 7.1 Inclusion Criteria	Added language to include the option for additional tumor types with high B7-H3 protein expression to be enrolled during the dose-escalation and cohort-expansion phase.	For the potential inclusion of additional tumor types with B7-H3 expression based on emerging clinical data.
2.	Section 2.0 STUDY SUMMARY, Study Design and Route of Administration Section 6.1 Overview of Study Design Section 8.1.1 General Administration Guidelines and Precautions	Added ±10 minutes window for TAK-280 infusion and clarified that infusion must be at least 30 minutes.	For clarity of the infusion times with allowed windows.
3.	Section 2.0 STUDY SUMMARY, Study Design and Dose Levels	Added language to allow for other dose levels and dosing regimens.	To allow flexibility in doses and dosing schedules based on the findings in the study.

Protocol Amendment 4			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	Section Number and Title	Description of Each Change and Rationale	
	Location	Description	Rationale
4.	Section 2.0 STUDY SUMMARY, Study Design, [REDACTED] Section 6.1.1.1 [REDACTED] Section 8.3 Dose-Escalation Rules	[REDACTED] [REDACTED] [REDACTED]	Updated for clarity.
5.	STUDY SUMMARY: Main Criteria for Inclusion Section 7.1 Inclusion Criteria Section 9.4.8 Pregnancy Test	Updated eligibility criteria for patients with [REDACTED] to allow 4 prior therapies for locally advanced or metastatic cancer.	To expand the inclusion of patients with [REDACTED] to those with more prior lines of treatment.
		Updated eligibility criteria to specify which lesions may be selected as measurable/target lesions.	To include more guidance about the selection of target lesions
		Updated contraception language to clarify the definition of women of childbearing potential and updated acceptable methods of contraception.	Revised in response to feedback from health authority.
6.	STUDY SUMMARY: Main Criteria for Inclusion Section 6.1.2 Backfill Patients in the Dose-Escalation Phase Section 7.1 Inclusion Criteria Section 9.4.16.2 Tumor Biopsies Appendix A Schedule of Events Appendix I Statistical Considerations for Paired Biopsy Specimens	Updated the requirements for pre-treatment and on-treatment tumor biopsies as follows: Added requirement for tumor biopsies in first 6 dose-escalation backfill patients in cohort-assigned doses [REDACTED] Removed criterion that tumor biopsies be required for patients only at specific study sites during cohort-expansion phase. Removed the starting dose cohort level of [REDACTED] for tumor biopsies in the dose-escalation phase	To provide a sufficient number of tumor biopsies for data analyses.

Protocol Amendment 4			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	Section Number and Title	Description of Each Change and Rationale	
	Location	Description	Rationale
7.	Section 4.1.1.1 mCRPC	Updated study rationale to include currently approved therapies to treat metastatic castration-resistant prostate cancer.	To provide accurate and complete information on available therapies for patients with metastatic castration-resistant prostate cancer.
8.	Section 5.1.3 Exploratory Objectives Section 5.2.3 Exploratory Endpoints Section 9.4.15 Radiographic Assessments Appendix A Schedule of Events	Added optional prebaseline tumor scans collected before screening to evaluate tumor growth.	To compare tumor growth before and after treatment with TAK-280, which could be a method to detect anti-tumor effect.
9.	Section 5.1.3 Exploratory Objectives Section 5.2.3 Exploratory Endpoints Section 9.4.16 Biomarker, Pharmacodynamic, and PK Samples Appendix A Schedule of Events	Removed collection of blood samples for circulating collagen levels.	Emerging clinical data do not support a need for collection of circulating collagen levels.
		Revised exploratory endpoint language.	To clarify exploratory endpoints.
10.	Section 6.1 Overview of Study Design Section 8.4.5 Criteria for Discontinuation of TAK-280	Added language to allow dosing with TAK-280 past 14 cycles.	To allow patients who are deriving benefit with TAK-280 to continue treatment.
11.	Section 6.1.2 Backfill Patients in the Dose-Escalation Phase	Removed limitation of pathologies into backfill.	To allow for patients with any tumor type to enter the backfill.
12.	Section 6.1.5 Study Stopping Rules	Added requirement of an approved amendment before restarting recruitment after halt in enrollment.	Revised in response to feedback from health authority.
13.	Section 8.2 Definitions of DLTs	Removed list of exclusions to hematologic dose-limiting toxicities.	Removed for clarity.
14.	Section 10.1.3 TEAE Definition	Added new section to define treatment-emergent adverse event.	Added for clarity.
15.	Section 10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events	Added language to specify the reporting period for pregnancies.	Added for clarity.

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Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	Section Number and Title	Description of Each Change and Rationale	
	<i>Location</i>	<i>Description</i>	<i>Rationale</i>
16.	Appendix J ASTCT ICANS Consensus Grading for Adults and Appendix K Management of ICANS	Updated to include full content of immune effector cell-associated neurotoxicity syndrome management guidelines, reference tables, and footnotes.	Revised for clarity and to correct missing information from the appendix in the previous version of the protocol.

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2.0 STUDY SUMMARY

Name of Sponsor: Takeda Development Center Americas, Inc	Compound: TAK-280
Title of Protocol: A Phase 1/2, First-in-Human, Open-Label, Dose-Escalation Study of TAK-280 in Patients With Unresectable Locally Advanced or Metastatic Cancer	PIND Number: 162135 EU CT No.: 2023-504012-16
Study Number: TAK-280-1501 (www.ClinicalTrials.gov: NCT05220098)	Phase: 1/2
Study Design: This is a phase 1/2, open-label, dose-escalation and randomized cohort-expansion study designed to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, immunogenicity, and preliminary antitumor activity of TAK-280 administered by intravenous (IV) infusion once a week (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 2 recommended doses for expansion (RDEs) of TAK-280 to be administered during the cohort-expansion phase. The dose-escalation phase will be followed by a cohort-expansion phase to further define the efficacy, safety and tolerability, PK, and pharmacodynamics of TAK-280 as a single agent and determine the recommended phase 2 dose (RP2D) in patients with metastatic castration-resistant prostate cancer (mCRPC), [REDACTED], [REDACTED], or other tumor types with high B7 homolog 3 protein (B7-H3) expression. TAK-280 will be administered as an IV infusion on Days 1, 8, 15, and 22 of a 28-day treatment cycle. During dose escalation, the TAK-280 infusion will be administered over 60 (±10) minutes [REDACTED] and the first cohort-assigned dose. Subsequent infusions may be administered over 30 (+10) minutes. The duration of the initial TAK-280 dose used in the cohort expansion phase will be based on findings from the safety and PK evaluation in the dose-escalation phase but must be at least 30 minutes. Tocilizumab is to be administered at the dose of 8 mg/kg at the onset of any signs potentially indicative of Grade 2 cytokine release syndrome (CRS), per American Society for Transplantation and Cellular Therapy (ASTCT) CRS consensus grading, defined by fever (a temperature of ≥38°C), hypotension not requiring vasopressors, and/or hypoxia requiring lowflow nasal cannula or blowby oxygen. The maximum dose administered at 1 time shall not exceed 800 mg. If no clinical improvement is observed after the first dose of tocilizumab, up to 3 additional doses may be administered at intervals of at least 8 hours between doses. In addition, administration of IV fluids, and other supportive measures are recommended, according to institutional practice. Early administration of tocilizumab is recommended to mitigate against more severe CRS (Lee et al. 2019). Dose escalation will begin with a single-patient cohort at each of the first 2 cohort-assigned dose levels, [REDACTED], and then the cohort size will be converted to at least 3 patients for all subsequent predefined dose levels of [REDACTED]. Administration of the initial TAK-280 cohort dose to the first 3 patients treated in each dose-escalation cohort will be staggered by a minimum of 48 hours. Intermediate cohort-assigned dose levels other than the predefined dose levels [REDACTED] and more-frequent dosing regimens may be explored selectively during the dose-escalation phase of the study, based on a review of the cumulative safety and exposure data and on agreement between the investigators and the sponsor. For both the dose-escalation and cohort-expansion phases, tumor assessments will be conducted every 8 weeks, starting on Cycle 1 Day 1 (C1D1) (ie, at the end of even-numbered cycles [eg, Day 28 of Cycles 2, 4, 6, 8, etc]). Patients will be eligible to receive treatment with TAK-280 until they experience confirmed disease progression, dose-limiting toxicities (DLTs), or unacceptable toxicity that necessitates permanent discontinuation of the study drug. After the last dose of study drug, all patients will enter the follow-up period and will be contacted every 12 weeks to ascertain their survival status by methods that include, but are not limited to, telephone, email, mail, or	

retrieval from online or other databases (eg, Social Security indexes). A patient will remain in follow-up until the patient has died, is lost to follow-up, has withdrawn consent, or until the follow-up has continued for a total of 48 weeks after the last dose of study drug, whichever occurs first.

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 of the study. Dose escalation will begin by initially enrolling patients with histologically proven, unresectable, locally advanced or metastatic cancers described in the literature as having enhanced B7-H3 expression. [REDACTED] tumors types will be included in the initial dose-escalation cohorts: [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED] mCRPC, [REDACTED]

[REDACTED] Patients with other tumor types with high B7-H3 expression may be enrolled after discussion and approval by the sponsor.

Decisions regarding dose escalation will be based on clinical safety, all available PK and pharmacodynamic data, and antitumor activity during the DLT-evaluation period, defined as the time between the initial dose of TAK-280 and Cycle 1 Day 28. Patients who have discontinued from TAK-280 during the DLT-evaluation period will complete the end-of-treatment (EOT) visit 30 days after the last dose and will enter the survival follow-up period. The severity of adverse events (AEs) will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0 for non-CRS toxicities and ASTCT CRS consensus grading (Lee et al. 2019) for CRS/infusion-related reaction (IRR) toxicities. DLTs will be defined separately for hematologic, nonhematologic, and hepatic nonhematologic events, as outlined later in the protocol. Patients who do not experience a DLT but are not DLT-evaluable will be replaced in the same dose-level cohort. Intermediate dose levels and alternative dosing regimens may be explored selectively during the dose-escalation phase of the study based on the cumulative safety data, and with agreement between the investigators and the sponsor. Any decision to implement an intermediate dose level or alternative dosing regimen will be documented and submitted to participating institutional review boards/independent ethics committees and regulatory authorities, per local requirements.

During the dose-escalation phase, all patients will be required to have continuous monitoring for signs or symptoms of CRS/IRRs in an inpatient facility after the administration of TAK-280. A minimum 24-hour overnight observation is required after the administration of all [REDACTED] and the first cohort dose. For the subsequent dose(s) in Cycle 1, patients must be monitored for at least 6 hours after infusion for signs or symptoms of CRS/IRRs. Observation for at least 4 hours after the administration of TAK-280 is required for all doses in Cycle 2. [REDACTED] Tocilizumab must be available at all times for use as needed to treat CRS/IRR symptoms.

Dose-escalation and de-escalation decisions will be based on a Bayesian Optimal Interval (BOIN) design along with considerations of safety, efficacy, PK, and biomarker assessments, and decisions will be made jointly by the sponsor and the investigators at meetings, including end-of-cohort meetings. The target toxicity rate for the maximum tolerated dose (MTD) is $\phi = 0.3$ (ie, 30%), and the maximum sample size is 27 DLT-evaluable patients for the dose-escalation phase. Dose escalation will begin with a single-patient cohort at each of the first 2 cohort-assigned dose levels, and then cohorts will be converted to a regular size of at least 3 patients for all other cohort-assigned dose levels. If a DLT is observed in a single-patient cohort, that cohort and all subsequent cohorts will be converted to a regular cohort size of approximately 3 patients, and dose-escalation or de-escalation decisions will follow the BOIN design.

The BOIN design uses the following rules, optimized to minimize the probability of incorrect dose assignment to guide dose escalation and de-escalation:

- If the observed DLT rate at the current dose is ≤ 0.236 , escalate the dose to the next higher cohort-assigned dose level.

- If the observed DLT rate at the current dose is >0.359 , de-escalate the dose to the next lower cohort-assigned dose level.
- Otherwise, stay at the current dose.

The dose-escalation phase will stop when 1 of the following occurs:

- The maximum sample size of 27 DLT-evaluable patients is reached.
- The lowest dose is eliminated.
- 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 the BOIN design.

[REDACTED]

Cohort-Expansion Phase:

The cohort expansion phase will be conducted in [REDACTED] indications: [REDACTED] mCRPC, and [REDACTED]. Additional tumor types may also be studied in the expansion phase based on emerging data. During the open-label, randomized, cohort-expansion phase, in 1 selected indication, approximately 40 patients ([REDACTED] patients for mCRPC if this is the selected indication for randomization) will be randomized 1:1 to receive either TAK 280 high RDE or low RDE determined from the dose-escalation phase of the study. Additionally, approximately 20 patients ([REDACTED] patients for mCRPC) in the remaining [REDACTED] indications to be studied in the cohort-expansion phase will receive the high RDE of TAK-280. [REDACTED]

[REDACTED] Based on safety and tolerability, PK, pharmacodynamics, and efficacy analyses across indications at [REDACTED] at the end of 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. [REDACTED]

Goals for the cohort-expansion phase of the study are the following:

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

Primary Objective:

- To characterize the safety, tolerability, and DLTs of TAK-280 to determine the MTD (if any) and RP2D.

Secondary Objectives: - 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 characterize the potential immunogenicity of TAK-280.																					
Patient Population: Patients aged ≥ 18 years or $\geq$ the local legal age of majority, as applicable, with unresectable, locally advanced or metastatic cancer who are intolerant to or did not respond to standard therapies.																					
Number of Study Participants: Approximately 142 to 182 total patients will be evaluated in this study. Dose-escalation phase: approximately 42 patients (including approximately 27 DLT-evaluable patients and approximately 15 backfill patients). Cohort-expansion phase: approximately 100 to 140 patients.	Number of Sites: Estimated total: approximately 35.																				
Dose Levels: The starting dose of TAK-280 is [REDACTED] [REDACTED] Based on observed data, intermediate dose levels may be assessed. Dose level minus 1 of [REDACTED] will be used if the starting dose is not tolerated.	Route of Administration: TAK-280 will be administered QW by IV infusion over 60 ($\pm$ 10) minutes (unless modified, as outlined in study procedures).																				
Duration of Treatment: Patients will be treated with TAK-280 for up to 14 treatment cycles. Each treatment cycle will be 28 days. Patients will be treated with TAK-280 until disease progression, unacceptable toxicity, or withdrawal from study occurs.	Period of Evaluation: Total time is expected to be approximately 37 months.																				
Main Criteria for Inclusion: - Age ≥ 18 years or $\geq$ the local legal age of majority, as applicable. - Criteria for disease state in dose escalation (2a) and cohort expansion (2b). Tumor histologies during dose escalation: Dose escalation will begin by initially enrolling patients with histologically or pathologically confirmed, unresectable, locally advanced or metastatic cancers that, based on literature reports, are considered to express B7-H3. Patients will be either ineligible for or intolerant of standard therapies, have no approved therapy with demonstrated benefit available, or have exhausted all available standard therapies. [REDACTED] tumor histology types will be included for the initial dose-escalation cohorts, as follows: <table border="1"> <tr><td>[REDACTED]</td><td>[REDACTED]</td></tr> <tr><td>[REDACTED]</td><td>[REDACTED]</td></tr> <tr><td>[REDACTED]</td><td>[REDACTED]</td></tr> <tr><td>[REDACTED]</td><td>[REDACTED]</td></tr> <tr><td>[REDACTED]</td><td>[REDACTED]</td></tr> <tr><td>[REDACTED]</td><td>[REDACTED]</td></tr> <tr><td>[REDACTED]</td><td>[REDACTED]</td></tr> <tr><td>[REDACTED]</td><td>[REDACTED]</td></tr> <tr><td>[REDACTED]</td><td>[REDACTED]</td></tr> <tr><td>[REDACTED]</td><td>[REDACTED]</td></tr> </table>		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
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- Platelet count $\geq 75 \times 10^3/\mu\text{L}$.
 - Hemoglobin ≥ 9.0 g/dL.
 - Absolute neutrophil count (ANC) $\geq 1.0 \times 10^3/\mu\text{L}$.
 - Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) $\leq 3.0 \times$ the upper limit of normal (ULN); for patients with hepatic metastases, ALT and AST $\leq 5 \times$ ULN.
 - Total bilirubin $\leq 1.5 \times$ ULN, except for patients with Gilbert's syndrome, who may be enrolled if the conjugated bilirubin is within normal limits.
 - Creatinine clearance ≥ 45 mL/minute (calculated by Cockcroft-Gault formula).
6. Archival tissue: Patients must consent to the acquisition of an existing formalin-fixed paraffin-embedded (FFPE) archival tumor sample, if available, either a block or unstained slides.
7. Tumor biopsy:
- Patients in dose-escalation DLT-evaluable cohorts are strongly encouraged to provide paired fresh tumor biopsy samples during screening (pretreatment) and within 7 days before Cycle 3 Day 1 (on treatment), as specified in the Schedule of Events ([SOE]; [Appendix A](#)), when a lesion is safely accessible for a low-risk biopsy procedure (those occurring outside the brain, lung/mediastinum, and intra-abdominal space or accessible by endoscopic procedures beyond the stomach or bowel).
 - During dose-escalation backfill and the cohort-expansion phase, similar paired tumor biopsies, preferably from the same lesion, will be required. Tumor biopsies will be required for the first 6 backfill patients enrolled at cohort-assigned dose levels [REDACTED]. The requirement for a biopsy specimen may be removed if endpoint criteria are met (see [Appendix I](#) for statistical considerations for paired biopsy specimens. The paired tumor biopsy is optional for patients with mCRPC limited to bone metastasis).
 - Tumor lesions used for biopsy should not be lesions used as one of the target lesions for response evaluation, unless no other lesions are suitable for biopsy. Tumor biopsy samples should be obtained only from lesions that are considered to be accessible with acceptable clinical risk in the judgment of the investigator. The sponsor should be contacted if the biopsy is considered to present a potentially unreasonable risk to the patient.
8. For the purpose of this study, a person of female birth sex is considered a woman of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhoea, a single FSH measurement is insufficient. WOCBP must meet the following criteria:
- Have a negative serum or urine pregnancy test result within 72 hours before the initiation of study drug administration.
 - Be willing to use 1 form of highly effective contraception and 1 additional effective barrier method of contraception throughout the study, starting at screening and through 90 days after the last dose of TAK-280. Contraception methods may be considered highly effective if they can achieve a failure rate of less than 1% per year when used consistently and correctly, including:
 - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral/intravaginal/transdermal.
 - Progestogen-only hormonal contraception associated with inhibition of ovulation: oral/injectable/implantable.
 - Intrauterine device.
 - Intrauterine hormone-releasing system.
 - Bilateral tubal occlusion.
 - Vasectomized partner (highly effective provided that partner is the sole sexual partner of the WOCBP study participant and the vasectomized partner has received medical assessment of the surgical success).

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of the risk associated with the study intervention[s]. Reliability of abstinence should be evaluated in relation to study duration and the preferred and usual lifestyle of the study participant.)
9. Male patients with partners of childbearing potential, even if surgically sterilized (ie, status postvasectomy), must agree to the following:
 - Use effective barrier contraception from the time of consent through 90 days after the last dose of TAK-280, or
 - Agree to practice true abstinence, if this is the established and preferred contraception method by the patient.
 - Agree to refrain from donating sperm from the time of consent through 90 days after the last dose of TAK-280.
 - In addition, have their partners use contraception (as documented for female patients) for the same period of time.
 10. Symptomatic central nervous system (CNS) metastases must have been treated, be asymptomatic for ≥ 14 days, and meet the following criteria at the time of enrollment:
 - No concurrent treatment for CNS disease (eg, surgery, radiation, corticosteroids ≥ 10 mg/d prednisone or equivalent).
 - No concurrent leptomeningeal disease or cord compression.
 11. Patients must be willing and able to comply with clinic visits and procedures outlined in the study protocol.

Main Criteria for Exclusion:

1. History of known autoimmune disease, except for:
 - Vitiligo.
 - Psoriasis not requiring systemic treatment for >1 year before receipt of TAK-280.
 - History of Graves' disease in patients now euthyroid for >4 weeks.
 - Hypothyroidism managed by thyroid hormone replacement.
 - Alopecia.
 - Well-controlled diabetes type 1.
2. Major surgery or traumatic injury within 8 weeks before the first dose of TAK-280.
3. Baseline prolongation of the QT interval with Fridericia correction method (QTcF) (eg, repeated demonstration of corrected QT interval [QTc] >480 ms, history of congenital long QT syndrome, or torsades de pointes). If patients are taking medications known to prolong the QTc at screening, patients may continue to take these medications as long as their baseline QTcF is <480 ms that are receiving such medications. Patients may not start using such medications on C1D1.
4. Unhealed wounds from surgery or injury.
5. Ongoing or active infection of Grade ≥ 2 .
6. History of any of the following ≤ 6 months before the first dose:
 - Congestive heart failure New York Heart Association Grade III or IV.
 - Unstable angina.
 - Myocardial infarction.
 - Unstable symptomatic ischemic heart disease.
 - Uncontrolled hypertension despite appropriate medical therapy.
 - Any ongoing symptomatic cardiac arrhythmias of Grade >2 (including acute atrial flutter/fibrillation, ventricular fibrillation, or ventricular tachycardia).

- Pulmonary embolism, or symptomatic cerebrovascular events, or any other serious cardiac condition (eg, pericardial effusion or restrictive cardiomyopathy).
 - Chronic, stable atrial fibrillation on stable anticoagulant therapy, including low-molecular-weight heparin, is allowed.
7. Oxygen saturation $<92\%$ on room air at screening or during C1D1 predose assessment.
 8. Inflammatory process that has not resolved ≥ 4 weeks before the first dose of study drug. Patients with chronic low-grade inflammatory processes such as radiation-induced pneumonitis are excluded regardless of duration.
 9. Clinically significant gastrointestinal disorders including the following:
 - Gastrointestinal perforation or unhealed ulcerations <6 months before study drug administration. Patients must have documented evidence (eg, from upper endoscopy or colonoscopy) of a completely healed area of prior perforation.
 - Gastrointestinal bleeding <2 months before study drug administration. Patients must have documented evidence (eg, from upper endoscopy or colonoscopy) of a completely healed area of prior bleeding.
 - Pancreatitis <6 months before the initiation of study drug. Patients must have a CT scan that is negative for evidence of remaining disease or normal pancreatic enzyme levels >4 weeks before the initiation of TAK-280.
 - Diverticulitis flare <2 months before study drug administration. Patients must have a CT scan demonstrating no evidence of remaining disease before the initiation of TAK-280.
 - History of Crohn's disease or ulcerative colitis.
 10. Vaccination with any live virus vaccine within 4 weeks or other vaccines within 2 weeks before the initiation of study drug administration. Inactivated annual influenza vaccination is allowed.
 11. History of bone marrow transplantation within the past 5 years or solid organ transplantation (as a recipient) and use of immunosuppressive agents.
 12. Known hypersensitivity to TAK-280 or any excipient [REDACTED] contained in the drug or diluent formulation, or known hypersensitivity to tocilizumab.
 13. Second primary invasive malignancy not in remission for ≥ 3 years. Exceptions include nonmelanoma skin cancer, cervical carcinoma in situ, resected melanoma in situ, or any malignancy considered to be indolent and never required therapy, with the exception of indolent lymphomas.
 14. Any serious underlying medical or psychiatric condition that would preclude informed consent or impair the patient's ability to receive or tolerate the planned treatment or comply with the protocol.
 15. Patients who are HIV, hepatitis B, or hepatitis C seropositive. Patients treated for hepatitis C must have viral titers of 0 for ≥ 2 years to be eligible. Patients with hepatitis B who have undetectable or ≤ 500 IU hepatitis B viral titers are eligible.
 16. Prior therapy before the planned start of TAK-280, as follows:
 - Cytotoxic chemotherapy, small-molecule inhibitors, radiation, interventional radiology procedure, or similar investigational therapies within ≤ 2 weeks or 5 half-lives, whichever is shorter.
 - Monoclonal antibodies, antibody-drug conjugates, radioimmunoconjugates, or similar therapies within ≤ 4 weeks.
 - Not recovered to Grade 1 or baseline or established as sequelae from all toxic effects of previous therapy (except alopecia, neuropathy, or autoimmune endocrinopathies with stable endocrine replacement therapy, or bone marrow parameters [any of Grade 1/2 permitted if directly related to bone marrow involvement]).
 - Concurrent use of hormones to maintain castrate levels of testosterone in patients with mCRPC or use for noncancer-related conditions (eg, insulin for diabetes, hormone replacement therapy) is acceptable.

Bisphosphonates are permitted for supportive care of patients with bone metastases (eg, breast or mCRPC).

17. Use of corticosteroids or other immunosuppressive medication, concurrently or within 14 days of the administration of TAK-280, except for:
- Topical, intranasal, inhaled, ocular, or intra-articular corticosteroids.
 - Physiologic doses of replacement steroid (eg, for adrenal insufficiency).
 - Steroid premedication for hypersensitivity reactions and antiemetic use.
 - Stable steroid dose (established for ≥ 28 days before the first dose of TAK-280) for previously treated brain metastasis. Corticosteroid dose on C1D1 should be ≤ 10 mg/d of prednisone or equivalent.
18. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test result during the screening period or a positive urine pregnancy test result on Day 1 before the first dose of study drug.

Main Criteria for Evaluation and Analyses:

Primary endpoint:

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

Secondary endpoints:

- 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 IV 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 be evaluated by using Prostate Cancer Working Group 3 criteria (Scher et al. 2016).
- Confirmed ORR (complete response [CR]+partial response [PR]).
- Duration of response (DOR), defined as the time from the date of first documentation of partial response (PR) or better to the date of the first documentation of PD or death due to any cause, whichever occurs first, for patients with a confirmed response (PR or better).
- Progression-free survival (PFS), defined as the time from the date of the first dose of TAK-280 to the date of the first documentation of PD or death due to any cause, whichever occurs first.
- Overall survival (OS), defined as the time from the date of the first dose of TAK-280 until death due to any cause.
- Disease control rate (DCR), defined as the percentage of patients who achieve PR or CR or SD, with a duration of ≥ 2 consecutive scans.
- Prostate-specific antigen (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 antidrug antibody [ADA] and neutralizing antibody [NAb], as appropriate).

Statistical Considerations:

The following analysis populations will be used for analysis of study data, as follows:

DLT-evaluable analysis set: All patients in the dose-escalation phase who 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.

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.

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 AE, clinical progression or death before first postinfusion radiographic tumor assessment.

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 AE, clinical progression or death before postinfusion PSA sample is collected.

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 will be used for PK analyses.

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.

Pharmacodynamic analysis set: Patients who received at least 1 dose of TAK-280 and had a baseline and at least 1 postbaseline pharmacodynamic assessment.

Statistical Methods:

General: Summary statistics will consist of the frequencies of each category of discrete variables, and of means, standard deviations, medians, minimum, and maximum values of continuous variables. Safety and antitumor activity summaries will be provided by dose level and schedule, and/or by tumor type. Response rates may be calculated for specific disease subgroups, if appropriate.

Efficacy: Response rates and DCR will be estimated along with 2-sided exact 95% confidence intervals (CIs) using response-evaluable analysis set and safety analysis set. DOR will be calculated for responders as the time from initial confirmed response (CR or PR) to the time of documented PD or death, whichever occurs first. Responders who complete the study without documented PD or death will be censored at the date of their last tumor assessment. PFS will be calculated as the time from the first dose of TAK-280 until documented PD or death from any cause. Patients with no PFS event will be censored at the date of their last tumor assessment. OS is defined as the time from the date of the first dose of TAK-280 to the date of death due to any cause. Kaplan Meier methods will be used to estimate the PFS and OS using safety analysis set and the DOR among the patients who have confirmed responses. PFS and OS rates at 8 weeks (2 cycles), 16 weeks (4 cycles) and 32 weeks (8 cycles) from the first dose of study drug will be computed along with CIs.

For patients with mCRPC, PSA response is defined as a reduction in baseline PSA level of $\geq 50\%$ maintained for at least 3 weeks. The percentage of patients with mCRPC who achieve PSA response will be summarized by point estimates with 2-sided exact 95% CIs. The percentage of patients with mCRPC with PSA reductions of $\geq 50\%$ at 6 months will also be estimated along with 95% exact CIs. These analyses will use the PSA response analysis set. Duration of PSA response is defined as the time from the date of the first PSA response to the date of the first documented PSA progression. Duration of PSA response and time to PSA progression will be analyzed descriptively by the Kaplan Meier method.

Other Assessments or Analyses:

PK Analysis: Individual TAK-280 plasma concentrations will be listed by sampling time and summarized by dose level. Individual and mean TAK-280 plasma concentration-time profiles for each treatment group will also be presented graphically. PK parameters will be listed and summarized by using descriptive statistics, including arithmetic and geometric mean, median, standard deviation, percentage coefficient of variation (%CV), minimum, and maximum. Population PK analyses may be conducted using data from this study alone or combined with data from other studies.

Immunogenicity Analysis: The percentage of patients who have no detectable ADA at baseline and become positive in this assay, the percentage of patients who have no detectable ADA at baseline and remain negative without detectable ADA, and those who have detectable and are positive for ADAs at baseline that increase or decrease in titer over the course of treatment will be summarized. Where applicable, NAb titers will be

summarized.

Pharmacodynamic Analysis: Summary statistics for pharmacodynamic parameters such as, but not limited to, those listed under Section 9.4.16 and 9.4.18 and corresponding changes from baseline will be summarized and/or may also be presented graphically. Possible associations between changes in pharmacodynamic measures of interest and TAK-280 dose, exposure, safety, and efficacy may be explored.

Sample Size Justification: The maximum sample size for the dose-escalation phase will be approximately 42 patients, including approximately 27 DLT-evaluable patients and approximately 15 backfill patients. The cohort-expansion phase has [REDACTED] planned for each cohort. The enrollment will be approximately 100 to 140 patients. Therefore, approximately 142 to 182 total patients will be evaluated in this study. Additional patients may be enrolled into each cohort to meet the evaluable sample size requirements if deemed appropriate.

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3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities except for those identified in the clinical supplier list in the study manual. The identified vendors will perform specific study-related activities either in full or in partnership with the sponsor.

3.2 Coordinating Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research, and study participation. The signatory coordinating investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

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3.3 List of Abbreviations

Abbreviation	Definition
%CV	percentage coefficient of variation
ADA	antidrug antibody
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ARPI	androgen receptor pathway inhibitor
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration-time curve
B7-H3	B7 homolog 3 protein
BID	twice daily
BiTE	Bispecific T-Cell Engager
BIW	twice weekly
BOIN	Bayesian Optimal Interval
BRCA	breast cancer gene
C1D1	Cycle 1 Day 1
CI	confidence interval
CL	total clearance
CNS	central nervous system
C _{max}	maximum observed plasma concentration
cmTAK-280	cleaved monomer of TAK-280
COBRA	Conditional Bispecific Redirected Activation
COVID-19	coronavirus disease 2019
CR	complete response
■	■
CRPC	castration-resistant prostate cancer
CRO	contract research organization
CRS	cytokine release syndrome
CT	computed tomography
cTAK-280	matrix metalloproteinase 9–cleaved TAK-280
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram

Abbreviation	Definition
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EOS	end of study
EOT	end-of-treatment
EU	European Union
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FIH	first-in-human
FLuc	firefly luciferase transduced
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLDH	glutamate dehydrogenase
GLP	Good Laboratory Practice
████	████████████████████
████	██
HR	hazard ratio
ICANS	immune effector cell-associated neurotoxicity syndrome
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IFN- γ	interferon gamma
IL	interleukin
IRB	institutional review board
iRECIST	Immunotherapy Response Evaluation Criteria in Solid Tumors
IRR	infusion-related reaction
IV	intravenous(ly)
KM	Kaplan-Meier
LFT	liver function test
████	████████████████████
MCP-1	monocyte chemotactic protein-1
mCRPC	metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MMP	matrix metalloproteinase
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NAb	neutralizing antibody
NCI CTCAE	National Cancer Institute Criteria for Adverse Events

Abbreviation	Definition
NOAEL	no-observed-adverse-effect-level
NOD-SCID	Nonobese diabetic severe combined immunodeficient
██████████	████████████████████
NSG	nonobese diabetic, severe combined immune deficiency gamma
██████████	████████████████████
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PC	prostate cancer
PD	progressive disease
PD-1	programmed death protein 1
PDL-1	programmed death ligand 1
PDx	programmed death protein 1 or programmed death ligand 1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency of Japan
PO	oral(ly) (drug route of administration)
PR	partial response
██████████	████████████████████
██████████	████████████████████
PSA	prostate-specific antigen
PSMA	prostate-specific membrane antigen
QW	once a week
QTc	corrected QT interval
QTcF	QT interval with Fridericia correction method
██████████	████████████████████
RDE	recommended doses for expansion
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SC	subcutaneous(ly)
██████████	████████████████████
SD	stable disease
sdAb	single-domain antibody
SOE	schedule of events
SUSAR	suspected unexpected serious adverse reaction
t _{1/2}	terminal disposition phase half-life
TDCC	T-cell-dependent cellular cytotoxicity
TEAE	treatment-emergent adverse event

Abbreviation	Definition
TGA	Therapeutic Goods Administration
TKI	tyrosine kinase inhibitors
t _{max}	time of first occurrence of maximum observed plasma concentration
TME	tumor microenvironment
████	████████████████████
██	██████████
UK	United Kingdom
ULN	upper limit of normal
US	United States
V _H	heavy-chain variable domain
V _L	light-chain variable domain
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

3.4 Corporate Identification

TDC Americas Takeda Development Center Americas, Inc

4.0 INTRODUCTION

4.1 Background

Takeda is developing the investigational therapeutic prodrug TAK-280 as a recombinant bispecific T-cell engager designed to target B7 homolog 3 protein (B7-H3, also known as CD276). TAK-280 was designed on the Takeda COnditional Bispecific Redirected Activation (COBRA) platform. This first-in-human (FIH) study of TAK-280 is a phase 1/2, open-label, dose-escalation and randomized cohort-expansion study designed to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, immunogenicity, and preliminary antitumor activity of TAK-280 administered once a week (QW) by intravenous (IV) infusion to patients with unresectable, locally advanced or metastatic cancer.

TAK-280 contains several design features that can potentially improve its safety profile, and its subsequent therapeutic efficacy over conventional T cell-engaging therapeutics.

TAK-280 is a polypeptide [REDACTED] that features the following domains as a full-length linear molecule, as depicted in [Figure 4.a](#):

- Two high-affinity, tumor-associated antigen binders (ie, anti-B7-H3, single-domain antibody [sdAb]).
- Unpaired CD3 ϵ binders (ie, CD3 ϵ heavy-chain variable domain [V_H] and CD3 ϵ light-chain variable domain [V_L]).
- CD3 binding domain blockers (ie, inactive V_H and inactive V_L).
- Protease cleavable linker(s) (ie, [REDACTED] amino acids).
- Albumin binding plasma half-life extender (ie, human serum albumin sdAb).

Figure 4.a TAK-280 Construct Design



α: anti; CD3: cluster of differentiation 3; CDR2: Complementarity-determining region 2; His6: histidine tag; HSA: human serum albumin; sdAb: single-domain antibody variable domain; mer: amino acid; Vh: heavy-chain variable domain; VI: light-chain variable domain.

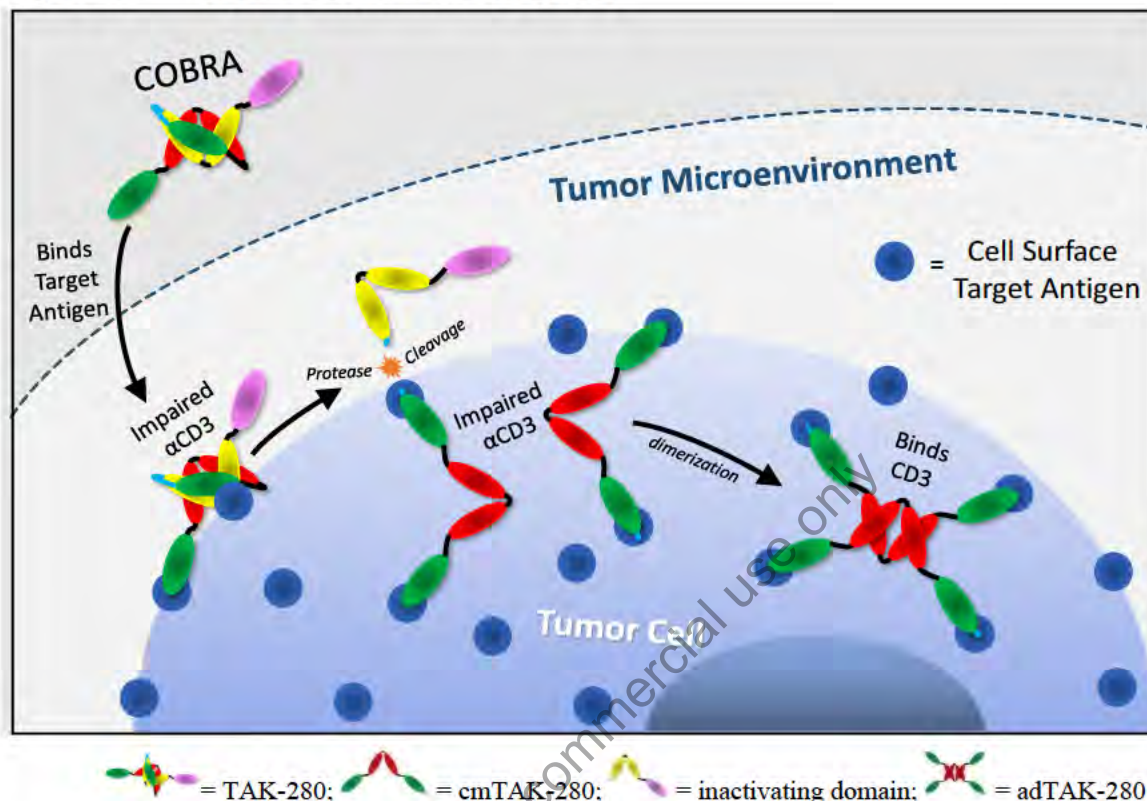
* The inactive anti-CD3 domains (Vh*, VI*) were created by substituting part or all of the normal CDR2 region with the Flag sequence (DYKDDDDK).

This unique arrangement of the molecular domains in the full-length molecule contributes to target binding and folded conformations of the uncleaved and cleaved COBRA pre- and post-cleavage ([Figure 4.a](#) and [Figure 4.b](#)). The COBRA T-cell engagers are administered systemically and are designed to persist in circulation as precursor molecules, by binding to serum albumin via the albumin-binding domain (shown in pink; [Figure 4.b](#)). This could provide a significant improvement in exposure kinetics over the Bispecific T-Cell Engager (BiTE), blinatumomab,

which has a short half-life ($t_{1/2} = 2$ hours) and requires continuous IV infusions over 4 to 8 weeks to maintain effective concentrations and achieve sustained T-cell mediated lysis of the tumor.

Upon administration of TAK-280, the high-affinity, target binding domains (shown in green in [Figure 4.a](#)) find the tumor-associated antigen in the tumor microenvironment (TME). During this time, the functional CD3 ϵ V_H/V_L domains (shown in red) are fully masked by their corresponding inactivated CD3 ϵ V_H/V_L domains (shown in yellow). Additionally, the incorporation of a constrained (8 aa) noncleavable linker between the functional CD3 ϵ -binding V_H/V_L domains (shown in red) prevents the functional CD3 ϵ -binding V_H/V_L from folding on itself and becoming activated. Specific protease cleavage in the TME releases the nonfunctional CD3 ϵ -blocking V_H/V_L domains, which are then rapidly cleared due to their relatively small size (~15-38 kDa). This ultimately results in the dimerization and formation of the active dimers (formed from the product of 2 cleaved COBRA molecules) with an active anti-CD3 binding site ([Figure 4.a](#) and [Figure 4.b](#)). Differential activity of the proteases in the TME (ie, matrix metalloproteinase [MMP]-9, [REDACTED]) is the primary determinant of COBRA anti-tumor activity. Additional information can be found in the TAK-280 Investigator's Brochure Edition 1.

Figure 4.b TAK-280 Mechanism of Action



α : anti; adTAK-280: active dimer form of TAK-280; B7-H3: B7 homolog 3 protein also known as CD276; cmTAK-280: cleaved monomer of TAK-280; COBRA: Conditional Bispecific Redirected Activation; TME: tumor microenvironment.

TAK-280 binds B7-H3 in prodrug form but does not bind CD3 ϵ . TAK-280 is cleaved by proteases in the TME, resulting in the formation of CD3 ϵ -binding active dimer. Concurrent loss of the albumin-binding, half-life-extension domain allows for rapid clearance of any active dimer that exits the TME.

4.1.1 Disease Background and Unmet Clinical Need

In this clinical study, patients with unresectable, locally advanced or metastatic cancer who experience failure or intolerance to standard therapies will be eligible for enrollment. The study will focus on enrolling patients with tumor types described in the literature as having enhanced B7-H3 expression, including

metastatic castration-resistant prostate cancer (mCRPC),

The rationale for selecting these distinct types of cancer is based on 3 factors: (1) the high level of unmet medical need for patients with these advanced diseases, (2) the relatively high level of B7-H3 expression observed in these cancers, and (3) the rapidly accumulating evidence (████████████████████) that immunomodulation with checkpoint inhibitors that enhance T-cell activity toward cancer cells has substantial antitumor activity in these tumors. Additional information is provided on the 3 tumor types of interest for the cohort-expansion phase of this study.

4.1.1.1 *mCRPC*

It is estimated that 268,490 men will be diagnosed and 34,500 men will die of prostate cancer (PC) in 2022, making it the most commonly diagnosed malignancy and the second leading cause of cancer death in men in the United States (US) (Siegel et al. 2022).

Antiandrogen therapy remains the standard systemic treatment in advanced and/or metastatic castration-sensitive disease; however, nearly all patients develop hormone-refractory disease. While docetaxel has been the traditional first-line therapy for mCRPC, second-generation new hormonal therapies such as abiraterone or enzalutamide have demonstrated substantial improvements in progression-free survival (PFS) and overall survival (OS) in mCRPC (Beer et al. 2017; Ryan et al. 2013). Cabazitaxel is another approved treatment option both in the European Union (EU) and the US for patients with mCRPC previously treated with a docetaxel-containing regimen. Recently, Olaparib was approved for the treatment of mCRPC in the US and EU. In the EU, it is approved in combination with abiraterone in patients for whom chemotherapy is not clinically indicated, or as a single agent in patients with breast cancer gene (BRCA)1/2-- mutations (germline and/or somatic) and who have progressed following prior therapy, including a new hormonal agent. In the US, the approved indication is only limited to patients who have deleterious or suspected deleterious mutations, either germline or somatic homologous recombination repair gene-mutation for monotherapy, or BRCA-mutation for combination with abiraterone. Although docetaxel is used in certain first-line settings as in symptomatic patients or those with large tumor volume, new hormonal therapies have largely replaced docetaxel as the preferred first-line therapy for mCRPC (Flaig et al. 2016). This situation did not change after the approval of cabazitaxel in both the US and EU in patients with mCRPC who have previously received docetaxel-containing regimen.

Separately, for patients with mCRPC with bone metastasis, radium-223, a radiopharmaceutical, is also approved in both the US and EU in patients who have received at least 2 previous treatments or who cannot receive other treatments. Another radiopharmaceutical, ¹⁷⁷Lu- prostate-specific membrane antigen (PSMA)-617, also approved in the EU for patients with PSMA-positive mCRPC, has shown significantly improved PFS outcomes (12.02 months vs 5.59 months, HR 0.41, 95% CI 0.29, 0.56) over the treatment with androgen receptor pathway inhibitor (ARPI), in taxane-naïve patients who are not candidates for poly adenosine diphosphate-ribose polymerase inhibition and who have progressed on prior ARPI (Sartor et al. 2023).

Similar to the PSMA-targeting bispecific T-cell engagers, TAK-280 targets another highly expressed target on PC (B7-H3) and has the potential to bring T cells to tumors and induce T-cell infiltration and attack on PC. The B7-H3 protein has been found to be highly expressed on 89% to 93% of PCs (Powderly et al. 2020; Zang et al. 2007). In addition, B7-H3 expression was observed to be increased with more aggressive disease and in metastases compared with benign prostate tissue (Benzon et al. 2017).

4.1.1.2

[REDACTED]

4.1.1.3

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4.1.2 Nonclinical Background

A brief summary of the TAK-280 nonclinical data is provided here; please refer to the TAK-280 Investigator's Brochure for a more detailed description.

Findings from both in vitro and in vivo studies support TAK-280's mechanism of action, efficacy, observed toxicity profile, and selection of the FIH dose.

[REDACTED], TAK-280 had strong and specific binding only to isoforms 1 and 2 of CD276 (B7-H3), the intended target (Report RP764). B7-H3 expression by immunohistochemistry in various tissues was comparable between humans (multiple donors) and cynomolgus monkeys (Report 20190631), the only pharmacologically-relevant species. HT-29 human CRC cells used for in vitro and in vivo modeling had relatively low-to-moderate levels of B7-H3 expression on the cell surface (Report TKD-BCS-01579-R1). In a T-cell-dependent cellular cytotoxicity (TDCC) assay, human peripheral blood mononuclear cells (PBMCs) had low-to-mid-picomolar cytotoxicity when co-cultured with B7-H3 expressing HT-29-firefly luciferase transduced (FLuc) tumor cells in the presence of increasing concentrations of TAK-280, which was most potent with the precleaved form (cTAK-280) and not present with the noncleavable form of TAK-280 ([REDACTED]; Report TKD-BCS-01581-R1 Amendment 1). Taken together, these data support the mechanism of action that TAK-280 can selectively bind B7-H3 on B7-H3-expressing tumor cells, and upon cleavage, induce T-cell-mediated tumor cell killing.

In a humanized nonobese diabetic, severe combined immunodeficient gamma (NSG) $\beta 2m^{null}$ Knockout mouse xenograft model, TAK-280 demonstrated antitumor activity when PBMCs were administered IV and HT-29 cells were implanted as subcutaneous tumors. Administration of TAK-280 IV once every 3 days for a total of 7 doses at [REDACTED] was associated with decreased tumor size while [REDACTED] did not have antitumor effects (Report TKD-BCS-01575-R1). These data suggest that cleavage is necessary for in vivo antitumor efficacy. TAK-280 PK and toxicokinetics demonstrating target-mediated drug disposition were observed following a single IV dose in NOD-SCID mice (nonlinear PK at doses ranging from [REDACTED] [Report TKD-BCS-01587-R1]). Single and repeat doses in the 2-week and 5-week toxicity studies in cynomolgus monkeys (1-hour and 30-minute IV infusion) demonstrated relatively nonlinear PK at doses ranging from [REDACTED] (Reports 20183241 and 20248408), although formation of antidrug antibody (ADA) at the later time points in the 5-week study reduced the number of quantifiable TAK-280 concentrations.

The in vivo toxicologic profile of TAK-280 was evaluated in a 2-week non-Good Laboratory Practice (GLP) study and a 5-week GLP-compliant toxicity study in male and female cynomolgus monkeys (Reports 20183241 and 20248408). In the 2-week non-GLP-compliant study, TAK-280 was administered IV via 60-minute infusion on Days 1 and 8 using either the same dose level each week, or a [REDACTED] regimen to examine the feasibility of reducing the cytokine response by [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED] In addition, this study evaluated the on-target toxicologic effects following administration of TAK-280 and demonstrated the lack of notable findings following [REDACTED] administration. The 5-week toxicity study in cynomolgus monkeys used an [REDACTED] [REDACTED] via 30-minute IV infusion) followed by a [REDACTED] recovery period. Nontolerated doses identified bone marrow toxicity affecting all hematopoietic lineages associated with decreases in clinical pathology parameters leading to multisystemic hemorrhage, and hepatotoxicity with correlating clinical pathology parameters of liver inflammation and injury. At tolerated doses, there was decreased red blood cell and platelet

parameters that correlated with compensatory increases in reticulocytes and microscopic observations of extramedullary hematopoiesis in multiple organs, acute phase response, transient decreases in leukocyte parameters, variable increases in liver enzymes lacking microscopic correlates, and transient dose-dependent increases in cytokines and expression of CD25 and/or Ki67 on lymphocytes. Most findings at tolerated doses were reversible or partially reversible at the end of the recovery period.

4.1.3 Clinical Background

This study (TAK-280-1501) is an FIH, dose-escalation and cohort-expansion study of TAK-280 designed to characterize the safety, tolerability, PK, pharmacodynamics, immunogenicity, and preliminary antitumor activity of TAK-280 administered by IV infusion QW in patients with unresectable, locally advanced or metastatic cancer. The study was initiated in Australia in April 2022 and is being expanded globally.

The projections of the possible risks and adverse events (AEs) that may occur or be observed in patients treated with TAK-280 are based on results from nonclinical investigations and early clinical tolerability data of closely related COBRA molecule, TAK-186.

4.2 Rationale for the Proposed Study

One of the major challenges facing the currently available T-cell engagers against solid tumors is the lack of highly expressed, unique, cell-surface antigens, such as those available to target in hematologic malignancies (eg, CD19). Most of the known, highly expressed, cell-surface antigens on solid tumors are also expressed widely on normal tissues (eg, epidermal growth factor receptor [EGFR] and epithelial cell adhesion molecule [or EpCAM]). In addition, the cell-surface antigens used to target hematologic malignancies are lineage-specific markers of cell types that can tolerate a significant degree of ablation (eg, CD19 in B-cell malignancies, B-cell maturation antigen in multiple myeloma), unlike the tissues expressing solid-tumor targets. Because T-cell engagers are highly potent molecules, even very low levels of cell-surface target-antigen expression on normal tissues (ie, on target off tumor activity) may lead to unacceptable toxicities. Thus, efficacy of current, inherently active anti-CD3 engagers are limited by toxicity (ie, on target off tumor activity) that can often appear quickly and severely, restricting the ability to administer these molecules at doses high enough to achieve meaningful tumor concentrations and antitumor activity with durable response ([Ishiguro et al. 2017](#); [Yu et al. 2017](#)).

The novel COBRA platform was developed to overcome this challenge. COBRAs are engineered to enable targeting of more widely expressed and validated tumor cell-surface antigens by generally limiting T-cell activation and subsequent cytotoxic activity to the TME.

TAK-280 is a novel, conditionally activated, bispecific T-cell engager designed to target B7-H3 being developed for the treatment of patients with advanced cancers. In the absence of proteolytic activation, TAK-280 is a prodrug that can bind to cell surface-expressed B7-H3 and circulating serum albumin (the latter extends the half-life of TAK-280 after administration), but it does not bind to CD3ε expressed on T cells until it is activated. As described in Section 4.1,

activation occurs through the protease cleavage of an internal peptide linker, see [Figure 4.a](#). Once cleaved, TAK-280 can then act as an anti-CD3 ϵ agonist, stimulating T-cell activation and a cytotoxic antitumor response against coengaged B7-H3-expressing cells.

Based on nonclinical data, the design features of TAK-280 described in Section 4.1 is expected to result in increased tolerability relative to potency compared with traditional CD3 bispecifics. TAK-280's cleavage-dependent conditionality, ability to engage tumor target antigen, and induce T-cell mediated tumor killing were demonstrated in a TDCC assay and humanized mouse tumor xenograft model. In the TDCC assay, only the cleavable forms (TAK-280 and cTAK-280 [most potent]) induced human T-cell-mediated cytotoxicity in B7-H3-expressing HT-29-FLuc tumor cells, whereas the noncleavable form (██████) did not induce T-cell mediated cytotoxicity. Similarly, in vivo administration of TAK-280 led to decreased tumor size in subcutaneous B7-H3-expressing HT29 tumors in NSG $\beta 2m^{null}$ mice humanized with IV human PBMCs, whereas ██████ did not have antitumor effects. In toxicity studies using the pharmacologically-relevant species (cynomolgus monkeys), on target toxicity effects were observed in animals administered TAK-280 but no notable effects were seen with administration of ██████.

4.2.1 Rationale for the Patient Population

TAK-280-1501 is an FIH, dose-escalation and expansion study of TAK-280. In the dose-escalation phase, patients will be enrolled with histologically confirmed, unresectable, advanced (locregionally recurrent, not amenable to curative therapy) or metastatic solid tumors who have no standard therapeutic option with a proven clinical benefit or who are ineligible or intolerant to these therapies. This study will focus on tumor types that, based on literature, are considered to express B7-H3, as summarized in Section 4.1. This patient population with B7-H3 expression also has the most favorable balance between patient risk and benefit for this phase 1 study. During dose escalation, this study will use a collection of tumor tissue and blood samples to identify pharmacodynamic biomarkers to support both dose selection and future patient selection/enrollment.

4.3 Potential Risks and Benefits

The potential effects listed are based on findings from nonclinical studies with TAK-280, preliminary clinical data from the closely related molecule TAK-186, and publicly available data regarding other bispecific T-cell engagers that are currently in clinical development. These effects may or may not develop in human patients treated with TAK-280. It is possible that administration of TAK-280 during a clinical study will result in events and toxicities that were not observed or predicted from the completed nonclinical studies conducted in animals and in studies with other bispecific T-cell engagers.

This clinical study protocol for TAK-280 includes mitigations and monitoring for the potential AEs specified for this compound by using close clinical monitoring, laboratory and imaging evaluations, including cardiac monitoring and disease assessment. The timing of these tests and evaluations is detailed in the schedule of events ([SOE] [Appendix A](#)). Additional tests and evaluations will be considered based on symptoms and findings observed in the study.

Guidelines for the management of clinical events are provided in Section 8.8.

4.3.1 CRS

In the GLP-compliant, repeat-dose toxicology study in monkeys, there were TAK-280–related increases in circulating cytokines at all dose levels. Interleukin (IL)-6, monocyte chemotactic protein-1 (MCP-1), and IL-10 levels were elevated after administration of TAK-280 on Days 1 and 8; they generally increased at 4, 8 and/or 24 hours after administration and returned to baseline levels by 48 to 72 hours after administration. Increases in interferon gamma (IFN- γ), granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor-alpha were noted sporadically in individual animals, but a clear relationship to TAK-280 could not be established. There were no TAK-280–related increases in IL-2. Additionally, emesis occurred after dosing on Days 1 and/or 8 in some monkeys at the low and high doses. At the highest dose level, there were clinical observations that correlated with the greatest increases of MCP-1, IL-6, and IL-10 after the Day 8 dose, including pale skin/mucous membranes, hunched posture, and decreased activity. Clinical pathology evidence of an acute-phase response with increases in C-reactive protein and triglycerides and decreases in albumin was noted at various time points. Results from the toxicity studies in nonhuman primates suggest a potential for cytokine release syndrome (CRS) in patients treated with TAK-280.

It is important for investigators to become familiar with identifying and managing CRS. A high level of vigilance is required to recognize the initial signs and symptoms in patients receiving TAK-280, which will permit early intervention to prevent progression to more severe CRS. Manifestations of CRS include, but are not limited to, pyrexia, chills, headache, nausea, vomiting, asthenia, hypotension, tachycardia, rash, wheezing, hypoxia, increased liver function test (LFT) results (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and total bilirubin), capillary leak syndrome, and disseminated intravascular coagulation. These manifestations can occur in any combination or in isolation; therefore, investigators must have a high level of suspicion that CRS may be the underlying cause if any one of these symptoms is observed.

4.3.2 Infusion-Related Reactions

Infusion-related reactions (IRRs) may be classified as a potential risk of IV administered TAK-280 therapy and will be monitored during clinical development. If an IRR occurs, patients will be monitored until the complete resolution of symptoms and treated as clinically indicated, including interruption and/or slowing of infusion rate as necessary. Interventions may include [REDACTED], antihistamines, IV saline, oxygen, bronchodilators, corticosteroids, and vasopressors, depending on the symptoms.

TAK-280 should be administered only in a clinical environment where resuscitation equipment is available for immediate use. Patients should receive full supportive care to treat IRRs or anaphylaxis according to institutional guidelines.

4.3.3 Liver Toxicity

B7-H3, the target of TAK-280, is expressed on hepatocytes. In the GLP-compliant, repeat-dose, toxicity study in cynomolgus monkeys, the 2 high-dose monkeys that were removed moribund from the study or died on Day 16 had mild to moderate mixed-cell inflammation in the liver, with secondary, moderate hepatocellular degeneration/necrosis that correlated with increases in ALT and glutamate dehydrogenase (GLDH) and with macroscopic findings of fluid accumulations and/or icterus. In animals that survived to scheduled necropsy, at the high dose of [REDACTED], there were minimal to moderate increases in ALT and/or GLDH at variable time points between Days 4 and 18 and minimal increases in total bilirubin, with no microscopic correlates at necropsy on Day 36. Results from the toxicity studies in nonhuman primates suggest a potential for liver toxicity effects in patients treated with TAK-280. Clinical data from a nonconditional, B7-H3 bispecific molecule (MGD009) suggest the potential for liver toxicity, including reversible elevations in transaminases with or without concurrent elevations in bilirubin. Patients will be closely monitored for LFT result elevations and for any clinical signs and symptoms of liver toxicity throughout the study and managed according to the guidelines provided in this protocol, including use of IV and oral (PO) steroids.

4.3.4 Hematologic Toxicity

In the GLP-compliant, repeat-dose, toxicity study in cynomolgus monkeys, the 2 high-dose monkeys that were removed moribund from the study or died on Day 16 had pale skin, large hematoma on the femoral vein, epistaxis, and generalized petechiae in 1 or both animals; also observed was moderate to marked decreased cellularity in the bone marrow affecting all hematopoietic lineages that correlated with decreased platelets and red blood cell mass and subsequent multisystemic hemorrhage. Microscopy revealed mild bone marrow fibroplasia, minimal to moderate extramedullary hematopoiesis, and minimal to marked hemorrhages in multiple organs. In animals that survived to scheduled necropsy at all doses [REDACTED], there was minimally to mildly decreased red blood cell mass between Days 4 and 36, with an appropriately responsive increase in reticulocytes. In animals at [REDACTED], there was mildly to markedly decreased platelet counts (with prominent decreases on Day 11 and evidence of rebound recovery before dosing on Days 8 and 15); minimally to mildly decreased neutrophils between Days 4 and 22 (with evidence of accelerated maturation and release from bone marrow); and, from Days 4 to 28, minimally to mildly increased lymphocytes, monocytes, and basophils at [REDACTED] only. Additionally, at [REDACTED], pale skin/mucous membranes and epistaxis were generally observed after dosing on Day 8. Minimal to mild extramedullary hematopoiesis was noted in multiple tissues at [REDACTED]. Results of the toxicity studies in nonhuman primates suggest a potential for bone marrow toxicity, anemia, and/or thrombocytopenia in patients treated with TAK-280.

To monitor the AEs of bone marrow toxicity in patients treated with TAK-280, complete blood counts with peripheral blood smear will be obtained regularly for all patients. If anemia, thrombocytopenia, or neutropenia occur, the TAK-280 dose will be modified according to the guidance in the protocol.

Prophylactic use of myeloid growth factors should be avoided during the first cycle of dose escalation. Transfusion and use of growth factors as necessary to manage anemia, thrombocytopenia, and neutropenia are permitted, consistent with American Society of Hematology/American Society of Clinical Oncology (ASCO) guidelines and institutional recommendations.

4.3.5 ADA

Administration of therapeutic antibodies may cause the formation of ADA. These may trigger hypersensitivity reactions or immune complex-mediated responses. All patients in the TAK-280 clinical study will be assessed for ADA formation. If the test result is positive, the neutralizing activity of ADA and their effect on TAK-280 PK, safety, and efficacy will be evaluated.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective of this study is:

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

5.1.2 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 characterize the potential immunogenicity of TAK-280.

5.1.3 Exploratory Objectives

The exploratory objectives of the study are:

- To evaluate circulating tumor DNA (ctDNA) before versus during treatment and to evaluate its correlation with TAK-280 antitumor activity.
- To explore the relationships between PK, pharmacodynamics, safety, and TAK-280 antitumor activity
- To evaluate relationships between baseline biomarkers including, but not limited to B7-H3 and PDL-1 expression in tumor biopsy specimens and TAK-280 antitumor activity.

- 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) 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).
- To evaluate tumor growth rates before and after treatment with TAK-280.

5.2 Endpoints

5.2.1 Primary Endpoint

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 Common Terminology Criteria for Adverse Events (NCI 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.

5.2.2 Secondary Endpoints

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 IV 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]+ 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).

5.2.3 Exploratory Endpoints

The exploratory endpoints are:

- Baseline characterization of B7-H3 expression in tumor tissue.
- Baseline characterization and change from baseline in PDL-1 expression in tumor tissue.
- Baseline assessment of biomarkers in the TME such as but not limited to tumor mutational burden and microsatellite instability (MSI-high) status as well as immune cell Changes from baseline in peripheral blood immune cell markers, including but not limited to, CD4 and CD8 T cells, natural killer (NK) cells.
- Determination of fold change of immune cell markers including but not limited to T cells, CD8+ and CD4+ T cell infiltration and activation state in pretreatment versus on-treatment biopsy specimens.
- 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](#))
- Evaluation of tumor growth rates using prebaseline tumor scan and tumor scans collected after treatment with TAK-280.

6.0 STUDY DESIGN

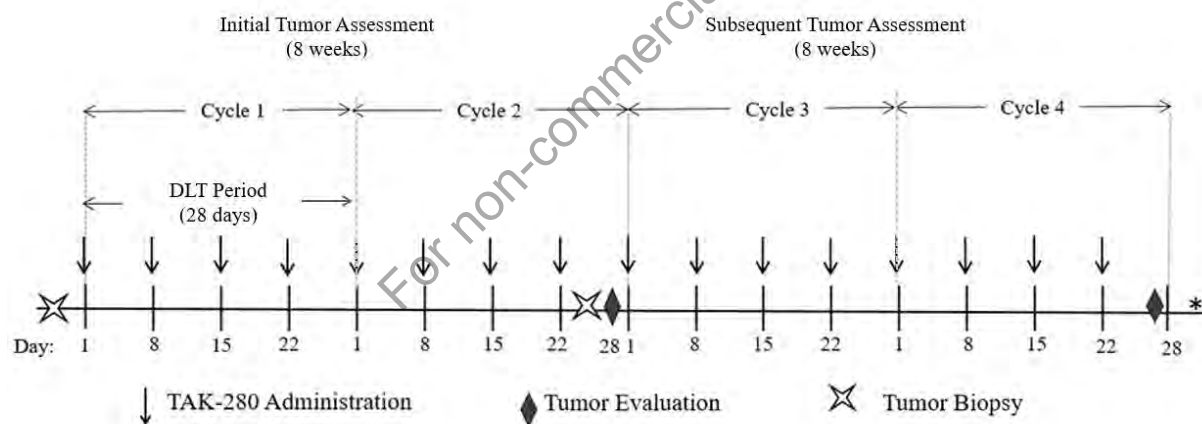
6.1 Overview of Study Design

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 IV 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], or other tumor types with high B7-H3 expression. Approximately 142 to 182 patients will be evaluated in this study.

The study treatment schema is presented in Figure 6.a.

Figure 6.a Study TAK-280-1501 Schema



CxDx: Cycle x Day x; DLT: dose-limiting toxicity.

Patients who do not experience DLT or other unacceptable toxicity may receive up to a total of 14 treatment cycles (28 days per cycle) depending on response to study treatment. The planned tumor evaluation will be reviewed by the investigator before the start of the next treatment cycle of TAK-280. The DLT-evaluation period is defined as the time between the initial dose of TAK-280 and C1D28. Patients who, in the opinion of the investigator, continue to receive clinical benefit at the end of 14 cycles with acceptable toxicity, and have no alternative treatment options, may continue therapy on a case-by-case basis following a request from the investigator and an agreement with the sponsor's medical monitor.

* Patients will enter a survival follow-up period after the last dose of study drug to be followed every 12 weeks for at least 48 weeks for survival by methods that include, but are not limited to, telephone, email, mail, or retrieval from online or other databases (eg, Social Security indexes).

The duration of administration of the initial TAK-280 RDEs to be used in the cohort-expansion phase will be based on findings from the safety and PK evaluation in the dose-escalation phase but must be at least 30 minutes. [REDACTED]

For both the dose-escalation and cohort-expansion phases, tumor assessments will be conducted every 8 weeks, starting from Cycle 1 Day 1 (C1D1) (ie, at the end of even-numbered cycles [eg, Day 28 of Cycles 2, 4, 6, 8, etc]). The dates of the tumor assessments are fixed after C1D1 is completed, regardless of future treatment delays. Patients will be eligible to receive treatment with TAK-280 until they experience confirmed disease progression, DLTs, or unacceptable toxicity that necessitates permanent discontinuation of the study drug.

After the last dose of study drug, all patients will enter the survival follow-up period and will be contacted every 12 weeks for survival status by methods that include, but are not limited to, telephone, email, mail, or retrieval from online or other databases (eg, Social Security indexes) until the patient has died, withdrawn consent, is lost to follow-up, or the follow up has continued for a total of 48 weeks after the last dose.

6.1.1 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. Dose escalation will begin by initially enrolling patients with histologically proven, unresectable, locally advanced or metastatic cancers described in the literature as having enhanced B7-H3 expression. [REDACTED] tumor types will be included in the initial dose-escalation cohorts: [REDACTED]

[REDACTED], mCRPC, [REDACTED]. Patients with other tumor types with high B7-H3 expression may be enrolled after discussion and approval by the sponsor.

Decisions regarding dose escalation will be based on clinical safety and all available PK and pharmacodynamic data, as well as antitumor activity during the DLT-evaluation period, defined as the time between the initial dose of TAK-280 and C1D28. Patients who have discontinued from TAK-280 during the DLT-evaluation period are to complete the end-of-treatment (EOT) visit 30 days (+10 days) after the last dose and enter the survival follow-up period. The severity of AEs will be graded according to the NCI CTCAE, Version 5.0 for non-CRS toxicities and ASTCT criteria (Lee et al. 2019) for CRS/IRR toxicities. DLTs will be defined separately for hematologic, nonhematologic, and hepatic nonhematologic events. A DLT will be defined as any of the AEs described in detail in Section 8.2 and occurring during the DLT-evaluation period. Patients who do not experience a DLT but are not DLT-evaluable will be replaced in the same dose-level cohort.

The dose-escalation phase will begin with a single-patient cohort at each of the first 2 cohort-assigned dose levels, [REDACTED] (Figure 8.a, Table 8-1), and then the cohort size will be converted to at least 3 patients for all subsequent predefined dose levels of [REDACTED] (Table 8-1). Administration of the initial TAK-280 cohort dose to the first 3 patients treated in each dose-escalation cohort will be staggered by a minimum of 48 hours.

Dose escalation and de-escalation decisions will be based on a Bayesian Optimal Interval (BOIN) design along with consideration of safety, efficacy, PK, and biomarker assessments, and decisions will be made jointly by the sponsor and the investigator at meetings, including end-of-cohort meetings. Dose-escalation rules are described in Section 8.3.

The exact dose escalation will also adhere to the following rules:

- Maximum dose increments for the next dose cohort will be limited to [REDACTED] if patients at the current cohort experience 1 Grade ≥ 2 event of CRS during the DLT evaluation period.

- Maximum dose increments for the next dose cohort will be limited to [REDACTED] if patients in a given dose cohort experience 2 or more Grade ≥ 2 events of CRS during the DLT evaluation period.
- Maximum dose increments will be limited to [REDACTED] if patients in a given dose cohort experience 2 DLTs during the DLT evaluation period.

In addition to the predefined dose levels, [REDACTED] levels and cohort dose levels may also be explored during the dose-escalation phase of the study based on the cumulative safety data and on agreement between the investigators and the sponsor. Cohort size other than 3 may also be considered. Any decision to implement an intermediate dose level or alternative dosing regimen will be documented and submitted to participating institutional review board (IRB)/independent ethics committee (IEC) and regulatory authorities, as appropriate, per local requirements.

6.1.1.1 [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- [REDACTED]
 - [REDACTED]
- - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
- - [REDACTED]
 - [REDACTED]
 - [REDACTED]
- - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
- - [REDACTED]
 - [REDACTED]
 - [REDACTED]
- - [REDACTED]
 - [REDACTED]

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[illegible]

[REDACTED]

[REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]

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[REDACTED]

Table 6-2

[REDACTED]

6.1.2 Backfill Patients in the Dose-Escalation Phase

A total of approximately 15 patients may be enrolled during the dose-escalation phase at dose levels not exceeding the MTD for further evaluation of [REDACTED], different schedules of premedications, safety, PK, pharmacodynamics, and preliminary anti-tumor activity of TAK-280, after discussion between the investigators and sponsor. The added patients will provide additional data to enable the selection of RDEs. Pre- and on-treatment fresh tumor biopsy specimens will be required for the first 6 backfill patients enrolled at cohort-assigned dose levels [REDACTED]. The requirement for biopsy specimens may be removed if endpoint criteria are met (see [Appendix I](#) for statistical considerations for paired biopsy specimens). The backfill patients are not counted into the maximum sample size by BOIN design.

6.1.3 Cohort-Expansion Phase

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, and [REDACTED]. Additional tumor types may also be studied in the expansion phase based on emerging data. One of the [REDACTED] indications will be selected as the indication for randomization. TAK-280 RDE will be evaluated in the indication in a randomized approach between the high and low RDE. TAK-280 will be evaluated in the remaining [REDACTED] indications at the high RDE.

Approximately 40 patients ([REDACTED] patients for mCRPC if this is the selected indication for randomization) will be randomized 1:1 to receive either TAK 280 high RDE or low RDE. Additionally, approximately 20 patients ([REDACTED] patients for mCRPC) in the remaining [REDACTED] indications to be studied in the cohort-expansion phase will receive the high RDE of TAK-280. [REDACTED]

[REDACTED] Based on safety and tolerability, PK, pharmacodynamic, and efficacy analyses across indications at the [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. [REDACTED].

Approximately 100 to 140 patients may be treated during the cohort-expansion phase of the study. The RP2D will be determined at end of the cohort-expansion phase on the basis of the assessment of efficacy, safety and tolerability, and PK/pharmacodynamic data.

Goals for this portion of the study are the following:

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

6.1.4 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.

6.1.5 Study Stopping Rules

The sponsor may stop the study, resulting in an immediate halt to study enrollment and a potential halt to treatment of ongoing patients, depending on the nature and severity of the toxicity. In the event enrollment is halted due to triggering of the stopping rules, recruitment will not be restarted until a protocol amendment has been reviewed by and communicated and submitted to the regulatory authorities.

A final decision to terminate the study, amend the protocol, or resume the study will be made only after a full review of safety data by the investigator(s) and the sponsor's safety management.

Any rate of fatal events related to treatment with TAK-280 with at least an [REDACTED] posterior probability that the true rate is greater than [REDACTED] will result in suspending the study (including suspending enrollment and suspending the treatment of ongoing patients).

Patient accrual to the Phase 2 part of this study will be suspended under the following circumstances starting with the first [REDACTED] patients and then every [REDACTED] patients up to a maximum of [REDACTED] patients in each dose cohort during the cohort-expansion phase:

- [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
- [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

The calculations use a prior beta distribution $B(1,1)$ for the binomially distributed toxicity rate.

6.2 Number of Patients

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] within each tumor histology. Because it is unknown which cohorts will continue enrolling to the predefined full expansion cohort, enrollment may be stopped early.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

The total time for a patient's study participation is expected to be approximately 27 months.

A screening period will be 28 days. Patients, including those who achieve a clinical response, may receive TAK-280 until they experience radiologic disease progression or until any other rule for treatment discontinuation is met. All patients will attend an EOT visit 30 days (+10 days) after the last dose or before the start of subsequent systemic anticancer therapy, whichever occurs first, to permit detection of any delayed AEs and to resolve any ongoing events. Patients with unresolved AEs will continue the periodic safety follow-up until complete resolution or stabilization (established as sequelae) occurs.

After the last dose of study drug, patients will be followed for survival every 12 weeks for at least 48 weeks until patient death, withdrawal of consent, or loss to follow-up earlier, whichever occurs first. The end-of-study (EOS) visit will be performed when the patient has completed the study using the same data collection method used for survival follow-up.

6.3.2 Study Completion Definition and Planned Reporting

The study will be considered as completed when all patients have completed the study (see Section 9.6).

In the event that the sponsor terminates the study, patients who are still receiving treatment at the time of the end of the study will undergo the EOT visit combined with the EOS visit 30 days (+10 days) after the last dose or before the start of subsequent systemic anticancer therapy, whichever occurs first. Patients previously discontinued from study treatment, who have not completed OS follow-up at the time of the end of study will undergo the EOS visit at the next scheduled survival follow-up visit.

6.3.3 Time Frames for Primary and Secondary Endpoints to Support Disclosures

Refer to Table 6-3 for disclosures information for all primary and secondary endpoints.

Table 6-3 Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
Primary		
Incidence of DLTs	Standard safety assessment	Up to approximately 1 month
Incidence and severity of TEAEs	Standard safety assessment	Up to approximately 37 months
Other safety endpoints (eg, clinical laboratory evaluations, ECGs, vital signs)	Standard safety assessment	Up to approximately 37 months

Table 6-3 Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
Secondary		
ORR (CR + PR)	ORR per RECIST Version 1.1	Up to approximately 37 months
DOR	Time from the date of first documentation of a PR or better to the date of the first documentation of PD or death due to any cause, whichever occurs first, for patients with a confirmed response (PR or better).	Up to approximately 37 months
PFS	Time from the date of first dose of TAK-280 to the date of first documentation of PD or death due to any cause, whichever occurs first.	Up to approximately 37 months
OS	Time from the date of first dose of TAK-280 until death due to any cause.	Up to approximately 37 months
DCR	Percentage of patients who achieve PR or CR or SD with a duration of ≥ 2 consecutive scans.	Up to approximately 37 months
PSA response (patients with mCRPC)	PSA reduction from baseline $\geq 50\%$ and confirmed at least 3 weeks later.	Up to approximately 37 months
Duration of PSA response (patients with mCRPC)	Time from first PSA response to first documented PSA progression.	Up to approximately 37 months
Time to PSA progression	Time from the date of first dose of TAK-280 to an increase of 25% or more and absolute increase of 2 ng/mL or more from the nadir	
PSA reductions of $\geq 50\%$ at 6 months (patients with mCRPC)	PSA reduction	Up to approximately 37 months
PK parameters after administration of TAK-280 (not limited to the following) $C_{\max}$, AUC, $t_{\max}$, $t_{1/2}$, CL, and V_d , for total TAK-280	Standard PK parameters	Up to approximately 37 months
TAK-280-induced ADA	Standard safety assessment	Up to approximately 37 months

ADA: antidrug antibody; AUC: area under the concentration-time curve; CL: total clearance; $C_{\max}$: maximum observed plasma concentration; CR: complete response; DCR: disease control rate; DLT: dose-limiting toxicity; DOR: duration of response; ECG: electrocardiogram; mCRPC: metastatic castration-resistant prostate cancer; MTD: maximum tolerated dose; ORR: overall response rate; OS: overall survival; PC: prostate cancer; PD: progressive disease; PFS: progression-free survival; PK: pharmacokinetic(s); PR: partial response; PSA: prostate-specific antigen; RECIST: Response Evaluation Criteria in Solid Tumors; RP2D: recommended phase 2 dose; SD: stable disease; $t_{1/2}$: terminal disposition phase half-life; TEAE: treatment-emergent adverse event; $t_{\max}$: time of first occurrence of maximum observed plasma concentration; V_d : volume of distribution.

- mCRPC.

b. **Tumor histologies during cohort expansion:** Patients will be eligible if they have histologically proven, unresectable, locally advanced, or metastatic malignant neoplasms for which no standard therapy with demonstrated benefit is currently available, have exhausted all available approved therapies, or are ineligible for or intolerant of standard therapy, as follows:

1. [REDACTED]
2. [REDACTED]
3. [REDACTED]
4. [REDACTED]
5. [REDACTED]
6. [REDACTED]
7. [REDACTED]
8. [REDACTED]
9. [REDACTED]
10. [REDACTED]
11. [REDACTED]
12. [REDACTED]
13. [REDACTED]
14. [REDACTED]
15. [REDACTED]
16. [REDACTED]
17. [REDACTED]
18. [REDACTED]
19. [REDACTED]
20. [REDACTED]
21. [REDACTED]
22. [REDACTED]
23. [REDACTED]
24. [REDACTED]
25. [REDACTED]
26. [REDACTED]
27. [REDACTED]
28. [REDACTED]
29. [REDACTED]
30. [REDACTED]
31. [REDACTED]
32. [REDACTED]
33. [REDACTED]
34. [REDACTED]
35. [REDACTED]
36. [REDACTED]
37. [REDACTED]
38. [REDACTED]
39. [REDACTED]
40. [REDACTED]
41. [REDACTED]
42. [REDACTED]
43. [REDACTED]
44. [REDACTED]
45. [REDACTED]
46. [REDACTED]
47. [REDACTED]
48. [REDACTED]
49. [REDACTED]
50. [REDACTED]
51. [REDACTED]
52. [REDACTED]
53. [REDACTED]
54. [REDACTED]
55. [REDACTED]
56. [REDACTED]
57. [REDACTED]
58. [REDACTED]
59. [REDACTED]
60. [REDACTED]
61. [REDACTED]
62. [REDACTED]
63. [REDACTED]
64. [REDACTED]
65. [REDACTED]
66. [REDACTED]
67. [REDACTED]
68. [REDACTED]
69. [REDACTED]
70. [REDACTED]
71. [REDACTED]
72. [REDACTED]
73. [REDACTED]
74. [REDACTED]
75. [REDACTED]
76. [REDACTED]
77. [REDACTED]
78. [REDACTED]
79. [REDACTED]
80. [REDACTED]
81. [REDACTED]
82. [REDACTED]
83. [REDACTED]
84. [REDACTED]
85. [REDACTED]
86. [REDACTED]
87. [REDACTED]
88. [REDACTED]
89. [REDACTED]
90. [REDACTED]
91. [REDACTED]
92. [REDACTED]
93. [REDACTED]
94. [REDACTED]
95. [REDACTED]
96. [REDACTED]
97. [REDACTED]
98. [REDACTED]
99. [REDACTED]
100. [REDACTED]

- [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
 - Patients should have received no more than 4 prior lines of therapies for locally advanced or metastatic cancer.
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
[REDACTED]
 - Patients should have received no more than 3 lines of prior therapy.
3. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 .
 4. Measurable disease per RECIST V1.1 by investigator except for patients with mCRPC with bone metastases only (these patients are allowed in the study). Lesions in previously irradiated areas (or other local therapy) should not be selected as measurable/target lesions, unless treatment was ≥ 6 months prior to start of treatment or there has been demonstrated progression with a clear margin to measure in that particular lesion.
 5. Acceptable laboratory parameters include the following:
 - Albumin ≥ 3.0 g/dL.
 - Platelet count $\geq 75 \times 10^3/\mu\text{L}$.
 - Hemoglobin ≥ 9.0 g/dL.
 - Absolute neutrophil count (ANC) $\geq 1.0 \times 10^3/\mu\text{L}$.
 - ALT/AST $\leq 3.0 \times$ the upper limit of normal (ULN); for patients with hepatic metastases, ALT and AST $\leq 5 \times$ ULN.
 - Total bilirubin $\leq 1.5 \times$ ULN, except for patients with Gilbert's syndrome, who may be enrolled if the conjugated bilirubin is within normal limits.
 - Creatinine clearance ≥ 45 mL/minute (calculated by Cockcroft-Gault formula).
 6. Archival tissue: Patients must consent to the acquisition of an existing formalin-fixed paraffin-embedded (FFPE) archival tumor sample, if available, either a block or unstained slides.
 7. Tumor biopsy:
 - Patients in dose-escalation DLT-evaluable cohorts are strongly encouraged to provide paired fresh tumor biopsy samples during screening (pretreatment) and within 7 days before C3D1 (on treatment), as specified in the SOE ([Appendix A](#)), when a lesion is safely accessible for a low-risk biopsy procedure (those occurring outside the brain,

lung/mediastinum, and intra-abdominal space or accessible by endoscopic procedures beyond the stomach or bowel).

- During dose-escalation backfill and the cohort-expansion phase, similar paired tumor biopsies, preferably from the same lesion, will be required. Tumor biopsies will be required for the first 6 backfill patients enrolled at cohort-assigned dose levels [REDACTED]. The requirement for a biopsy specimen may be removed if endpoint criteria are met (see [Appendix I](#) for statistical considerations for paired biopsy specimens). The paired tumor biopsy is optional for patients with mCRPC limited to bone metastasis.
 - Tumor lesions used for biopsy should not be lesions used as one of the target lesions for response evaluation, unless there are no other lesions suitable for biopsy. Tumor biopsy samples should be obtained only from lesions that are considered to be accessible with acceptable clinical risk in the judgment of the investigator. The sponsor should be contacted if the biopsy is considered to present a potentially unreasonable risk to the patient. See Section 9.4.16.2 for additional guidance for tumor biopsies.
8. For the purpose of this study, a person of female birth sex is considered a woman of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhoea, a single FSH measurement is insufficient. WOCBP must meet the following criteria:
- Have a negative serum or urine pregnancy test result within 72 hours before the initiation of study drug administration.
 - Be willing to use 1 form of highly effective contraception and 1 additional effective barrier method of contraception throughout the study, starting at screening and through 90 days after the last dose of TAK-280. Contraception methods may be considered highly effective if they can achieve a failure rate of less than 1% per year when used consistently and correctly, including:
 - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral/intravaginal/transdermal.
 - Progestogen-only hormonal contraception associated with inhibition of ovulation: oral/injectable/implantable.
 - Intrauterine device.
 - Intrauterine hormone-releasing system.
 - Bilateral tubal occlusion.

- Vasectomized partner (highly effective provided that partner is the sole sexual partner of the WOCBP study participant and the vasectomized partner has received medical assessment of the surgical success).
 - Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of the risk associated with the trial intervention[s]. Reliability of abstinence should be evaluated in relation to study duration and the preferred and usual lifestyle of the study participant.)
9. Male patients with partners of childbearing potential, even if surgically sterilized (ie, status postvasectomy), must agree to the following:
- Use effective barrier contraception from the time of consent through 90 days after the last dose of TAK-280, or
 - Agree to practice true abstinence, if this is the established and preferred contraception method by the patient.
 - Agree to refrain from donating sperm from the time of consent through 90 days after the last dose of TAK-280.
 - In addition, have their partners use contraception (as documented for female patients) for the same period of time.
10. Symptomatic central nervous system (CNS) metastases must have been treated, be asymptomatic for ≥ 14 days, and meet the following criteria at the time of enrollment:
- No concurrent treatment for CNS disease (eg, surgery, radiation, corticosteroids ≥ 10 mg/d prednisone or equivalent).
 - No concurrent leptomeningeal disease or cord compression.
11. Patients must be willing and able to comply with clinic visits and procedures outlined in the study protocol.

7.2 Exclusion Criteria

1. History of known autoimmune disease, except for:
 - Vitiligo.
 - Psoriasis not requiring systemic treatment for >1 year before receipt of TAK-280.
 - History of Graves' disease in patients now euthyroid for >4 weeks.
 - Hypothyroidism managed by thyroid hormone replacement.
 - Alopecia.
 - Well-controlled diabetes type 1.
2. Major surgery or traumatic injury within 8 weeks before the first dose of TAK-280.

3. Baseline prolongation of the QT interval with Fridericia correction method (QTcF) (eg, repeated demonstration of corrected QT interval [QTc] >480 ms, history of congenital long QT syndrome, or torsades de pointes). If patients are taking medications known to prolong the QTc (examples provided in [Appendix G](#)) at screening, patients may continue to take these medications as long as their baseline QTcF is <480 ms that are receiving such medications. Patients may not start using such medications on C1D1. Please refer to Section 8.6 (Permitted Concomitant Medications and Procedures) for more details.
4. Unhealed wounds from surgery or injury.
5. Ongoing or active infection of Grade ≥ 2 .
6. History of any of the following ≤ 6 months before the first dose:
 - Congestive heart failure New York Heart Association Grade III or IV. ([Appendix H](#)).
 - Unstable angina.
 - Myocardial infarction.
 - Unstable symptomatic ischemic heart disease.
 - Uncontrolled hypertension despite appropriate medical therapy.
 - Any ongoing symptomatic cardiac arrhythmias of Grade >2 (including acute atrial flutter/fibrillation, ventricular fibrillation, or ventricular tachycardia).
 - Pulmonary embolism, or symptomatic cerebrovascular events, or any other serious cardiac condition (eg, pericardial effusion or restrictive cardiomyopathy).
 - Chronic, stable atrial fibrillation on stable anticoagulant therapy, including low-molecular-weight heparin, is allowed.
7. Oxygen saturation <92% on room air at screening or during the C1D1 predose assessment.
8. Inflammatory process that has not resolved for ≥ 4 weeks before the first dose of study drug. Patients with chronic low-grade inflammatory processes such as radiation-induced pneumonitis are excluded regardless of duration.
9. Clinically significant gastrointestinal disorders including the following:
 - Gastrointestinal perforation or unhealed ulcerations <6 months before study drug administration. Patients must have documented evidence (eg, upper endoscopy or colonoscopy) of a completely healed area of prior perforation.
 - Gastrointestinal bleeding <2 months before study drug administration. Patients must have documented evidence (eg, from upper endoscopy or colonoscopy) of a completely healed area of prior bleeding.
 - Pancreatitis <6 months before the initiation of study drug. Patients must have a CT scan that is negative for evidence of remaining disease or normal pancreatic enzyme levels >4 weeks before the initiation of TAK-280.

- Diverticulitis flare <2 months before study drug administration. Patients must have a CT scan demonstrating no evidence of remaining disease before the initiation of TAK-280.
 - History of Crohn's disease or ulcerative colitis.
10. Vaccination with any live virus vaccine within 4 weeks or other vaccines within 2 weeks before the initiation of study drug administration. Inactivated annual influenza vaccination is allowed.
 11. History of a bone marrow transplantation within the past 5 years or solid organ transplantation (as a recipient) and use of immunosuppressive agents.
 12. Known hypersensitivity to TAK-280 or any excipient () contained in the drug or diluent formulation, or known hypersensitivity to tocilizumab.
 13. Second primary invasive malignancy not in remission for ≥ 3 years. Exceptions include nonmelanoma skin cancer, cervical carcinoma in situ, resected melanoma in situ, or any malignancy considered to be indolent and never required therapy, with the exception of indolent lymphomas.
 14. Any serious underlying medical or psychiatric condition that would preclude informed consent or impair the patient's ability to receive or tolerate the planned treatment or comply with the protocol.
 15. Patients who are HIV, hepatitis B, or hepatitis C seropositive. Patients treated for hepatitis C must have viral titers of 0 for ≥ 2 years to be eligible. Patients with hepatitis B who have undetectable or ≤ 500 IU hepatitis B viral titers are eligible.
 16. Prior therapy before the planned start of TAK-280, as follows:
 - Cytotoxic chemotherapy, small-molecule inhibitors, radiation, interventional radiology procedure, or similar investigational therapies within ≤ 2 weeks or 5 half-lives, whichever is shorter.
 - Monoclonal antibodies, antibody-drug conjugates, radioimmunoconjugates, or similar therapies within ≤ 4 weeks.
 - Not recovered to Grade 1 or baseline or established as sequelae from all toxic effects of previous therapy (except alopecia, neuropathy, or autoimmune endocrinopathies with stable endocrine replacement therapy, or bone marrow parameters [any of Grade 1/2 permitted if directly related to bone marrow involvement]).
 - Concurrent use of hormones to maintain castrate levels of testosterone in patients with PC or use for noncancer-related conditions (eg, insulin for diabetes, hormone replacement therapy) is acceptable. Bisphosphonates are permitted for supportive care of patients with bone metastases (eg, breast cancer or PC).

17. Use of corticosteroids or other immunosuppressive medication, concurrently or within 14 days of administration of TAK-280, except for:
- Topical, intranasal, inhaled, ocular, or intra-articular corticosteroids.
 - Physiologic doses of replacement steroid (eg, for adrenal insufficiency).
 - Steroid premedication for hypersensitivity reactions and antiemetic use.
 - Stable steroid dose (established for ≥ 28 days before the first dose of TAK-280) for previously treated brain metastasis. Corticosteroid dose on C1D1 should be ≤ 10 mg/d of prednisone or equivalent.
18. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test result during the screening period or a positive urine pregnancy test result on Day 1 before first dose of study drug.

8.0 STUDY DRUG

8.1 TAK-280 Study Drug Preparation

All protocol-specific criteria for the administration of study drug must be met and documented before drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

TAK-280 will be provided as a sterile, preservative-free lyophilizate for IV administration. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Administration of the study drug should begin immediately after its preparation.

8.1.1 General Administration Guidelines and Precautions

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

The calculated dose will be based on the patient's weight measured within 3 days of the first dose of TAK-280 (baseline). On Day 1 of subsequent treatment cycles, a change in body weight of $\pm 10\%$ from baseline will result in recalculation of the dose.

For details on dose calculations, dosing solution preparation, administration instructions, and information on shelf-life, refer to the pharmacy manual.

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The dose of TAK-280 for administration must be prepared by the study pharmacist or appropriately qualified staff using an aseptic technique.

TAK-280 is a recombinant bispecific T-cell engager designed to target B7-H3; therefore, it is possible that TAK-280 may induce severe and/or fatal CRS.

TAK-280 should NOT be administered as an IV push or bolus and usage of ancillary devices including infusion lines and administration devices other than those provided by Takeda requires the sponsor's written approval.

The starting dose of TAK-280 will be [REDACTED] administered by IV infusion on Days 1, 8, 15, and 22 of a 28-day treatment cycle. If a less frequent administration is indicated by safety and/or PK/pharmacodynamic findings, an alternative schedule can be decided on without a protocol amendment. The decision to switch to the less intensive schedule will be made by the investigators and sponsor's medical monitor and documented in writing.

The TAK-280 dose will be administered as an IV infusion over 60 (± 10) minutes with a commercially available syringe pump. Based on emerging data (eg, severity of IRRs), infusion time may be adjusted to shorter or longer than 60 minutes on agreement with the sponsor and investigators; however, infusion time will not be less than 30 minutes. The infusion may be slowed or stopped and restarted for any associated IRRs. All infusion times must be recorded.

During the dose-escalation phase, all patients will be required to have continuous monitoring for signs or symptoms of CRS/IRRs in an inpatient facility after the administration of TAK-280. [REDACTED]

[REDACTED] For the subsequent dose(s) in Cycle 1, patients must be monitored for at least 6 hours after infusion for signs or symptoms of CRS/IRRs. Observation for at least 4 hours after the administration of TAK-280 is required for all doses in Cycle 2. In addition, the sponsor strongly recommends overnight observation after all infusions in Cycles 1 and 2 (see the SOE: [Appendix A](#) Tables A1, A2, A3). [REDACTED]

[REDACTED] Tocilizumab must be available at all times for use as needed to treat CRS/IRR symptoms.

For all doses in all treatment cycles, patients can be monitored overnight if the patient develops symptoms suggestive of CRS during the postinfusion observation period.

All precautionary hospitalizations are considered planned for the purposes of the study and should not be considered serious adverse events (SAEs). If the hospitalization changes from precautionary to necessary for treatment, the event should be reported as an SAE.

Standard-of-care measures to treat CRS, including the use of IV fluids, tocilizumab, steroids, or low-flow oxygen by nasal cannula, are not considered SAE justification.

Vital signs (temperature, blood pressure, pulse rate, respiratory rate, and oxygen saturation) will be assessed at timepoints as described in the SOE ([Appendix A](#)). Patients may be discharged with noncritical and clinically stable or slowly improving toxicities if deemed appropriate by the investigator. At the time of discharge, patients and their caregivers will be educated on potential symptom development, including but not limited to fever, dyspnoea, low blood pressure, and

dizziness. They will also be instructed to contact the investigator and seek immediate medical attention should any symptom of concern arise.

Infusion or allergic reactions may occur with the infusion of protein-based therapeutics. In all cases, TAK-280 administration should occur in an area where resuscitation equipment, diagnostic equipment, and medications (such as tocilizumab, epinephrine, antihistamines, corticosteroids, IV fluids, vasopressors, oxygen, bronchodilators, [REDACTED]) are readily available. Treatment must be stopped and assessment for CRS (including pulmonary toxicity and IRRs) must be done if the patient experiences symptoms consistent with these toxicities. The management of IRRs and CRS is detailed in Section 8.8.1.

As with other potentially toxic compounds, caution should be exercised in handling TAK-280. The use of gloves is recommended. After topical exposure, AEs could include redness or blistering. Given the rare possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. Administration through a central port is always preferred over a peripheral line.

For detailed information on the preparation and administration of TAK-280, refer to the pharmacy manual.

8.2 Definitions of DLTs

TAK-280 dosing should be withheld if AEs that potentially meet the criteria for a DLT occur, pending resolution of the event and an assessment for relatedness to TAK-280.

During the dose-escalation phase, the decision to escalate the dose will be based on DLTs defined as any of the events listed in this section, if they are considered to be related to study drug by the investigator and occur during the DLT-evaluation period (defined as the time between the initial dose of TAK-280 and Cycle 1 Day 28). AEs for which the relationship to study drug cannot be ruled out should also be considered as related to study drug. The severity of non-CRS AEs will be graded according to the NCI CTCAE Version 5.0 and ASTCT criteria (Lee et al. 2019) for CRS/IRR toxicity.

DLT criteria are defined as follows:

Hematologic DLTs:

- Grade 4 neutropenia lasting >5 days.
- Grade ≥ 3 febrile neutropenia.
- Grade 4 thrombocytopenia.
- Grade 3 thrombocytopenia and clinically significant bleeding.

Hepatic Nonhematologic DLTs:

- Grade 4 AST/ALT elevation without CRS or any Grade 3 or higher elevation lasting longer than 72 hours, regardless of the presence or absence of liver metastases.
- Grade 3 bilirubin defined by an increase of $>5 \times \text{ULN}$.
- Grade 3 bilirubin defined by an increase of $>3 \times$ to $5 \times \text{ULN}$ and not resolving to Grade 2 (ie, $>1.5 \times$ to $3 \times \text{ULN}$) within 7 days and Grade 1 (ie, $>\text{ULN}$ to $1.5 \times \text{ULN}$) within 14 days. Steroids must be tapered to $\leq 10 \text{ mg/d}$ of prednisone or equivalent by Day 14.
- Any event meeting all 3 criteria for the Hy's law, as follows:
 - AST and/or ALT $>3 \times \text{ULN}$.
 - Concurrent elevation of total bilirubin $>2 \times \text{ULN}$ with or without signs of cholestasis.
 - No alternative etiology can be identified.

Nonhematologic DLTs:

Nonhematologic DLTs are Grade ≥ 3 nonhematologic events with the following exceptions:

- Grade 3 electrolyte abnormality lasting <72 hours, without associated clinical complications, and with response to supportive treatment.
- Grade 3 fever lasting <72 hours and not associated with hemodynamic instability.
- Grade 3 nausea or vomiting resolving to Grade ≤ 1 within 72 hours with or without medical intervention.
- Grade 3 amylase and/or lipase elevation not associated with either clinical or radiographic evidence of pancreatitis requiring hospitalization.
- Grade 3 diarrhoea, constipation, abdominal pain, cramping, dyspepsia or dysphagia resolving to Grade ≤ 1 within 72 hours with or without medical therapy.
- Grade 3 fatigue resolving to Grade 1 within <7 days.
- Grade 3 endocrinopathy controlled with hormone supplementation and does not result in hospitalization, dose modification, or withholding of study drug.
- Grade 3 inflammatory reaction secondary to antitumor response (eg, metastatic disease, lymph nodes) resolving to Grade ≤ 1 within 7 days.

Although severe toxicity may occur at any time during the study, only those events occurring during the DLT-evaluation period (ie, the time between the initial dose of TAK-280 and C1D28) will influence decisions regarding dose escalation, expansion of a dose level, or evaluation of intermediate dose levels and more-frequent dosing regimens. Patients will be monitored through all treatment cycles of therapy for treatment-related toxicities.

8.3 Dose-Escalation Rules

Dose-escalation and de-escalation rules are shown in [Figure 8.a](#) and [Table 8-1](#). Dose escalation will begin with a single-patient cohort at each of the first [REDACTED] dose levels, [REDACTED]. Then, cohorts for dose escalation will be converted to a cohort size of at least 3 patients for all subsequent dose levels of [REDACTED] ([Table 8-1](#)).

Dose-escalation and de-escalation decisions will be guided by BOIN design, along with the considerations of safety, efficacy, and biomarker assessments, where decisions will be made jointly by the sponsor and the investigator at meetings, including end-of-cohort meetings.

[REDACTED]

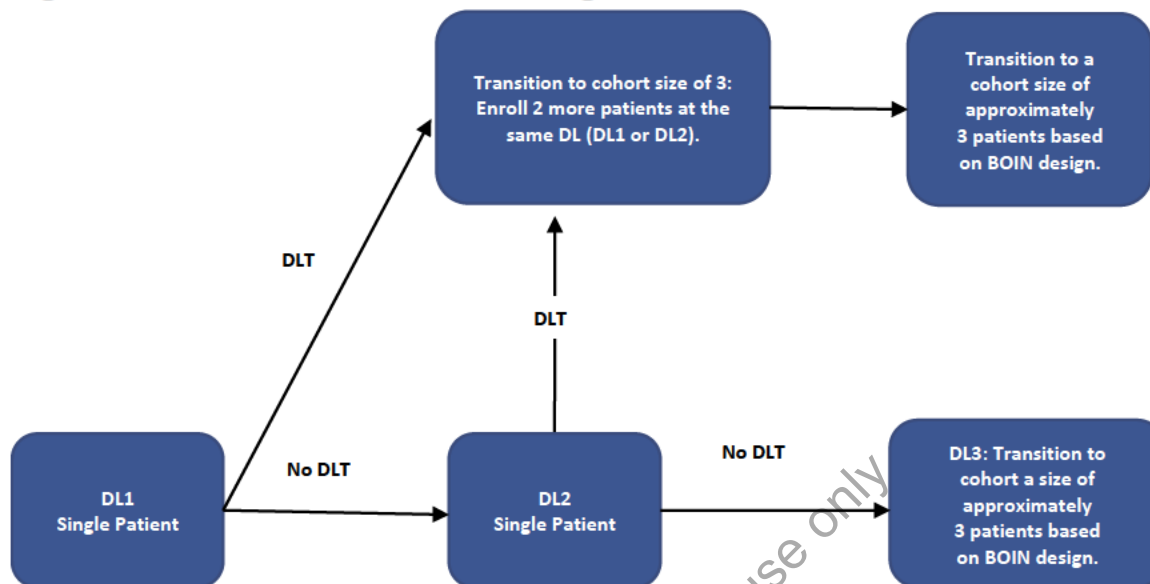
The dose escalation will also adhere to the following rules:

- Maximum dose increments for the next dose cohort will be limited to [REDACTED] if patients at the current cohort experience 1 Grade ≥ 2 event of CRS during the DLT evaluation period.
- Maximum dose increments for the next dose cohort will be limited to [REDACTED] if patients in a given dose cohort experience 2 or more Grade ≥ 2 events of CRS during the DLT evaluation period.
- Maximum dose increments will be limited to [REDACTED] if patients in a given dose cohort experience 2 DLTs during the DLT evaluation period.

As described by Liu and Yuan ([Liu and Yuan 2015](#)), the BOIN design is based on the observed toxicity probabilities (observed DLT rate) for each dose level. The decision for dose escalation and de-escalation involves a comparison of the observed DLT rate at the current dose with a pair of fixed, prespecified dose-escalation and de-escalation boundaries. In addition, for the purpose of overdose control, dose-elimination rules are implemented based on recommendations by Liu and Yuan ([Liu and Yuan 2015](#)) ([Appendix F](#)).

The target toxicity rate for the MTD in this study is $\phi = 0.3$ (ie, 30%), and the maximum sample size is 27 DLT-evaluable patients for the dose-escalation phase.

Figure 8.a Dose-Escalation Plan in Single-Patient Cohorts in the First 2 Dose Levels



BOIN: Bayesian Optimal Interval; DL: dose level; DLT: dose-limiting toxicity.

If no DLTs (see Section 8.2) occur in the [REDACTED] cohort, then a single patient will be enrolled into the [REDACTED] dose cohort. If no DLTs occur in the [REDACTED] cohort, then dose escalation will transition to an approximately 3-patient cohort design at the [REDACTED] dose level. If a DLT occurs during the DLT-evaluation period for either the [REDACTED] dose, 2 more patients will be enrolled at the dose level at which the DLT occurred, and dose escalation in all subsequent dose levels will be based on BOIN design with at least 3 patients dosed at each dose level. The dose escalation/de-escalation rules optimized to minimize the probability of incorrect dose assignment are as follows (refer to Table 8-1):

1. Treat the first cohort of patients.
2. Assign a dose to the next cohort of patients, as follows:
 - If the observed DLT rate at the current dose is ≤ 0.236 , escalate the dose to the next higher cohort-assigned dose level.
 - If the observed DLT rate at the current dose is > 0.359 , de-escalate the dose to the next lower cohort-assigned dose level.
 - Otherwise, stay at the current dose level.
3. Repeat Step 2 until:
 - The maximum sample size of 27 DLT-evaluable patients is reached.
 - The lowest dose is eliminated.

- 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 the BOIN design.

Additional patients may be needed for dose escalation based on a review of the cumulative safety and exposure data and on agreement between the investigators and the sponsor. [REDACTED]

Table 8-1 depicts the rule of dose escalation and de-escalation in any dose level.

Table 8-1 Dose-Escalation/De-Escalation Rule for the BOIN Design

Number of Evaluable Patients Treated	1	2	3	4	5	6	7	8	9	10	11	12
Escalate if the number of DLTs is $\leq$	0	0	0	0	1	1	1	1	2	2	2	2
Deescalate if the number of DLTs is $\geq$	1	1	2	2	2	3	3	3	4	4	4	5
Eliminate if the number of DLTs is $\geq$	NA	NA	3	3	4	4	5	5	5	6	6	7

BOIN: Bayesian Optimal Interval; DLT: dose-limiting toxicity.

The number of DLTs is the number of patients with at least 1 DLT. When none of the actions (ie, escalate, de-escalate, or eliminate) is triggered, stay at the current dose for treating the next cohort of patients.

For the purpose of overdose control, dose and higher levels will be eliminated from further examination if the posterior probability $\Pr(p_j > 0.3 | \text{data}) > 0.95$ and at least 3 evaluable patients have been treated at dose level j , where p_j is the true DLT rate of dose level j , $j = 1, \dots, 8$. When the lowest dose is eliminated, stop the dose escalation for safety.

After dose escalation is complete, the MTD will be selected based on isotonic regression. Specifically, the MTD is selected as the dose for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate of 30%. If there are ties, select the higher dose level when the isotonic estimate is lower than the target toxicity rate, and select the lower dose level when the isotonic estimate is greater than or equal to the target toxicity rate.

Intermediate dose levels other than the predefined dose levels ([REDACTED]), more-frequent dosing regimens, [REDACTED], and more conservative dose escalation decisions may be explored selectively during the dose-escalation phase of the study,

based on a review of the cumulative safety and exposure data and on agreement between the investigators and the sponsor. Any decision to implement an intermediate dose level will be documented and submitted to participating IRBs/IECs and regulatory authorities, as appropriate, per local requirements.

8.4 Dose-Modification Guidelines

8.4.1 Dose Delays

For patients experiencing potential DLTs in the DLT evaluation period and AEs potentially meeting the criteria of treatment discontinuation (Section 8.4.5) after that, or the criteria for beginning the next dose of study drug is not met, the next scheduled dose of study drug should be withheld pending assessment, management, and resolution of the toxicity (Section 8.2).

If the toxicity is assessed to be unrelated to study drug or if it does not meet DLT criteria or criteria for treatment discontinuation, and in all other cases of dose delays due to different reason related or not related to the treatment, then therapy can be restarted at the same dose administered upon resolution of the toxicity to Grade ≤ 1 or baseline in severity, or when determined by the investigator to be clinically appropriate.

Resumption of TAK-280 therapy will be conducted as follows:

- For AEs potentially meeting the criteria for a DLT, TAK-280 dosing should be withheld pending resolution of the event and TAK-280 attribution assessment within the time limits described in Section 8.2. If the dose is delayed while the patient is confirmed as not having a DLT, the patient may become DLT not evaluable.

■ [REDACTED]

- If the treatment is delayed by ≥ 14 days for any reason considered related to the treatment, resulting in a dose interval of ≥ 21 days between doses, treatment should be permanently discontinued.
- If TAK-280 is to be restarted when there is no scheduled administration, the site should perform all the required predose assessments as listed in SOE (Appendix A) before the dose can be resumed.
- If TAK-280 is to be restarted after dose delay when there is a scheduled dose administration, then the original dose is considered as missed. For example, if C2D8 administration is delayed to C2D15, then the C2D8 will be considered as missed and C2D15 is considered C2D15, not C2D8 and Cycle 2 remains 28 days.

8.4.2 Criteria for Beginning or Delaying the Next Dose of Study Drug

Dosing with TAK-280 will be weekly with 1 treatment cycle every 28 days. To receive the next dose of TAK-280, the following criteria must be met:

- ANC must be $\geq 1000/\text{mm}^3$.
- Platelet count must be $\geq 75,000/\text{mm}^3$.
- For therapy to resume, toxicity considered to be related to treatment with TAK-280, including both hematologic and nonhematologic toxicities, must have resolved to Grade ≤ 1 , to the patient's baseline values, or to a level considered acceptable by the physician (eg, hypophosphatemia that can be managed by PO replacement).

If the patient does not meet these criteria for re-treatment, initiation of the next dose should be withheld until the criteria have been met.

8.4.3 Criteria for Dose Interruption During Infusion of TAK-280

Patients must be monitored for any signs and symptoms of infusion reactions during TAK-280 infusion. The TAK-280 infusion should be interrupted if an IRR is suspected, and the infusion rate reduced or permanently discontinued based on the severity of the IRR per investigator discretion. In addition, the treatment should be immediately interrupted and discontinued if the adverse event occurs and the criteria for discontinuation is met. For other AEs not meeting the criteria for treatment discontinuation, investigators should use their clinical judgement to decide either to interrupt treatment, to continue treatment at a reduced infusion rate, or to continue treatment at the original infusion rate. For patients who undergo planned surgery while on study, the surgery should be performed at least 4 days after the administration of TAK-280. Dosing with TAK-280 should not be restarted until at least 7 days after surgery. Patients must meet the criteria for restarting treatment specified in Section 8.4.2.

For treatment to be resumed after a drug interruption, the AE that led to the interruption must have resolved to Grade ≤ 1 , to the patient's baseline values, or to a level considered medically acceptable by the investigator for those asymptomatic laboratory findings that are expected to be corrected quickly.

8.4.4 Criteria for Dose Reduction

Inpatient dose reductions are not allowed, with the exception of: (1) reducing the infusion rate during re-challenge in patients with CRS/IRR, and (2) dose reductions in patients receiving TAK-280 at a dose that is subsequently determined to exceed the MTD.

Total dose reduction after calculation due to body weight decrease is allowed only if the patient's weight decreases by $>10\%$ from the weight measured at baseline to calculate the dose.

8.4.5 Criteria for Discontinuation of TAK-280

Patients who tolerate TAK-280 without confirmed PD may receive up to 14 treatment cycles of TAK-280 until any one of the following criteria for discontinuation is met:

- Occurrence of a non-CRS/IRR drug-related AE that meets DLT criteria at any time during treatment*.
- Occurrence of a CRS/IRR that meets the DLT definition at any time during treatment*.
- Recurrence of Grade ≥ 3 AE that previously led to drug interruption and is considered at least possibly related to TAK-280 treatment*.
- Dose delay of ≥ 14 days due to toxicity possibly related to study drug that results in a dosing interval of ≥ 21 days between doses*.
- Progressive disease by RECIST V1.1 by the investigator*.
- Clinical progression (no imaging test performed to assess tumor status, but the investigator considers that patient decline is caused by tumor progression).
- Completion of protocol-defined maximum duration of treatment.
- Study terminated by sponsor.
- Withdrawal of patient consent.
- Per investigator discretion, it is in the best interest of the patient to discontinue study drug.
- Lost to follow-up.
- Significant/important protocol deviation (after discussion with sponsor)
- Death.
- Pregnancy.

* Patients meeting these criteria but otherwise experiencing substantial clinical benefit with acceptable toxicity, based on the investigator's request, may continue therapy on a case-by-case basis with agreement from the sponsor's medical monitor.

If a patient is withdrawn from the study or from TAK-280 dosing for any reason other than disease progression, the sponsor must be alerted within 24 hours via an immediately reportable event form.

8.4.6 Inpatient Dose Escalation

Inpatient dose escalation during the dose escalation phase is only allowed after discussion with the sponsor. For a patient to be eligible for inpatient dose escalation, the patient must continue on study without decline in performance status, without evidence of PD by imaging or clinical deterioration, and without any significant, unacceptable, or irreversible toxicities related to the treatment.

The dose level that the patient receives after escalation should not exceed the MTD so far in the study.

Total dose increase after calculation due to an increase of body weight is allowed only if the patient's weight increases by >10% from the weight measured at baseline.

8.5 Excluded Concomitant Medications and Procedures

All concomitant medications and blood products administered during the patient's participation in the study until the EOT visit must be recorded in the source document and on the electronic case report form (eCRF). All changes in infusions, including interruptions and their duration as well as reductions in rate and duration must be recorded.

Coronavirus disease 2019 (COVID-19) vaccination is not required but encouraged because oncology patients receiving treatment are a vulnerable group. COVID-19 vaccination status and any previous diagnoses of COVID-19 must be recorded in the source document and on the eCRF. The following guidance is provided to coordinate the timing of COVID-19 vaccination and study treatment:

- Patients in screening should schedule their second dose or booster dose of COVID-19 vaccine at least 2 weeks before Day 1 (assuming the vaccine is a 2-dose vaccine). If a single-dose vaccine is administered, the single dose should be at least 2 weeks before Day 1.
- Vaccination during Cycle 1 is discouraged.
- Starting with Cycle 2, at least 7 days must elapse from the last treatment with study drug to COVID-19 vaccination, and 7 days must elapse from vaccination to the next study treatment.

The following medications and procedures are prohibited during the study:

- Alcohol, herbal supplements, and medications associated with potential hepatic injury. The study medical monitor should be contacted in advance if there is any uncertainty about the potential liver toxicity of the concomitant medication to be administered.
- Other antineoplastic therapies, including chemotherapy, small-molecule inhibitors (eg, tyrosine kinase inhibitors) or biologics, are not allowed. The exception is hormonal therapy to maintain castrate levels of testosterone in patients with castration-sensitive PC.
- For patients who require palliative radiotherapy (ie, cumulative dose <30 Gy, limited field of distribution) for reasons other than disease progression, treatment with TAK-280 may be delayed for a maximum of 3 weeks. Palliative radiotherapy should not be given concurrently with TAK-280. Treatment with palliative therapy should be initiated at least 24 hours after receipt of TAK-280. TAK-280 may be restarted 1 day after the completion of palliative radiotherapy if there were no complications associated with the radiotherapy. Palliative radiotherapy fields also should not overlap tumor lesions that have previously been designated as target lesions. In the event that this is medically necessary for palliative purposes, the patient may continue in the study, but the patient will no longer be evaluable for objective response from the time palliative radiotherapy is initiated.

- Patients should not receive other investigational drugs during the period of study treatment.
- Because TAK-280 has a mechanism of action dependent on the engagement of T lymphocytes, the use of corticosteroids should be limited to the extent possible. Chronic doses of corticosteroids in excess of 10 mg/d of prednisone or equivalent is prohibited other than for the management of drug-related AEs. Steroids may be used in the treatment of suspected TAK-280–associated AEs in consultation with the sponsor’s medical monitor. Steroids for topical, ophthalmic, inhaled, or nasal administration are allowed.
- The use of other immunosuppressive agents is prohibited unless they are being used to treat or prevent an AE.
- Live vaccines should be avoided for 3 months after the last dose of TAK-280.

Any potential deviation from the guidelines should be discussed in advance with the medical monitor before the treatment is given.

8.6 Permitted Concomitant Medications and Procedures

All concomitant medications (defined as any medication given during the study), including prescription and over-the-counter medications, influenza vaccines, and significant nondrug therapies (such as physical therapy and blood transfusions), should be recorded in the designated eCRF from the signing of the informed consent form (ICF) through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first. Patients must be instructed not to take any medications, including over-the-counter medications and herbal supplements, without first consulting with the investigator.

The following medications and procedures are permitted while the patient is receiving the study drug:

- Topical, intranasal, inhaled steroids (eg, for the treatment of asthma) are permitted.
- Patients should be transfused with red blood cells and platelets as clinically indicated.
- Concomitant treatment with bisphosphonates or denosumab will be allowed for patients with evidence of lytic destruction of bone or with osteopenia, according to the ASCO Clinical Practice guidelines or institutional practice in accordance with the product label, unless specifically contraindicated.
- Hormones to maintain castrate levels of testosterone in patients with castration sensitive PC or for noncancer-related conditions (eg, insulin for diabetes, hormone replacement therapy) are acceptable.
- Local radiation of isolated lesions for palliative intent (eg, pain control) is acceptable provided that the requirement for radiation does not represent a progression of the disease and that the radiated lesion is not a target lesion.
- Cautious use of medications that are known to prolong the QTc (examples provided in [Appendix G](#)) is permissible if the patient is taking such medications continuously at the time

of enrolling in this study and as long as the patient's baseline QTcF is <480 ms. Patients may not start using such medications on C1D1. If needed for certain medical conditions, the patient may take such medications after completion of the triplicate electrocardiogram (ECG) collections on C1D2. Cautious use means, for example, to confirm that a patient does not have underlying cardiac conditions such that use of such medication may increase their risk.

Supportive measures consistent with optimal patient care may be given throughout the study.

TAK-280 administration-mediated elevation in cytokines has the potential to modulate cytochrome P450 (CYP) enzymes. Therefore, patients who are administered sensitive CYP enzyme substrates (see examples on the US FDA website [fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers, Drug Development and Drug Interactions | Table of Substrates, Inhibitors and Inducers, Accessed 12 May 2023]) will be closely monitored for side effects.

8.7 Precautions and Restrictions

8.7.1 Prior Therapy

Prior therapy restrictions are described in the inclusion/exclusion criteria.

8.7.2 Fluid and Food Intake

There are no requirements for fasting and no restrictions for fluid or food intake by the patients during the study other than within 4 hours before triplicate ECGs when food should be limited to bland snacks.

8.7.3 Patient Activity Restrictions

Patients will be hospitalized overnight or monitored during study drug administration, as outlined in Section 8.1.1. There are no additional restrictions on patient activities and no requirement for patient confinement during the study.

Patients will be required to carry a patient emergency card detailing the treatment site and investigator's contact information, clinical study information and a 24-hour emergency contact number. This card should be presented when a patient is being treated by a nonstudy healthcare provider or emergency medical services to provide an opportunity for the provider to contact the treating site and/or obtain important study information relevant to the patient's care.

It is not known what effects TAK-280 has on human pregnancy or development of the embryo or fetus; therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age and male patients should use effective methods of contraception through defined periods during and after study treatment as specified.

Female patients must meet 1 of the following criteria:

- Postmenopausal for at least 1 year before the screening visit.

- Surgically sterile.
- For WOCBP: agreement to practice 1 highly effective method and 1 additional effective (barrier) method of contraception at the same time, from the time of signing of the ICF through 90 days after the last dose of study drug, OR
- Agreement to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhoea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Male patients, even if surgically sterilized (ie, status post vasectomy), must agree to 1 of the following criteria:

- Agreement to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, OR
- Agreement to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Male patients must agree to refrain from donating sperm from the time of consent through 90 days after the last dose of TAK-280.

Before starting treatment, male patients should be advised to seek counseling regarding sperm storage, and female patients should be advised to seek counseling regarding egg storage.

It is not known whether TAK-280 is secreted into breast milk. Mothers should not breastfeed during the entire study treatment period and for 90 days after the last dose of study drug.

8.8 Management of Clinical Events

If dose alterations are necessary as a result of the events detailed, please refer to Section 8.4.

8.8.1 Management of CRS/IRRs

Patients must be monitored for signs and symptoms of CRS as described in the SOE, including maintenance of a patient diary on non-dose administration days during Cycle 1 ([Appendix A](#)). Patients will also be required to carry a patient emergency card during study participation.

Management of CRS requires close collaboration with specialists in neurology, pulmonology, cardiology, radiology, and/or critical care medicine, as necessary. Given the potential risk of CRS, the sponsor works with the on-site pharmacy to confirm that anti-IL-6 agents such as tocilizumab are on site and available. In circumstances where tocilizumab is not available, other anti-IL-6 agents (eg, siltuximab) will be considered acceptable treatment for CRS, under the condition that this is consistent with local institutional guidelines/practice and that the

availability of the anti-IL-6 agent(s) is(are) confirmed with the site investigator before patient enrollment.

Investigators should differentiate CRS from other critical clinical conditions, including infusion related reactions, sepsis, capillary leak syndrome, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome. Fever is an important clinical sign that should raise the suspicion of impending CRS. If fever develops, institutional guidelines for management should be followed and patients should be frequently reassessed for signs of CRS. Strongly consider admission for close observation. For patients experiencing Grade ≥ 2 CRS, ECG telemetry is recommended. Echocardiogram could be obtained as clinically indicated.

The diagnosis and management of CRS is based on clinical parameters as described in [Table 8-2](#). Ferritin, C-reactive protein, and serum cytokine concentrations should NOT be used for clinical management decisions.

Table 8-2 Management of CRS/Infusion Reactions

CRS Grade	Management of Patient
Grade 1: Non-life-threatening symptoms/Symptomatic treatment	Slow infusion rate by 50%. Monitor patient for worsening of condition. Continue rate at 50% reduction and increase infusion rate to the original rate by increasing by 25% after 30 minutes and continue to increase incrementally to 100% rate every 30 minutes as tolerated.
Grade 2: Symptoms Require and Respond to Moderate Intervention	Stop the infusion. Disconnect the infusion tubing. To avoid exacerbation of CRS: Do Not Flush the Tubing – ASPIRATE RESIDUAL DRUG FROM THE PORT LUMEN. Administer: - Tocilizumab 8 mg/kg to a maximum of 800 mg; if no clinical improvement after first dose, up to 3 additional doses permissible administered at intervals of at least 8 hours between doses. - Methylprednisolone 80-120 mg or hydrocortisone 50-100 mg [REDACTED] per investigator's clinical judgment. [REDACTED] [REDACTED] Oxygen/bronchodilators/IV fluids as deemed necessary. Follow [REDACTED] guidelines for the next scheduled dose administration when prior CRS/infusion reaction was Grade >1 . Administer next dose no sooner than the next scheduled day for infusion. Monitor for worsening condition. Consider obtaining laboratory evaluations for cytokine evaluation (at least IL-2, IL-6, IL-10). If the CRS occurred while the infusion was ongoing, then begin the next TAK-280 infusion at a 50% reduced rate and then increase every 30 minutes by 25% as tolerated. No need to reduce the infusion rate if the reaction occurred after completion of the previous infusion.

Table 8-2 Management of CRS/Infusion Reactions

CRS Grade	Management of Patient
Grade 3: Symptoms Require and Respond to Aggressive Intervention	Stop the infusion. Disconnect the infusion tubing. To avoid exacerbation of CRS: Do Not Flush the Tubing – ASPIRATE RESIDUAL DRUG FROM THE PORT LUMEN. Administer: • Tocilizumab 8 mg/kg to a maximum of 800 mg; if no clinical improvement after first dose, up to 3 additional doses permissible administered at intervals of at least 8 hours between doses. • Methylprednisolone 80-120 mg or hydrocortisone 50-100 mg ■■■■■ per investigator's clinical judgment. ■ ■■■■■ ■ ■■■■■ • IV fluids, supplemental oxygen, and bronchodilator as indicated. • Other medications/treatment as medically indicated. If symptoms have resolved to baseline within 24 hours, a rechallenge may be considered at the next scheduled dose. If the reaction occurred while the infusion was ongoing, then begin TAK-280 infusion at a 50% reduced rate and then increase every 30 minutes by 25% as tolerated. No need to reduce the infusion rate if the reaction occurred after completion of the infusion. Follow ■■■■■ guidelines for the next scheduled dose when prior CRS/infusion reaction was Grade >1. No further doses of TAK-280 if Grade 3 CRS does not resolve or return to ≤Grade 1 within 24 hours despite medical management. No further doses of TAK-280 if a second Grade 3 CRS occurs at the time of rechallenge.
Grade 4: Life-Threatening Symptoms	Stop the infusion, disconnect the infusion tubing. Do Not Flush the Tubing – ASPIRATE RESIDUAL DRUG FROM THE PORT LUMEN. Administer: • Tocilizumab 8 mg/kg to a maximum of 800 mg; if no clinical improvement after first dose, up to 3 additional doses permissible administered at intervals of at least 8 hours between doses. • Methylprednisolone 80-120 mg or hydrocortisone 50-100 mg ■■■■■ ■ ■■■■■ ■ ■■■■■ • IV fluids, supplemental oxygen, and bronchodilators as indicated. Other medications/treatment as medically indicated. Vasopressors or bronchodilators, ventilatory support as indicated. Notify the sponsor's medical monitor immediately. Report the event as an SAE. (See Section 10.2). No further doses of TAK-280 should be given.

CRS: cytokine release syndrome; IL: interleukin; IV: intravenous; PO: by mouth; SAE: serious adverse event.

Early administration of IV fluids and tocilizumab is highly recommended for the management of CRS/IRR (in both the dose-escalation and cohort-expansion phases).

Medications and supportive measures for the treatment of severe CRS/IRR should be available for immediate use during study drug administration. These include, but are not limited to the following:

- Tocilizumab 8 mg/kg, not exceeding 800 mg in a single administration.
- Epinephrine SC.
- Antihistamines (██████████).
- Corticosteroids (eg, hydrocortisone, ██████████).
- IV fluids (normal saline).
- Vasopressors.
- Oxygen (high and low flow by nasal cannula and by continuous positive airway pressure machine).
- Bronchodilators.
- Antipyretics.

Resuscitation equipment and other supplies should also be available. The patient should be treated according to the best available local practices and procedures. All supportive measures consistent with optimal patient care will be provided throughout the study according to institutional standards. In some instances, the signs and symptoms of CRS are similar to those of infection. Patients should be evaluated carefully for the presence of infection, obtaining cultures and/or initiating empiric antibiotic therapy as appropriate based on the assessment of the investigator.

To further mitigate the risk of CRS during this study, vital signs will be measured frequently during and after infusion of TAK-280 (Lee et al. 2019). Close monitoring of vital signs and clinical condition will continue if the patient experiences symptoms that could be consistent with CRS. Patients will be observed overnight as outlined in Section 8.1.1. Additionally, patients will be asked to record their oral temperature twice daily (BID) (first in the morning and last in the evening), and any time the patient feels febrile, in a patient diary during Cycle 1, that should be brought to the site at each visit during through C2D1. If a patient experiences a temperature $\geq 100.4^{\circ}\text{F}$ (38°C) at any time on study, the patient will be instructed to call the investigator immediately.

In addition, a safety check of patients will be performed by the site approximately 48 hours after the end of the infusion for each TAK-280 dose administered in Cycles 1, 2, and 3, ██████████. In-person or remote safety check (eg, via telephone) is allowable.

[REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]

[illegible]

- During the dose-escalation phase, patients will require overnight monitoring in an inpatient facility as outlined in Section 8.1.1.

8.8.1.1.5 *No Reactions of Grade >1 to the Dose on Day 1*

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Postinfusion on Subsequent Infusions:

- IV hydration is 250 to 1000 mL normal saline administered over 2 hours (can be modified based on patient weight, and clinical status).

Patients will be monitored postinfusion as outlined in the SOE ([Appendix A](#)).

8.8.1.1.6 *Grade 2 or Higher Reaction to the Day 1 Dose of TAK-280*

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

During the Infusion (Required)

- If the reaction occurred while the infusion was ongoing: Begin TAK-280 infusion at a 50% reduced rate, then increase every 30 minutes by 25%, as tolerated. There is no need to reduce the infusion rate if the reaction occurred after completion of the prior infusion.

Postinfusion for Subsequent Infusions (Required):

- Patients will be monitored as outlined in the SOE ([Appendix A](#)).
- IV hydration: 500 to 1000 mL normal saline administered over 2 hours (can be modified based on patient weight, and clinical status).

8.8.1.1.7 Dose Delay and Interruptions

For dose delays of ≥ 14 days, refer to Section [8.4.1](#) for restarting rules.

8.8.1.2 Grading of IRRs/CRS

CRS should be graded based on the grade of reaction according to the ASTCT grading criteria. IRRs/CRS will be graded as described in [Table 8-3](#).

Table 8-3 ASTCT Criteria for Grading CRS/IRRs

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever ^a	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$
		With		
Hypotension	None	Not requiring vasopressors	Requiring vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or ^b		
Hypoxia	None	Requiring low-flow nasal cannula ^c or blow-by	Requiring high-flow nasal cannula ^c , facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation, or mechanical ventilation)

Source: Lee et al, 2019 ([Lee et al. 2019](#)).

ASTCT: American Society for Transplantation and Cellular Therapy; BiPAP: bilevel continuous positive airway pressure; CPAP: continuous positive airway pressure; CRS: cytokine release syndrome; CTCAE: Common Terminology Criteria for Adverse Events; IRR: infusion-related reaction.

Organ toxicities associated with CRS may be graded according to CTCAE Version 5.0, but they do not influence CRS grading.

^a Fever is defined as temperature $\geq 38^{\circ}\text{C}$ not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is based on hypotension and/or hypoxia.

^b CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, in a patient with temperature of 39.5°C , hypotension requiring 1 vasopressor, and hypoxia requiring low-flow oxygen by nasal cannula, CRS is classified as Grade 3.

^c Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

8.8.2 Management of LFT Abnormalities

In addition, elevation of circulating cytokines can cause transient increases in liver enzymes and bilirubin levels (Baumgart et al. 2009). In case of LFT abnormalities, it is recommended that the liver chemistry tests be repeated, and results reviewed, in 24 to 48 hours. Guidelines for management of transient increases in LFTs are presented next.

8.8.2.1 Management of Transaminase Elevations

The following are management guidelines for investigators to use along with their clinical assessment and acumen for a patient who is developing increases in transaminases during TAK-280 treatment:

- Grade 1 elevations: No specific therapy required.
- Grade 2 elevations: For elevations in transaminases $3 \times$ to $5 \times$ ULN, rule out viral and other etiologies. Consider imaging studies (such as ultrasonography or CT) and liver biopsy to ascertain the etiology of the liver dysfunction. Withhold TAK-280 and consider starting prednisone 60 mg/d divided BID PO.
 - If improvement to Grade ≤ 1 does not occur in ≤ 48 hours, then consider IV steroids such as methylprednisolone at 2 mg/kg/d divided BID or PO steroids such as prednisone 60 to 120 mg/d divided BID.
 - Monitor LFT results at least twice weekly (BIW) (or more frequently as clinically appropriate in the judgment of the investigator) until transaminases have returned to Grade ≤ 1 .
 - Taper PO steroids as clinically indicated with improvement in liver function.
 - If improvement to Grade ≤ 1 does not occur within 14 days, discontinue TAK-280.
 - Resume TAK-280 at the next scheduled dose if no more than 2 doses were missed.
- Grade 3 elevations: Withhold TAK-280.
 - Elevations in transaminases $>10 \times$ ULN:
 - Permanently discontinue TAK-280.
 - Begin immediate IV steroids; suggested is methylprednisolone at a dosage of 2 mg/kg/d divided BID.
 - Consider additional immunosuppression therapy for patients whose condition does not respond to corticosteroid therapy within 3 to 5 days.
 - Monitor LFT results at least BIW (or more frequently as clinically appropriate in the judgment of the investigator) until transaminases have returned to Grade 1 or baseline.

- Elevations in transaminases $>5 \times$ but $\leq 10 \times$ ULN:
 - Begin immediate IV steroids; suggest methylprednisolone at a dosage of 2 mg/kg/d divided BID.
 - Consider additional immunosuppression, as mentioned for patients who do not respond to corticosteroid therapy within 3 to 5 days.
 - Monitor LFT results at least BIW (or more frequently as clinically appropriate in the judgment of the investigator) until transaminases have returned to Grade 1 or baseline.
 - If the elevation does not improve to Grade 2 within 7 days and to Grade 1 within 14 days, discontinue TAK-280.
 - Resume TAK-280 administration if the following conditions are met:
 - Laboratory elevations improve to Grade ≤ 2 within 7 days and improve to Grade ≤ 1 or baseline within 14 days.
 - Steroids have been tapered to ≤ 10 mg/d of prednisone or equivalent.
 - On the resumption TAK-280, AST, ALT, and total and direct bilirubin laboratory values will be evaluated at least QW for 3 consecutive weeks.
 - Permanently discontinue TAK-280 treatment in the case of a second increase of AST or ALT to Grade ≥ 3 .
- Grade 4 elevation: Discontinue TAK-280 and treat as for Grade 3 elevation.

8.8.2.2 *Management of Bilirubin Elevations*

The following are management guidelines for investigators to use along with their clinical assessment and acumen for a patient who is developing increases in bilirubin during TAK-280 treatment:

- Grade 1 elevations: No specific therapy required.
- Grade 2 elevations: Withhold TAK-280 until improvement to Grade ≤ 1 .
 - Rule out viral and other etiologies. Consider imaging studies (such as ultrasonography or CT) and liver biopsy to ascertain the etiology of the liver dysfunction. Consider PO steroids.
 - If improvement to Grade ≤ 1 does not occur within 14 days, discontinue TAK-280 and begin PO steroid.

- Grade 3 elevations: Withhold TAK-280.
 - Elevations in total bilirubin $>5 \times \text{ULN}$: Permanently discontinue TAK-280 and initiate IV steroids; recommended is methylprednisolone at a dosage of 2 mg/kg/d divided BID.
 - If no response to corticosteroid therapy is observed within 3 to 5 days, consider adding immunosuppression therapy.
 - Monitor LFT results at least BIW (or more frequently as clinically appropriate in the judgment of the investigator) until total bilirubin has returned to Grade ≤ 1 .
- Elevations in total bilirubin $>3.0 \times$ but $\leq 5 \times \text{ULN}$:
 - Begin immediate IV steroids; suggested is methylprednisolone at a dosage of 2 mg/kg/d divided BID. Consider additional immunosuppression therapy as mentioned for patients who do not respond to corticosteroid therapy within 3 to 5 days.
 - Monitor liver function results, including total bilirubin, at least BIW (or more frequently as clinically appropriate in the judgment of the investigator) until total bilirubin has returned to Grade 1 or baseline.
 - If the elevation does not improve to Grade 2 within 7 days and to Grade 1 within 14 days, discontinue TAK-280.
 - Resume TAK-280 administration if the following criteria are met:
 - Laboratory elevations downgrade to Grade ≤ 2 within 7 days and improve to Grade ≤ 1 or baseline within 14 days.
 - Steroids have been tapered to ≤ 10 mg/d of prednisone or equivalent.
 - On the resumption of TAK-280, evaluate AST, ALT, and total bilirubin at least QW for 3 consecutive weeks.
- Permanently discontinue TAK-280 in the case of a second increase of total bilirubin to Grade ≥ 3 .
- Grade 4 elevations: Discontinue TAK-280 and treat as for Grade 3 elevation.

8.8.3 Management of Thrombocytopenia

The following guidelines are recommended actions for the management of thrombocytopenia according to the CTCAE grading criteria:

- Grade 1 (149,000–75,000 mm^3) or Grade 2 (74,999–50,000 mm^3) without bleeding: no specific therapy required.
- Grade 3 (25,000–49,999/ mm^3) without bleeding:
 - Withhold TAK-280 and begin immediate IV steroids. Consider additional immunosuppression therapy for patients whose condition does not respond to corticosteroid therapy within 3 to 5 days.

- Monitor blood counts at least BIW (or more frequently as clinically appropriate in the judgment of the investigator) until platelets have returned to Grade 1 or baseline.
- If the platelet count does not improve to Grade 2 within 7 days and to Grade 1 within 14 days, discontinue TAK-280.
- Resume TAK-280 administration if the following conditions are met:
 - Platelet counts improve to Grade ≤ 2 within 7 days and improve to Grade ≤ 1 or baseline within 14 days.
 - Steroids have been tapered to ≤ 10 mg per day of prednisone or equivalent.
- On the resumption of TAK-280, platelet levels will be evaluated at least QW for 3 consecutive weeks.
- Permanently discontinue TAK-280 treatment in the case of a second decrease of platelets to Grade ≥ 3 .
- Grade 4 ($<25,000/\text{mm}^3$) without bleeding:
 - Withhold TAK-280 begin immediate IV steroids. Consider additional immunosuppression therapy for patients whose condition does not respond to corticosteroid therapy within 3 to 5 days.
 - Consider platelet transfusion to prevent and minimize bleeding.
 - Obtain a hematology consultation.
 - Blood counts should be monitored more frequently.
 - Permanently discontinue TAK-280 if the thrombocytopenia recurs on rechallenge.
- Platelets $<10,000$ cells/ μL , or thrombocytopenia Grade ≥ 3 associated with Grade 2 bleeding:
 - Permanently discontinue TAK-280.
 - Platelet transfusion to minimize bleeding.
 - Obtain a hematology consultation.

8.8.4 Management of Anemia

The following guidelines are recommended actions for the management of anemia according to the CTCAE grading criteria:

- If Grade 3, transfuse packed red blood cells as clinically indicated and resume dose at 1 dose level lower.
- If Grade 4, permanently discontinue TAK-280.

8.8.5 Immune-Related AEs

The mechanism of action of TAK-280 is unlikely to cause breaking of immunologic tolerance in normal tissues as is observed with checkpoint blockade. In addition, this phenomenon was not observed in nonclinical safety studies. Therefore, AEs that are clearly immune-related AEs (eg, hypophysitis, pneumonitis, hypothyroidism, hyperthyroidism) will be reported as AEs.

8.8.6 Management of Neurologic Adverse Events

Patients should be monitored for neurologic toxicities throughout the study including immune effector cell-associated neurotoxicity syndrome (ICANS). Symptoms include, but are not limited to, speech disorders, convulsions, disturbances in consciousness, confusion, disorientation, or coordination and balance disorders. If these or other neurologic toxicities are observed, the sponsor's medical monitor must be consulted. The investigator should also exclude other causes of neurologic symptoms, including the progression of brain metastases, cerebral infarction, cerebral hemorrhage, or infection. A basic neurologic examination using the Immune Effector Cell-associated Encephalopathy assessment tool will be conducted to evaluate neurologic status at baseline and the examination will be repeated as clinically indicated from the occurrence of the first suspected symptoms of ICANS until resolution.

If these or other neurologic toxicities are observed, the sponsor's medical monitor must be consulted. The investigator should also exclude other causes of neurologic symptoms, including the progression of tumor brain metastases, cerebral infarction, cerebral hemorrhage, or infection.

The grading of ICANS will be performed per the ASTCT ICANS Consensus Grading for Adults (Lee et al. 2019) and investigators will manage ICANS per local practice. Guidelines for grading and managing ICANS are provided in [Appendix J](#) and [Appendix K](#).

8.9 Blinding and Unblinding

This is an open-label study.

8.10 Description of Investigational Agents

TAK-280 drug product is a sterile, preservative-free lyophilizate for IV administration contained in [REDACTED]. The drug product also contains other excipients, including [REDACTED]. TAK-280 drug product is reconstituted with [REDACTED].

For specific information about the storage and handling of TAK-280 drug product, refer to the pharmacy manual associated with this study protocol.

8.11 Preparation, Reconstitution, and Dispensation

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever the solution and container permit.

Detailed dosage preparation instructions are provided in the directions for use in the pharmacy manual.

The drug product will be administered by IV infusion over 60 minutes. Detailed dosage preparation instructions are provided in the directions for use in the pharmacy manual.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products or other diluents.

[REDACTED]

TAK-280 must not be administered as an IV push or bolus.

More detailed instructions for drug product administration are provided in the pharmacy manual.

TAK-280 is an anticancer drug, and, as with other potentially toxic compounds, caution should be exercised when handling TAK-280.

8.12 Packaging and Labeling

TAK-280 injection will be labeled as investigational drug product. All label information will fulfill requirements specified by local governing regulations. Additional details are provided in the pharmacy manual.

8.13 Storage, Handling, and Accountability

Complete receipt, inventory, accountability, reconciliation, and destruction records will be maintained by authorized personnel at the study site for all used and unused study drug [REDACTED]

[REDACTED] A drug dispensing log, including records of drug received from the sponsor and drug dispensed to patients will be provided and kept at the study site. For all study sites, the local country sponsor personnel or designee will provide appropriate documentation that must be completed for study drug accountability, return, and destruction. Instructions are provided in the pharmacy manual.

TAK-280 must be stored in a secure, limited-access location, according to the conditions specified on the drug label, and it must remain in the original carton until dispensed. The investigator or designee must confirm that appropriate temperature conditions have been maintained and that any temperature excursions are reported and resolved before use. Please refer to the pharmacy manual for additional instructions.

8.14 Other Protocol-Specified Materials

Information about supplies required by the site for drug administration is provided in the pharmacy manual. Clinical supplies other than study drug to be provided by the sponsor or designee are specified in the study manual.

9.0 STUDY CONDUCT

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), applicable regulatory requirements, and International Council for Harmonisation (ICH) guidelines.

9.1 Study Personnel and Organizations

The contact information for the project clinician for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator, and other vendors participating in the study can be found in the study manual.

For 24-hour contact information, please refer to the study manual or equivalent.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the IRB/IEC.

9.3 Treatment Group Assignments

The dose-escalation phase of the study is not randomized. In the cohort-expansion phase, patients in the selected indication for randomization will be randomized 1:1 to the low RDE or high RDE.

9.4 Study Procedures

Refer to the SOE ([Appendix A](#)) for timing of assessments. Additional details are provided as necessary in the sections that follow. Evaluations during the screening period are to be conducted within 28 days before administration of the first dose of the study drug. Unless otherwise noted, evaluations during the treatment period must occur before drug administration on scheduled visits.

Tests and procedures should be performed on schedule for all visits. The timing of PK and pharmacodynamic assessments is specified in the SOE ([Appendix A](#)).

9.4.1 Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted unless those procedures are performed as part of the patient's standard care.

9.4.2 Patient Demographics

The birth year, race, ethnicity, and sex of the patient are to be recorded during screening.

9.4.3 Medical History

During the screening period (within 28 days before first dose of TAK-280), a complete medical history will be compiled for each patient.

The medical history will emphasize the background and progress of the patient's malignancy and include a description of prior therapies for it.

In addition, concomitant medications will be recorded as specified in Section 9.4.9.

Prior courses of systemic cancer therapy (eg, chemotherapy, immunotherapy, etc) and best response to each therapy will be documented in the medical records and on the eCRF.

9.4.4 Physical Examination

Physical examinations will be completed per standard of care at the times specified in the SOE ([Appendix A](#)).

Physical examination will include measurement of height (baseline only) and weight and examination of the skin; head, eyes, ears, nose, and throat; lymph nodes; heart; chest; lungs; abdomen; extremities; and neurologic systems. Directed physical examinations will be performed within each treatment cycle as specified in the SOE ([Appendix A](#)).

Weight will be measured during screening, on C1D1, and then before the Day 1 dose of TAK-280 in each treatment cycle.

9.4.5 Patient Height

Height will be measured only during screening.

9.4.6 Vital Signs

Vital signs including temperature, pulse rate, blood pressure, respiratory rate, and oxygen saturation will be obtained as specified in the SOE ([Appendix A](#)). It is recommended vital signs be obtained with the patient in a seated, semirecumbent, or supine position after an appropriate rest (approximately 5 minutes in this position).

Patients will be given a diary in which they will record oral temperature BID (first in the morning and last in the evening) and any time the patient feels febrile during Cycle 1, as specified in the SOE ([Appendix A](#)). The diary should be brought to the site at each visit through C2D1 and reviewed by study staff. If patients experience a temperature $\geq 100.4^{\circ}\text{F}$ (38°C) at any time during the study, they will be instructed to call the study investigator. Sites will report clinically significant fever as AEs according to NCI CTCAE Version 5.0 guidelines, if clinically applicable.

9.4.7 ECOG Performance Status

Performance status will be assessed by using the ECOG scale (see [Appendix E](#) for a description of the scale) at the times specified in the SOE ([Appendix A](#)).

9.4.8 Pregnancy Test

The pregnancy test must be a beta-human chorionic gonadotropin test, and either urine or serum can be used. Women who are not of childbearing potential (status post hysterectomy, status post bilateral oophorectomy or salpingectomy, or postmenopausal) and men do not need to have the test performed. Postmenopausal is defined as no menses for 12 months without an alternative medical cause. An FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhoea, a single FSH measurement is insufficient.

WOCBP must have a confirmed negative pregnancy test result at screening (serum test only) and within 72 hours before the first dose of study drug (either urine or serum test). The pregnancy test (either urine or serum test) must also be completed on Day 1 of each treatment cycle and at the EOT assessment.

9.4.9 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF from the time of informed consent is signed through 30 days after the last dose of study drug or the start of subsequent systemic antineoplastic therapy, whichever occurs first. See [Section 8.5](#) and [Section 8.6](#) for a list of medications and therapies that are prohibited or allowed during the study.

9.4.10 AEs

Monitoring of AEs, including SAE, will be conducted throughout the study as specified in the SOE ([Appendix A](#)). Refer to [Section 10.0](#) for details regarding definitions, documentation, and reporting of AEs and SAEs.

Protocol-related AEs and SAEs (ie, AEs related to a protocol procedure but not related to TAK-280) will be collected from the time the patient has consented to study participation until the EOT visit or start of new anticancer therapy.

AEs reported between the time the patient signed the ICF and the administration of the first dose of study drug will be captured as medical history if they are not protocol related.

Disease progression of the malignancy during the study, assessed by measurement of malignant lesions on radiographs or other methods, should not be reported as an AE. However, worsening of signs and symptoms of the malignancy during the study should be reported as AEs in the appropriate section of the eCRF.

9.4.11 Enrollment

Enrollment is defined as the time of initiation of the first dose of study drug. Procedures for completing enrollment information are described in the study manual.

9.4.12 ECGs

Twelve-lead ECGs will be obtained according to the SOE ([Appendix A](#)) to evaluate the potential cardiac effects of TAK-280, including the QT interval. It is recommended that, to the extent possible, ECGs be obtained before meals at approximately the same time of the day to minimize diurnal variations.

ECGs obtained during screening, before the initial dose of TAK-280 dose, and on Day 1 of each treatment cycle and Days 8 and 15 of Cycle 1 will be obtained in triplicate (3 ECGs per time point at approximately 1-minute intervals). (Note: The ECG obtained before the initial dose does not need to be repeated if the screening ECG was obtained within 72 hours before the initial dose of TAK-280.) ECGs obtained at other time points will be single evaluations unless triplicate ECGs are clinically indicated. Local interpretation will be used for data analysis purposes.

Triplicate 12-lead ECG measurements are performed by using standard ECG equipment. Within 4 hours before the triplicate ECG, food should be limited to bland snacks. Patients are required to be in the supine position for 15 minutes, which is the ECG collection window (ie, at least 5 minutes before and up to 10 minutes during the 3 ECG collections for each planned time point). After the patient has been in the supine position for at least 5 minutes, triplicate ECGs will be collected on the ECG equipment. Each of these triplicate ECG collections will be recorded into the clinical database, along with the exact date and time for each collection. The following ECG parameters must be recorded in the clinical database for each triplicate collection: RR interval, PR interval, QRS duration, QT interval, and heart rate (60/RR interval).

When the timing of ECG or vital signs measurements coincides with the timing of blood collection (eg, for a PK sample), the ECG measurements and vital signs measurements should be completed first, followed by blood sampling. The frequency and timing of ECG collection for safety may be modified based on emerging data and agreement between sponsor and investigators.

9.4.13 Clinical Laboratory and Tumor Marker Evaluations

All blood, biopsy, and urine samples will be collected at the times specified in the SOE ([Appendix A](#)). Clinical laboratory tests for hematology, chemistry, pregnancy, urinalysis, coagulation time, and endocrine evaluation (collectively referred to as “safety labs”), and tumor marker levels relevant to the diagnosis will be performed locally. Safety labs should be performed and reviewed before study drug administration. Safety labs, tumor marker levels, and other clinical laboratory tests to be performed locally are listed in [Appendix B](#).

If an unexplained clinically significant abnormal laboratory result occurs, the test should be repeated immediately and followed up until the value has returned to the normal range and/or the abnormality is adequately explained.

Other tests for measures such as PK, ADA, cytokines, leukocyte subsets, T-cell activation status, expression of markers of T cells, T-cell infiltration, and tumor B7-H3 expression will be performed at a sponsor-specified central laboratory or specialty laboratory (refer to the laboratory manual). Please consult the laboratory manual for specific directions for collecting and processing samples.

If creatinine clearance is to be estimated, the Cockcroft-Gault formula will be used, as follows:

$$\text{Estimated creatinine clearance} \\ = [(140 - \text{age}) * \text{mass}] / [72 * \text{serum creatinine concentration}],$$

where age is in y, mass is in kg, and serum creatinine concentration is in mg/dL.

For female patients, the result should be multiplied by 0.85.

9.4.14 Disease Assessment

Tumor assessments will be conducted at screening using CT and/or MRI at time intervals specified in the SOE ([Appendix A](#)). Tumor assessments will be conducted every 8 weeks, starting from C1D1 (ie, at the end of even numbered cycles [eg, Day 28 of Cycles 2, 4, 6, 8, etc]). The dates of the tumor assessments are fixed after C1D1 is performed, completed regardless of delays of Day 1 in future treatment cycles. The scans should be reviewed before the next treatment cycle is started. Treatment will continue until patients have experienced radiological disease progression per RECIST 1.1 by the investigator, or any other of the criteria of treatment discontinuation is met.

During survival follow-up, every effort should be made to continue monitoring the patient's disease status by radiologic imaging every 12 weeks, and data reported should be reported in the eCRF until objective disease progression, new anticancer therapy, or death occurs. This should be attempted for all patients who are discontinued from study treatment because of reasons other than PD if they have not started any other cancer-directed therapy.

When response is assessed, special consideration should be given to the tumor response characteristics associated with immunotherapy, as follows:

1. Measurable tumor size reduction may require longer treatment duration with immunotherapy than with a cytotoxic regimen.
2. Response to immunotherapy may occur after the appearance of PD, as assessed per conventional RECIST V1.1 criteria. In particular, small, new lesions may appear in the presence of other responsive target lesions (pseudoprogression).
3. Durable SD may represent antitumor activity of immunotherapy.

Therefore, patients in the study will also be evaluated for PD per iRECIST criteria ([Seymour et al. 2017](#)) This modification allows patients who are otherwise clinically stable, but who have met conventional RECIST V1.1 PD criteria ([Eisenhauer et al. 2009](#)) for therapy, to continue at the discretion of the investigator pending confirmation of progression at the next scheduled tumor assessment. This approach allows for limited treatment beyond the initial objective disease progression, in patients who are tolerating therapy and clinically stable despite initial

radiographic evidence of disease progression. It has been demonstrated that in some patients treated with T cell–directed, immunomodulatory agents, treatment beyond initial objective progression can achieve an objective response after an initial period characterized by growth of target lesions.

In this study, patients treated with TAK-280 will be permitted to continue treatment beyond PD defined by RECIST 1.1 if the following criteria are met:

- The investigator assesses an overall clinical benefit from continued treatment with TAK-280. The assessment of clinical benefit should consider whether the patient is clinically deteriorating and unlikely to receive further benefit from continued treatment.
- The patient can tolerate the study drug.
- The patient’s ECOG performance status is stable.
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of PD (eg, CNS metastases).
- The patient has provided written informed consent that encompasses any reasonably foreseeable risks or discomforts and alternative treatment options.

The decision to continue treatment beyond PD should be discussed with the Takeda medical monitor and documented in the study records. Then, the patient may remain in the study and continue to receive monitoring according to the protocol-defined SOE. Any additional imaging acquired in patients after PD that is considered clinically stable should also be collected.

Treatment should be discontinued permanently on documentation of further PD, where the first PD is taken as the baseline. If the patient experiences rapid clinical deterioration, as perceived by the investigator before radiographic assessment within 8 weeks of first PD, the investigator can discontinue the study treatment without objective evidence of disease progression and report it as “symptomatic deterioration.”

9.4.15 Radiographic Assessments

Baseline tumor imaging consists of at least either CT or MRI for all patients. The subsequent on-treatment tumor assessments should use the same imaging modality as was used for the baseline assessment.

For this study, CT scans and/or MRIs should be acquired with IV contrast unless contraindicated.

CT or MRI of the brain at screening will be performed when clinically indicated (eg, suspicion of brain metastases), and repeat brain scans will be performed only if the screening brain scan was positive or as clinically indicated.

Anatomic measurements (summed across target lesions) will be collected at baseline and each subsequent evaluation. In addition, nonmeasurable disease and new lesions will be documented and their statuses evaluated. Radiographs and bone scans should be collected as clinically indicated. Determination of disease status will be based on local investigator assessment. Tumor assessments for all patients should continue per protocol even if dosing is interrupted.

Additionally, collection of the most recent prebaseline tumor scan collected before screening will be requested. This collection is optional and should be at least 4 weeks apart from the baseline image and preferably use the same imaging modality and include same anatomic regions as the baseline scans.

Radiographic images will be maintained at the site and deidentified copies of all imaging scans (including those from screening and any unscheduled scans) may be collected and transferred to the sponsor for storage or any future analysis.

9.4.16 Biomarker, Pharmacodynamic, and PK Samples

9.4.16.1 Primary Specimen Collection

Instruction manuals and supply kits will be provided for pharmacodynamic laboratory assessments. The following samples will be analyzed at a central, specialty, or local laboratory:

- Blood samples for PK/ADA analysis.
- Blood samples for cancer-associated proteins.
- Blood samples for cytokine analysis.
- Whole blood for peripheral immune activity.
- Whole blood for ctDNA.
- Pretreatment and posttreatment tissue samples for assessment of readouts including, but not limited to, biomarker expression, immunoregulatory markers, and immune cell infiltration.

Procedures for the acquisition, handling, and processing of pharmacodynamic biomarker specimens are provided in the laboratory manual. Samples are to be obtained at the time points specified in the SOE and in the PK, immunogenicity, and pharmacodynamic biomarkers blood sampling schedules ([Appendix A](#)), Tables A1 through [A6](#)).

9.4.16.2 Tumor Biopsies

Archived Tumor Sample

Archival FFPE tumor tissue or a minimum of 10 unstained slides of the tumor tissue (ie, tumor tissue obtained at the time of the patient's original diagnosis and/or at the time of subsequent procedures conducted as part of the patient's standard care) will be collected from all enrolled patients in both the dose-escalation and expansion phases to assess baseline features such as gene mutations, gene signatures, tumor mutation burden, protein expression, immune cell content, or biomarkers of response or resistance to TAK-280 that may emerge from future nonclinical or clinical studies. See the laboratory manual for details.

Fresh Tumor Biopsy Samples

Patients are strongly encouraged to provide paired fresh tumor biopsy samples during screening (pretreatment) and within 7 days before C3D1 (on treatment), as specified in the SOE

(Appendix A), when a lesion is safely accessible for a low-risk biopsy procedure (those occurring outside the brain, lung/mediastinum, and intra-abdominal space or accessible by endoscopic procedures beyond the stomach or bowel).

During the dose-escalation phase, pre- and on-treatment fresh tumor biopsy specimens will be required for the first 6 backfill patients enrolled at cohort-assigned dose levels [REDACTED]

During the cohort-expansion phase, similar paired tumor biopsies, preferably from the same lesion, will be required. The requirement for a biopsy specimen may be removed if endpoint criteria are met (see Appendix I for statistical considerations for paired biopsy specimens). The paired tumor biopsy is optional for patients with mCRPC limited to bone metastasis.

Tumor lesions used for biopsy should not be lesions used as one of the target lesions for response evaluation, unless no other lesions are suitable for biopsy. Tumor biopsy samples should be obtained only from lesions that are considered to be accessible with acceptable clinical risk in the judgment of the investigator. The sponsor should be contacted if biopsy is considered to present a potentially unreasonable risk to the patient.

- Biopsy should not be performed on lesions used as RECIST V1.1 target lesions unless no other lesions are suitable for biopsy.
- If a RECIST V1.1–defined target lesion is used for biopsy, it must be ≥ 2 cm in longest diameter.
- Lesions to be biopsied should not have been previously irradiated unless the lesions have clear evidence of growth after radiation.
- Multiple lesions may be used to obtain the biopsy sample. Whenever possible, the on-treatment biopsy sample should be obtained from the same lesion used for pretreatment biopsy.
- Lesions to be biopsied should be of sufficient size to enable acquisition of at least 3 tumor biopsy cores using a 16-gauge biopsy needle. Exceptions to the gauge of the needle may be considered after consultation with the sponsor’s medical monitor.
- As many as 3 additional biopsy cores may be obtained if this can be accomplished with acceptable clinical risk in the judgment of the investigator.
- Excisional or punch biopsies are allowed if these can be performed with acceptable clinical risk in the judgment of the investigator.
- Fine-needle aspiration biopsies are not allowed.
- Immediate confirmation of the adequacy of the biopsy specimen and the presence of malignant cells in the tumor biopsy are strongly encouraged.
- If the pretreatment biopsy sample is deemed inadequate for testing and evaluation, the planned on-treatment biopsy is not required.

- Additional instructions for processing and storing tumor biopsy specimens are provided in the laboratory manual.
- For patients who do not have a baseline archived tumor sample, the volume of the tumor biopsy sample should be enough for the tests intended for both pretest samples and archived tumor samples.

All samples will be stored at the study sponsor's facility or at a contract laboratory facility until assessments are completed and checked.

9.4.17 PK Measurements

9.4.17.1 PK Sample Collection

Details regarding the preparation, handling, and shipping of the PK samples are provided in the laboratory manual. Blood samples for PK and ADA evaluation will be collected at the time points shown in the SOE ([Appendix A](#), Tables [A4](#) through [A6](#)). Blood samples will be collected from the arm contralateral to the site of IV infusion.

If an indwelling catheter is used, the fluid in the catheter will be removed and discarded before the blood sample is collected for PK assessment.

9.4.18 Pharmacodynamic Measurements

In this study, several biomarkers and pharmacodynamic measurements will be assessed to test for correlation with safety and, if possible, with efficacy. These biomarkers will be used to identify potential pharmacodynamic activity and patients who have a heightened probability of response or of adverse reactions to TAK-280. The biomarker sample analyses will be performed if or when required. Because new techniques continue to be developed, the method and laboratory that will be recommended for the biomarker analysis cannot be anticipated. The biomarker and pharmacodynamic specimen collection time points are displayed in the SOE ([Appendix A](#)), Tables [A3](#) through [A6](#).

Details regarding the preparation, handling, and shipping of samples are provided in the laboratory manual.

The following biomarkers, including but not limited to, will be analyzed:

- Characterize biomarkers and the pharmacodynamic activity of TAK-280 by evaluating markers such as, not limited to, tumor protein markers (eg, PSA), cytokines (eg, IL-2, IL-6, IL-10, IFN γ), T cell phenotypes (eg, activation, proliferation, exhaustion).
- Evaluate tumor biopsies for B7-H3 and PDL-1 expression, as well as characteristics of the TME and changes post-treatment (eg, T-cell infiltration and activation).
- Longitudinal ctDNA monitoring of patient specific somatic mutations from baseline tumor.

9.4.19 DNA Measurements

As detailed in the SOE ([Appendix A](#)), peripheral blood will be collected during screening to extract DNA as a control sample for DNA mutation analysis from archived tumor and/or fresh tumor biopsy samples. In addition, the extracted DNA from such samples may be used in eventual pharmacogenomic evaluation to study the effect of genetic polymorphism, such as drug metabolizing enzymes and/or transporters that may be implicated in the disposition of TAK-280.

9.4.20 Immunogenicity Sample Collection

Blood samples for the assessment of ADA will be collected at time points specified in the SOE ([Appendix A](#)), Tables A3 through [A6](#)). Samples must be collected before study drug is administered on a dosing day and, optionally at unscheduled visits for a patient who experiences an AE considered by the investigator to be consistent with hypersensitivity/IRR. A sample will be assessed for neutralizing ADA if a positive ADA result is confirmed.

ADA sampling will be obtained before infusion to coincide with the days when PK samples are collected (SOE, [Appendix A](#), Tables [A3](#) through [A6](#)).

9.4.21 Changes to Study Procedures Due to COVID-19 Pandemic

The following information provides guidance regarding changes to the study procedures that could be implemented for study participants or study sites affected by the COVID-19 pandemic. This guidance takes references from the Food and Drug Administration (FDA) Guidance and the European Medicines Agency Guidance ([EMA 2021](#); [FDA 2021](#)).

Because the COVID-19 pandemic may peak in different regions at different times and because restrictions implemented by local laws and recommendations may vary, any decision about procedural changes should be made on a case-by-case basis by the investigator in consultation with the study team and the medical team sponsor's medical monitor/designee as needed, while maintaining patient safety and confidentiality as the priority.

Procedural changes due to COVID-19 may include the following:

- If necessary, informed consent from a potential or current study participant may be obtained via alternate methods, including but not limited to, electronic informed consent, a remote consenting process, or an electronic face-to-face consent interview (if approved by the IRB/IEC) when these individuals are unable to travel to the site.
- Deviations from the protocol-specified procedures (eg, not collecting a protocol-specified specimen, such as postdose bloodwork) will be recorded as related to COVID-19.
- Allow transfer of study participants to investigational sites away from risk zones or closer to their home to new sites or sites already participating in the study.

9.5 Completion of Study Treatment (for Individual Patients)

Patients will be considered to have completed study treatment if they discontinue the study drug for any of the reasons listed in this section.

Patients may receive up to 14 treatment cycles of TAK-280 until any of the following conditions are met:

- Patient meets criteria for objective PD by RECIST by the investigator. (Patients meeting the criteria for radiological progression but otherwise experiencing substantial clinical benefit with acceptable toxicity based on investigator opinion may continue therapy on a case-by-case basis with agreement from the sponsor's medical monitor.)
- Occurrence of non-CRS/IRR drug-related AE that meets DLT criteria at any time during treatment.
- Occurrence of a CRS/IRR DLT that meets DLT definition at any time during treatment.
- Sponsor, investigator, or regulatory agency terminates the study.
- Investigator withdrawal of patient.
- Clinical progression (no imaging test performed to assess tumor status, but the investigator considers that patient decline is caused by tumor progression).
- Withdrawal of patient consent.
- Lost to follow-up.
- Completion of protocol defined therapy.
- Pregnancy.
- Withdrawal of patient due to an AE (after discussion with sponsor).
- Protocol deviation (after discussion with sponsor).
- Initiation of another systemic anticancer treatment.
- Death.
- CR (after discussion with sponsor).

If a patient is withdrawn from the study or from TAK-280 dosing for any reason other than disease progression, the sponsor must be alerted within 24 hours.

Toxicity will be evaluated according to NCI CTCAE, Version 5.0.

Once the study drug has been discontinued, all study procedures outlined for the EOT visit will be completed as specified in the SOE ([Appendix A](#)). The primary reason for study drug discontinuation will be recorded on the eCRF. Note that some patients may discontinue study drug for reasons other than PD before completing the full treatment course; these patients will remain in the study as outlined in the SOE ([Appendix A](#)) until a criterion presented in [Section 9.6](#) is met.

In the case of study termination by the sponsor, eligible patients may have continued access to TAK-280, as described in [Section 6.4](#).

9.6 Completion of Study/EOS Visit (for Individual Patients)

Patients will be considered to have completed the study if any of the following is met:

- Death.
- Completed survival follow-up.
- Withdrawal by patient.
- Study terminated by the sponsor.
- Lost to follow-up.

The EOS visit will be performed when the patient completes the study. The EOS visit should be performed using the same data collection method used for survival follow-up. The reason for study completion must be recorded.

9.7 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

Tests and procedures should be performed on schedule; however, unless otherwise specified, occasional changes are allowable within a 3-day window with permission of the medical monitor for holidays, vacations, and other administrative reasons. If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor.

9.8 Immune-Mediated AE Follow-Up

Patients will have an onsite follow-up visit to assess immune-mediated AEs 90 (+7) days after the last dose of TAK-280, unless subsequent systemic anticancer therapy is started before this time. Relevant laboratory tests and examinations may be required if an immune-mediated AE is suspected. All immune-mediated AEs must be reported as specified in Section 10.2.

The immune-mediated follow-up visit may be combined with the first posttreatment survival follow-up, if the survival follow-up visit is an onsite visit.

9.9 Posttreatment Survival Follow-up

Patients will enter a survival follow-up period after the last dose of study drug to 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).

In addition, the start of another systemic anticancer treatment for the disease under study will be collected.

NOTE: Treatment-related SAEs that occur during the survival follow-up period must be reported to the Global Pharmacovigilance department or designee. This includes deaths that the

investigator considers related to study drug that occur during posttreatment follow-up. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of SAEs.

10.0 AES

10.1 Definitions

10.1.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient or study participant who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AE Definition

AE means any untoward medical occurrence in a patient or patient administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

10.1.3 TEAE Definition

Treatment-emergent adverse event (TEAE) includes all immune-related AEs after the first dose of study drug until 90 days after the last dose of study drug, and all other AEs after the first dose of study drug until 30 days after the last dose of study drug. 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.

10.1.4 SAE Definition

SAE means any untoward medical occurrence that at any dose:

- Results in **death**.
- Is **life-threatening**. (Refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization**. (See clarification in the paragraph in Section 10.2 on planned hospitalizations).

- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life-threatening, or require hospitalization, but may be considered serious when, on the basis of appropriate medical judgment, it may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined by using the NCI CTCAE, Version 5.0 (2010). Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4) because the terms *serious* and *severe* are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell WBC count of 1000/mm³ to less than 2000/mm³ is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as a single comprehensive event.

Regardless of causality, SAEs must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee within 24 hours of becoming aware of the event. This will be done by transmitting an electronic data capture (EDC) SAE report. If transmission of an EDC SAE report is not feasible, then a facsimile of the completed Takeda paper-based SAE form will be sent. A sample of the paper-based SAE form and processing directions are in the study manual. Information in the SAE report or form must be consistent with the data provided on the eCRF.

If information not available at the time of the first report becomes available at a later date, then the investigator will transmit a follow-up EDC SAE report (or a paper-based SAE form if an EDC SAE report is not feasible) or provide other documentation immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the study are not to be considered AEs unless the condition deteriorated in an unexpected manner during the study (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the severity (toxicity grade) of the event and the relationship of the event to study drug administration.

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 5.0 (2010). The criteria are provided in the study manual.

Relationship of the event to study drug administration (ie, its causality) will be determined by the investigator responding yes (related) or no (unrelated) to this question: Is there a reasonable possibility that the AE is associated with the study drug?

10.3 Monitoring of AEs and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the signing of informed consent through 30 days after administration of the last dose of study drug or before initiation of new anticancer therapy (whichever comes first) and recorded in the eCRFs.
- Immune-mediated AEs will be reported through 90 days after the last dose of study drug unless subsequent systemic anticancer therapy is started before this time.
- SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the signing of informed consent through 30 days after administration of the last dose of study drug or before initiation of new anticancer therapy (whichever comes first) and recorded in the eCRF.

Only related SAEs occurring greater than 30 days after the last dose of study drug (until patient completes the study or starts new anticancer therapy) must be reported to the Takeda Global Pharmacovigilance department or designee.

SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately (no later than 24 hours) by sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately (no later than 24 hours) by sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Pregnancies are to be reported through 90 days after the last dose of study drug.

10.5 Procedures for Reporting Product Complaints (Including Overdose)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately report this via the phone numbers or email addresses provided.

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, the SAE should be reported.

10.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and IRBs and IECs, as applicable, in accordance with national regulations. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited reports within 7 days for fatal and life-threatening events and within 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be enough to consider changes in the investigational medicinal product's administration or in the overall conduct of the study. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

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

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the data management plan. If selected for coding, AEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each patient who signs an ICF.

The sponsor or its designee will supply investigative sites with access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, contract research organization (CRO) partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designee) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for the change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor (or designee) will be permitted to review the patient's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating patients, medical records, temporary media such as thermal-sensitive paper, source worksheets, all original signed and dated ICFs, patient authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copies of eCRFs including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and the sponsor (or designees). Any source documentation printed on degradable thermal-sensitive paper should be photocopied by the site and filed with the original in the patient's chart to ensure long-term legibility. Furthermore, ICH E6 (ICH E6 Section 4.9.5)

requires the investigator to retain essential documents specified in ICH E6 (ICH E6 Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 (Section 4.9.5) states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the clinical study site agreement between the investigator and sponsor.

Refer to the clinical study site agreement for the sponsor's requirements for record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

The primary analysis of this study will be conducted when all patients have discontinued therapy, or, if they are continuing therapy, when patients have data available through approximately 6 months of follow-up, whichever occurs first.

13.1.1 Analysis Sets

DLT-evaluable analysis set: The DLT-evaluable analysis set will include 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-evaluable analysis set will be used to guide dose escalation decisions and to determine the MTD.

Safety analysis set: The safety analysis set will include 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.

Response-evaluable analysis set: The response-evaluable analysis set will include 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.

PSA response analysis set: The PSA response analysis set will include 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.

PK analysis set: The PK analysis set will include 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.

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.

Pharmacodynamic analysis set: The pharmacodynamic analysis set will include all patients who received at least 1 dose of TAK-280 and had baseline and at least 1 postbaseline pharmacodynamic assessment.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Patient demographic and baseline characteristics will be summarized descriptively. Variables to be analyzed include sex, age, race, medical history, prior medications/therapies, ECG findings, and other parameters as appropriate. For continuous variables, descriptive statistics (number, mean, standard deviation, median, minimum, and maximum) will be provided. For categorical variables, patient numbers and percentages will be provided. Categories for missing data will be presented as needed.

13.1.3 Efficacy Analysis

Efficacy is not the primary endpoint for this study. Secondary efficacy endpoints include ORR, DOR, PFS, OS, and DCR; and PSA response, duration of PSA response, time to PSA progression, and the percentage of patients with prostate-specific antigen reductions of $\geq 50\%$ at 6 months (for patients with mCRPC only). No formal statistical tests will be performed for these secondary endpoints.

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

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.

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.

OS is defined as the time from the date of the first dose of TAK-280 to the date of death due to any cause.

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 (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 (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 (patients with mCRPC only).

ORR and DCR will be summarized by using point estimates with 2-sided exact 95% confidence intervals (CIs) using the response-evaluable analysis set and safety analysis set. PFS and OS will be analyzed descriptively by using the Kaplan-Meier (KM) method for the safety analysis set. DOR will also be analyzed by using the KM method for the patients who have confirmed response. PFS and OS rates at 8 weeks (2 cycles), 16 weeks (4 cycles) and 32 weeks (8 cycles) from the first dose of study drug will be computed along with CIs.

The percentage of patients with mCRPC who achieve PSA response will be summarized by point estimates with 2-sided exact 95% CIs. The percentage of patients with mCRPC with PSA reductions of $\geq 50\%$ at 6 months will also be estimated along with 95% exact CIs. These analyses will use the PSA response analysis set. Duration of PSA response will be analyzed descriptively by the KM method among patients who have PSA response; time to PSA progression will be analyzed descriptively by the KM method using the safety analysis set.

13.1.4 PK Analysis

13.1.4.1 PK Noncompartmental Analysis

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:

- $C_{\max}$.
- $t_{\max}$.
- Area under the concentration-time curve from time 0 to time of the last quantifiable concentration ($AUC_{0-\text{last}}$).
- Area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\text{inf}}$).
- $t_{1/2}$.
- Total clearance (CL).
- Volume of distribution at steady state after IV administration (V_{ss}).

PK parameters will be individually listed and summarized using descriptive statistics, including arithmetic and geometric mean, median, standard deviation, percentage coefficient of variation (%CV), geometric %CV, minimum, and maximum. Individual TAK-280 concentration-time data

and individual PK parameters will be presented in listings and tabulated by using summary statistics by dose level. Individual and mean concentration-time profiles will be plotted by dose level.

13.1.4.2 PK Sampling Intended for Population PK Analysis

The PK data collected in this study may contribute to future population PK analyses of TAK-280. These population PK analyses may additionally include data collected in other TAK-280 clinical studies. The plan for the population PK analysis will be defined separately and the results reported separately.

13.1.5 Pharmacodynamic Analysis

Summary statistics will be generated based on changes from baseline for pharmacodynamic parameters including those listed in Section 9.4.16 and Section 9.4.18. Results will be summarized and/or may also be presented graphically. Possible associations between changes in pharmacodynamic measures of interest and TAK-280 dose, exposure, safety, and efficacy may be explored.

13.1.6 PK/Pharmacodynamic Analysis

The relationship between TAK-280 plasma exposure and pharmacodynamic response (eg, degree of immune activation, changes in cytokines/chemokines, gene expression changes, etc) will be explored on an ongoing basis in the pharmacodynamic population as PK and pharmacodynamic data become available. To understand the PK/pharmacodynamic relationships of TAK-280, contribute to the selection of RDEs and the RP2D, and potentially explore alternative dose levels and/or dosing regimens. If applicable, these analyses will be reported separately and summarized in the clinical study report.

13.1.7 Immunogenicity Analyses

The percentage of patients who have no detectable ADA at baseline and become positive in this assay, the percentage of patients who have no detectable ADA at baseline and remain negative without detectable ADA, and those who have detectable and are positive for ADAs at baseline that increase or decrease in titer over the course of treatment will be summarized. Where applicable, NAb titers will also be assessed. The effect of immunogenicity on PK, safety, and efficacy will be examined.

13.1.8 ECG Analysis

A summary of ECG abnormalities will be presented by visit. ECG parameters (QT, QT interval with Bazett correction method, QTcF interval, PR interval, QRS interval, and heart rate) will be summarized at each scheduled time point, along with mean change from baseline to each posttreatment time point.

13.1.9 Safety Analysis

Safety will be evaluated as the frequency of AEs; severity and types of AEs; and changes from baseline in patients' vital signs, weight, and clinical laboratory results in the safety analysis set.

Exposure to study drug and reasons for discontinuation will be tabulated.

TEAEs will be tabulated according to the MedDRA and will include the following categories:

- TEAEs.
- Drug-related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher drug-related TEAEs.
- The most commonly reported TEAEs (ie, those reported by $\geq 10\%$ of all patients).
- SAEs (related and regardless of relationship to the study drug).
- Any TEAE leading to death.
- TEAEs leading to study-drug modification and discontinuation.

The incidence of DLTs will be tabulated in the DLT-evaluable analysis set.

Descriptive statistics for the actual values of clinical laboratory parameters (and/or change from baseline in clinical laboratory parameters) will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters.

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs and weight will be tabulated by scheduled time point. ECOG performance scores will be summarized by using a shift table.

Shift tables for laboratory parameters will be generated for changes in NCI CTCAE grade from baseline to worst postbaseline value. Graphical displays of key safety parameters, such as scatterplots of baseline values versus worst postbaseline values, may be used to understand the TAK-280 safety profile.

All concomitant medications collected from the first dose of study drug throughout the study period will be classified by Preferred Term, according to the WHO Drug Dictionary.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of TAK-280.

13.2

[illegible]

Table 13-1

[illegible]

Sample Size

The sample size in the cohort-expansion phase of the study is approximately 100 to 140 patients. Additional patients may be enrolled into each cohort to meet the evaluable sample size requirements or to explore the low RDE further if deemed appropriate.

the low RDE further if deemed appropriate.

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All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized) including, but not limited to, the investigator's binder, study medication, patient medical records, informed consent documentation, documentation of patient authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that enough time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study patients. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the patient's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or IEC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the patient, or confound interpretation of the primary study assessment.

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a patient or the reliability and robustness of the data generated, it may be reported to regulatory authorities as a serious breach of GCP and the protocol.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the US FDA, the United Kingdom [UK] Medicines and Healthcare products Regulatory Agency [MHRA], the Pharmaceuticals and Medical Devices Agency of Japan [PMDA], and the Australian Therapeutic Goods Administration [TGA]). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, patients) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the responsibilities of the investigator that are listed in [Appendix C](#). The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable local requirements of each participating region. The sponsor or designee will require documentation noting all names and

titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members because of privacy and conflict of interest concerns should instead provide a Federalwide Assurance number or comparable number assigned by the US Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the investigator's brochure, a copy of the ICF, and, if applicable, patient recruitment materials and advertisements and other documents required by all applicable laws and regulations must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and patient informed consent must be obtained and submitted to the sponsor or designee before commencement of the study, ie, before shipment of the sponsor-supplied drug or study-specific screening activity. The IRB or IEC approval must refer to the study by its exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. If required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. The sponsor will ship drug/notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from the competent authority to begin the study. Until the site receives drug/notification, no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by patients, local safety reporting requirements, reports, and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor (or designee).

Patient incentives should not exert undue influence for participation. Payments to patients must be approved by the IRB or IEC and sponsor.

15.2 Patient Information, Informed Consent, and Patient Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the patient's personal and personal health information for purposes of conducting the study. The ICF and the patient information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, and the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to

withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and, if applicable, the patient authorization form. The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) must be written in a language fully comprehensible to the prospective patient. It is the responsibility of the investigator to explain the detailed elements of the ICF, patient authorization form (if applicable), and patient information sheet (if applicable) to the patient. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. If the patient is not capable of rendering adequate written informed consent, then the patient's legally acceptable representative may provide such consent for the patient in accordance with applicable laws and regulations.

The patient, or the patient's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and, (2) decide whether to participate in the study. If the patient, or the patient's legally acceptable representative, determines that he or she will participate in the study, then the ICF and patient authorization form (if applicable) must be signed and dated by the patient, or the patient's legally acceptable representative, at the time of consent and before the patient enters into the study. The patient or the patient's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using a ballpoint pen with either blue or black ink. The investigator must also sign and date the ICF and patient authorization (if applicable) at the time of consent and before the patient enters into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, patient authorization form (if applicable), and patient information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the patient signs the informed consent in the patient's medical record. Copies of the signed ICF, the signed patient authorization form (if applicable), and patient information sheet (if applicable) shall be given to the patient.

All revised ICFs must be reviewed and signed by relevant patients or the relevant patient's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the patient's medical record, and the patient should receive a copy of the revised ICF.

15.3 Patient Confidentiality

The sponsor and designees affirm and uphold the principle of the patient's right to protection against invasion of privacy. Throughout this study, a patient's source data will be linked to the sponsor's clinical study database or documentation only via a unique identification number. As permitted by all applicable laws and regulations, limited patient attributes, such as sex, age, or

date of birth, and patient initials may be used to verify the patient and accuracy of the patient's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, US FDA, UK MHRA, Japan PMDA, Australian TGA), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the patient's original medical records (source data or documents) including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a patient's study participation, and autopsy reports. Access to a patient's original medical records requires the specific authorization of the patient as part of the informed consent process (see Section 15.2).

Copies of any patient source documents that are provided to the sponsor must have certain identifying personal information removed, eg, patient name, address, and other identifier fields not collected on the patient's eCRF.

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the clinical study site agreement. In the event of any discrepancy between the protocol and the clinical study site agreement, the clinical study site agreement will prevail.

15.4.2 Clinical Trial Registration

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, Takeda will, at a minimum, register interventional clinical trials it sponsors anywhere in the world on www.ClinicalTrials.gov or other publicly accessible websites on or before start of study, as defined by Takeda policy/standards. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

As needed, Takeda and investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Takeda may assist

participants or potential participants in finding a clinical trial by helping them locate trial sites closest to their homes by providing the investigator name, address, and phone number via email/phone or other methods preferred by callers requesting trial information. Once patients receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established patient screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov, clinicaltrialsregister.eu, and other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda policy/standards, applicable laws, and/or regulations.

Data Sharing

The sponsor is committed to responsible sharing of clinical data with the goal of advancing medical science and improving patient care. Qualified independent researchers will be permitted to use data collected from patients during the study to conduct additional scientific research, which may be unrelated to the study drug or the patient's disease. The data provided to external researchers will not include information that identifies patients personally.

15.5 Insurance and Compensation for Injury

Each patient in the study must be insured in accordance with the regulations applicable to the site where the patient is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study patients. Refer to the clinical study site agreement regarding the sponsor's policy on patient compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Events

Table A1 Schedule of Events, [REDACTED]

Evaluation/Procedure	Screening (Within 28 Days of First Dose)	Cycle 1 ^a						Cycle 2						Cycle 3				Cycle 4 and Beyond					EOT ^b	Immune- mediated AE Follow- up ^c	Survival Follow- up/EOS ^d
	Day	1	2	3	8	15	22	1	2	8	15	22	28	1	8	15	22	1	8	15	22	28			Q12W
Visit window (±) days ^e		0	0	0	3	3	3	3		3	3	3	-6	3	3	3	3	3	3	3	3	-6	+10	+7	7
Administer TAK-280 ^f		X			X	X	X	X		X	X	X		X	X	X	X	X	X	X	X				
Postinfusion observation ^g		X			X	X	X	X		X	X	X		X	X	X	X	X	X	X	X				
ICF ^h	X																								
Medical history ⁱ	X																								
Physical examination/directed physical examination ^j	X	X ^k			X	X	X	X		X	X	X		X	X	X	X	X	X	X	X		X		
ECOG performance status	X	X						X						X				X					X		
ECG ^l	X	X ^j	X	X	X	X	X	X						X				X							
Vital signs ^m	X	X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	X	X	X		X		
Height	X																								
Weight	X	X ^k			X	X	X	X		X	X	X		X	X	X	X	X	X	X	X		X		
Eligibility checklist and patient registration ⁿ	X																								
Patient diary review ^o					X	X	X	X																	
LABORATORY ASSESSMENTS																									
Comprehensive chemistry panel ^p	X	X ^k	X		X	X	X	X			X			X		X		X					X		
Special chemistry ^p	X	X ^k					X	X						X				X					X		
Hematology ^p	X	X ^k			X	X	X	X			X			X		X		X		X			X		
Coagulation ^p	X	X ^k					X	X						X				X					X		
Endocrine tests ^{p,q}	X													X				X ^q					X ^q		
Urinalysis ^p	X	X ^k					X	X						X				X					X		

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Evaluation/Procedure	Screening (Within 28 Days of First Dose)	Cycle 1 ^a						Cycle 2						Cycle 3				Cycle 4 and Beyond					EOT ^b	Immune- mediated AE Follow- up ^c	Survival Follow- up/EOS ^d
	Day	1	2	3	8	15	22	1	2	8	15	22	28	1	8	15	22	1	8	15	22	28			Q12W
Visit window (±) days ^e		0	0	0	3	3	3	3		3	3	3	-6	3	3	3	3	3	3	3	3	-6	+10	+7	7
Pregnancy test ^{Pr}	X	X ^k						X						X				X					X ^r		
PK ^s		X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X ^t					X		
ADA ^s		X				X	X	X		X	X	X		X	X	X	X ^t					X			
Flow cytometry (subset) ^s		X	X	X	X	X	X	X	X		X			X											
EFFICACY ASSESSMENTS																									
Tumor marker ^u	X							X						X				X					X ^u		
ctDNA ^s		X												X				X ^t					X		
Cytokine sampling ^s		X	X	X	X	X	X	X	X					X	X										
Tumor assessment (CT/MRI) ^v	X												X									X	X ^v		X ^w
Brain MRI/CT, if applicable ^x	X												X									X	X ^x		X ^w
Archival tissue ^y	X																								
Fresh Biopsy ^z	X													X											
Survival follow-up contact ^{aa}																									X
SAFETY ASSESSMENTS																									
Safety check ^{bb}		X			X	X	X			X	X	X		X	X	X	X								
Concomitant medications	Continuous																								
Assessment for AEs	Continuous																								
Immune-mediated AEs	Continuous																						X		

ADA: antidrug antibody; AE: adverse event; BID: twice daily; CRS: cytokine release syndrome; CT: computed tomography; CTCAE: Common Terminology Criteria for Adverse Events; ctDNA: circulating tumor DNA; CxDx: Cycle x Day x; DLT: dose-limiting toxicity; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOI: end of infusion; EOS: end of study; EOT: end of treatment; FFPE: formalin-fixed paraffin-embedded; FT4: free thyroxine; hCG: human chorionic gonadotropin; HEENT: head, eyes, ears, nose, and throat; ICANS: immune effector cell-associated neurotoxicity syndrome; ICE: Immune Effector Cell-associated Encephalopathy; ICF: informed consent form; IRR: infusion-related reaction; MRI: magnetic resonance imaging; PD: progressive disease; PK: pharmacokinetic(s); Q: every; SOI: start of infusion; TSH: thyroid-stimulating hormone; W: week(s).

^a For patients in the dose-escalation cohorts, the DLT-evaluation period is defined as the time between the initial TAK-280 dose and C1D28.

^b EOT visits will be conducted 30 days (+10 days) after last TAK-280 dose or before the start of subsequent systemic anticancer therapy, whichever occurs first.

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^c Patients will attend a follow-up visit to assess immune-mediated AEs 90 days (+ 7 days) after last TAK-280 dose, unless subsequent systemic anticancer therapy is started before this time. Relevant laboratory tests and examinations may be required if immune-mediated AE is suspected.

^d The EOS visit should be performed when the patient finishes the survival follow-up, withdraws consent, or is lost to follow-up or when the study is terminated. EOS information may be collected by methods that include, but are not limited to, telephone, email, mail, or retrieval from online or other databases (eg, Social Security indexes).

^e Visit and assessment windows are presented as guidance. Specific assessment window allowances are listed in the respective footnotes that follow. Out-of-window visits/time points will not be considered protocol deviations unless they affect patient safety or data integrity; these will be assessed by the medical monitor before database closure.

^f TAK-280 will be administered over 60 ($\pm$ 10) minutes. Based on emerging data (eg, severity of the IRRs), the infusion time may be adjusted to shorter or longer than 60 minutes on agreement with the sponsor and investigator; however, infusion time will not be less than 30 minutes. The start time and stop time of each TAK-280 infusion must be documented. A minimum of a 4-day interval should occur between doses of TAK-280.

^g Postinfusion observations: During the dose-escalation phase only, the following observations are required:

Overnight observation: C1D1 (a minimum 24-hour observation period is required for all patients after the administration of the first cohort dose. Refer to [Table A2](#) for [REDACTED] and [Table A3](#) [REDACTED]).

6-hour observation: C1D8, C1D15, and C1D22.

4-hour observation: C2D1, C2D8, C2D15, and C2D22.

The sponsor strongly recommends overnight observation after all infusions in Cycles 1 and 2.

Starting with Cycle 3, investigators can monitor patients after each infusion for a duration based on their clinical assessment of each patient.

For all doses in all cycles, the patient can be monitored overnight if the patient develops symptoms suggestive of CRS during the postinfusion observation period.

^h Informed consent is to be obtained before enrollment. Study-specific procedures must be conducted only after informed consent is obtained.

ⁱ One prebaseline tumor scan collected before screening is optional. The prebaseline tumor scan should have been collected at least 4 weeks prior to the baseline scan, and should use the same imaging modality and include same anatomical regions as the baseline scan. Deidentified copies of these scans may be collected and transferred to the sponsor or designee (eg, central imaging vendor/imaging contract research organization) for storage and any future analysis.

^j Physical examination/directed physical examination: Complete physical examination including examination of skin, HEENT, lymph nodes, heart, chest, lungs, abdomen, extremities, and neurologic systems will be performed at screening, on Day 1 of each cycle. If the screening physical examination was completed within -7 to 0 days of C1D1, a complete physical examination does not need to be repeated. On all other days, a directed physical examination will be performed and focused on areas based on the patient's recent medical history and the investigator's clinical discretion. A basic neurologic examination using the ICE assessment tool will be conducted to evaluate neurologic status at baseline and repeated as clinically indicated after the first symptoms of ICANS are suspected until resolution.

^k Need not be repeated if performed during screening within 72 hours of C1D1.

^l ECGs at screening; on C1D1, C1D8, C1D15; and on Day 1 of each subsequent cycle beginning with Cycle 2 will be obtained in triplicate (approximately 1 minute apart). ECGs obtained at other time points will be single evaluations unless triplicate ECGs are clinically indicated. If the infusion is interrupted, ECGs will be obtained and based on the time when infusion resumes.

Screening: ECG performed in triplicate at 1 time point within 28 days of the first dose of TAK-280.

Note: Predose ECG before initial dose of TAK-280 can be omitted if screening ECG is performed within 72 hours of SOI.

Cycle 1: Days 1, 8, 15, and 22: Preinfusion within -30 to 0 minutes of SOI, at EOI (within 0 to +30 minutes of EOI), and at 1 hour after EOI (within $\pm$ 30 minutes).

Day 2: 24 hours after EOI (within $\pm$ 3 hours).

Day 3: 48 hours after EOI (within $\pm$ 3 hours).

All other ECGs: Preinfusion (within -30 to 0 minutes) on TAK-280 infusion days.

^m Vital signs: These include temperature, pulse rate, blood pressure, respiratory rate, and oxygen saturation. If the infusion is interrupted, vital signs will be obtained and based on the time when infusion resumes.

Cycle 1 Days 1, 8, 15, and 22: Preinfusion (within -30 to 0 minutes); at 15 and 30 minutes after SOI (within ± 5 minutes for each time point); at EOI (within ± 5 minutes); and at 1, 2, 3, 4, 5 and 6 hours after EOI (within ± 10 minutes for each time point).

Day 2: 24 hours after EOI (within ± 3 hours).

Day 3: 48 hours after EOI (within ± 3 hours).

Cycle 2: Preinfusion (within -30 to 0 minutes), at EOI (within ± 5 minutes), and at 1 and 4 hours after EOI (within ± 15 minutes for each time point).

Starting with Cycle 3: Preinfusion (within -30 to 0 minutes) and at EOI (within ± 5 minutes). Post-EOI vital sign monitoring can be deferred if patient has been clinically stable and per the investigator's discretion.

ⁿ Register patient: Administration of the initial TAK-280 cohort dose to the first 3 patients treated in each dose-escalation cohort will be staggered by a minimum of 48 hours.

^o Through the end of Cycle 1, on nondosing days or when the patient is not hospitalized, patients will be asked to record their oral temperature BID (first in the morning and last in the evening) and any time the patient feels febrile in a patient diary, which should be brought to the site at each visit through C2D1. If a patient experiences a temperature $\geq 100.4^{\circ}\text{F}$ (38°C) at any time during the study, they will be instructed to call the investigator. Clinically significant fever will be reported as AEs according to CTCAE Version 5.0 guidelines.

^p Laboratory assessments: See [Appendix B](#) for the list of laboratory tests. Samples will be collected within 72 hours before dosing and analyzed by the local laboratory. Samples collected on treatment days will be before SOI.

^q Thyroid function tests, including TSH and FT₄, to be performed at screening, on Day 1 of every other cycle beginning at Cycle 3, and EOT.

^r Pregnancy test: A serum test for women of childbearing potential should be performed as indicated. Test results must be reviewed before study drug infusion. Testing should also be performed at the EOT visit if previous testing was completed >7 days before the EOT visit.

^s See [Appendix A](#) Tables A4 through A6 for specific time points and details.

^t PK, ADA, and ctDNA: After Cycle 3, collection will occur only in Cycles 5, 7, 9, 11, and 13.

^u Tumor marker levels that are elevated at baseline or that have a history of being elevated will be followed. Perform this assessment at EOT only if the previous evaluation was >6 weeks before the EOT visit.

^v Tumor assessment time points will remain fixed by the C1D1 date regardless of subsequent delayed or missed doses of TAK-280. Perform these at baseline (within 28 days of the first dose), on Day 28 (-6 days) on even-numbered cycles (ie, Cycles 2, 4, 6, 8, 10, 12, and 14), and at EOT (perform only if the previous evaluation was >6 weeks before the EOT visit). Imaging should be done using contrast enhanced CT or MRI (unless contrast is contraindicated). The same technique with appropriate contrast usage (CT or MRI) used at screening should be used throughout the study. Imaging should include chest, abdomen and pelvis, as well as any other anatomical region appropriate for the participant's disease. Deidentified copies of all imaging scans (including those collected before screening scans, screening scans, and any unscheduled scans) may be collected and transferred to the sponsor or designee (eg, central imaging vendor/imaging contract research organization) for storage and any future analysis as needed.

^w Data are collected only for standard-of-care assessments. See Section 9.4.15 for guidance on tumor assessments during the follow-up period.

^x Contrast enhanced CT or MRI of the brain (unless contrast is contraindicated) will be performed in cases where it is clinically indicated (eg, suspicion of brain metastases), and repeat brain scans will be performed only if the screening brain scan was positive or as clinically indicated. Perform at baseline (within 28 days of the first dose), on Day 28 (-6 days) on even-numbered cycles (ie, Cycles 2, 4, 6, 8, 10, 12, and 14), and at EOT (perform only if the previous evaluation was >6 weeks before the EOT visit).

^y Patients must allow acquisition of an existing FFPE tumor tissue sample. Tissue sample(s) may be submitted to the central laboratory by C1D15. Refer to the laboratory manual for specific instructions.

^z Pretreatment and on-treatment biopsies are strongly encouraged for patients in dose-escalation DLT-evaluable cohorts, and are required for the first 6 backfill patients enrolled at cohort-assigned dose levels [REDACTED]. During the cohort-expansion phase, similar paired tumor biopsies, preferably from the same lesion, will be required. The pretreatment biopsy sample should be obtained within 28 days of first dose of TAK-280. The on-treatment tumor biopsy should be performed within 7 days before the C3D1 infusion. If the pretreatment biopsy sample is deemed inadequate for testing and evaluation, the planned on-treatment biopsy will not be required. See Section 9.4.16 for additional guidance on tumor biopsies. The requirements for this biopsy may be removed once endpoint criteria are met.

^{aa} All patients will enter a survival follow-up period after the last dose of study drug is given, to be followed every 12 weeks for at least 48 weeks for survival. Survival information and death details may be collected by methods that include, but are not limited to, telephone, email, mail, or retrieval from online or other databases (eg, Social Security indexes).

^{bb} A safety check of patients will be performed by the site staff approximately 48 hours after EOI for each TAK-280 dose administered in Cycles 1, 2, and 3. In-person or remote safety check (eg, via telephone) is allowable.

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Table A2 Schedule of Events

Evaluation/Procedure	Screening (Within 28 Days of First Dose)	Cycle 1 ^a							Cycle 2							Cycle 3				Cycle 4 and Beyond					EOT ^b	Immune-mediated AE Follow-up ^c	Survival Follow-up /EOS ^d
	Day	1	2	8	9	10	15	22	1	2	8	15	22	28	1	8	15	22	1	8	15	22	28			Q12W	
Visit window (±) days ^e		0	0	3	0	0	3	3	3		3	3	3	-6	3	3	3	3	3	3	3	3	-6	+10	+7	7	
Administer TAK-280 ^f		X		X			X	X	X		X	X	X		X	X	X	X	X	X	X	X					
Postinfusion observation ^g		X		X			X	X	X		X	X	X		X	X	X	X	X	X	X	X					
ICF ^h	X																										
Medical history ⁱ	X																										
Physical examination/directed physical examination ^j	X	X ^k		X			X	X	X		X	X	X		X	X	X	X	X	X	X	X		X			
ECOG performance status	X	X							X						X				X					X			
ECG ^l	X	X ^k	X	X	X	X	X	X	X	X					X				X								
Vital signs ^m	X	X	X	X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	X	X		X			
Height	X																										
Weight	X	X ^k		X			X	X	X		X	X	X		X	X	X	X	X	X	X	X		X			
Eligibility checklist and Patient Registration ⁿ	X																										
Patient diary review ^o				X			X	X	X																		
LABORATORY ASSESSMENTS																											
Comprehensive chemistry panel ^p	X	X ^k	X	X	X		X	X	X			X			X		X		X					X			
Special chemistry ^p	X	X ^k		X			X	X							X				X					X			
Hematology ^p	X	X ^k		X			X	X	X			X			X		X		X		X			X			
Coagulation ^p	X	X ^k		X			X	X							X				X					X			
Endocrine tests ^{p, q}	X														X				X ^q					X ^q			
Urinalysis ^p	X	X ^k					X	X							X				X					X			
Pregnancy test ^{p, r}	X	X ^k						X							X				X					X ^r			

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Evaluation/Procedure	Screening (Within 28 Days of First Dose)	Cycle 1 ^a							Cycle 2							Cycle 3				Cycle 4 and Beyond					EOT ^b	Immune-mediated AE Follow-up ^c	Survival Follow-up /EOS ^d		
	Day	1	2	8	9	10	15	22	1	2	8	15	22	28	1	8	15	22	1	8	15	22	28			Q12W			
Visit window (±) days ^e		0	0	3	0	0	3	3	3		3	3	3	-6	3	3	3	3	3	3	3	3	-6	+10	+7	7			
PK ^s		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X ^t					X					
ADA ^s		X					X	X	X		X	X	X		X		X		X ^t					X					
Flow cytometry (subset) ^s		X	X	X	X	X	X	X	X	X		X			X														
EFFICACY ASSESSMENTS																													
Tumor marker ^u	X								X						X				X					X ^u					
ctDNA ^s		X													X				X ^t					X					
Cytokine sampling ^s		X	X	X	X	X	X	X	X	X					X	X													
Tumor assessment (CT/MRI) ^v	X													X									X	X ^u		X ^w			
Brain MRI/CT, if applicable ^x	X													X									X	X ^x		X ^w			
Archival tissue ^y	X																												
Fresh Biopsy ^z	X														X														
Survival follow-up contact ^{aa}																										X			
SAFETY ASSESSMENTS																													
Safety check ^{bb}		X		X			X	X	X		X	X	X		X	X	X	X											
Concomitant medications	Continuous																												
Assessment for AEs	Continuous																												
Immune-mediated AEs	Continuous																												
																												X	

ADA: antidrug antibody; AE: adverse event; BID: twice daily; CRS: cytokine release syndrome; CT: computed tomography; CTCAE: Common Terminology Criteria for Adverse Events; ctDNA: circulating tumor DNA; CxDx: Cycle x Day x; DLT: dose-limiting toxicity; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOI: end of infusion; EOS: end of study; EOT: end of treatment; FFPE: formalin-fixed paraffin-embedded; hCG: human chorionic gonadotropin; HEENT: head, eyes, ears, nose, and throat; ICANS: immune effector cell-associated neurotoxicity syndrome; ICE: Immune Effector Cell-associated Encephalopathy; ICF: informed consent form; IRR: infusion-related reaction; [REDACTED]; MRI: magnetic resonance imaging; PD: progressive disease; PK: pharmacokinetic(s); Q: every; SOI: start of infusion; W: week(s).

^a For patients in the dose-escalation cohorts, the DLT-evaluation period is defined as the time between the initial TAK-280 dose and C1D28.

^b EOT visits will be conducted 30 days (+10 days) after last TAK-280 dose or before the start of subsequent systemic anticancer therapy, whichever occurs first.

^c Patients will attend a follow-up visit to assess immune-mediated AEs 90 days (+ 7 days) after last TAK-280 dose, unless subsequent systemic anticancer therapy is started before this time. Relevant laboratory tests and examinations may be required if immune-mediated AE is suspected.

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^d The EOS visit should be performed when the patient finishes the survival follow-up, withdraws consent, or is lost to follow-up or when the study is terminated. EOS information may be collected by methods that include, but are not limited to, telephone, email, mail, or retrieval from online or other databases (eg, Social Security indexes).

^e Visit and assessment windows are presented as guidance. Specific assessment window allowances are listed in the respective footnotes that follow. Out-of-window visits/time points will not be considered protocol deviations unless they affect patient safety or data integrity; these will be assessed by the medical monitor before database closure.

^f TAK-280 will be administered over 60 ($\pm$ 10) minutes. Based on emerging data (eg, severity of the IRRs), the infusion time may be adjusted to shorter or longer than 60 minutes on agreement with the sponsor and investigator; however, infusion time will not be less than 30 minutes. The start time and stop time of each TAK-280 infusion must be documented. After the DLT-evaluation period, a minimum of a 4-day interval should occur between doses of TAK-280.

^g Postinfusion observations: During the dose-escalation phase only, the following observations are required for Cycles 1 and 2:

Overnight observation: C1D1, C1D8 (a minimum 24-hour observation period is required for all patients after the administration [REDACTED] and the first cohort dose. Refer to [Table A1](#) [REDACTED] and [Table A3](#) [REDACTED]).

6-hour observation: C1D15, and C1D22.

4-hour observation: C2D1, C2D8, C2D15, and C2D22.

The sponsor strongly recommends overnight observation after all infusions in Cycle 1 and Cycle 2.

Starting with Cycle 3, investigators can monitor patients after each infusion for a duration based on their clinical assessment of each patient.

For all doses in all cycles, the patient can be monitored overnight if the patient develops symptoms suggestive of CRS during the postinfusion observation period.

^h Informed consent is to be obtained before enrollment. Study-specific procedures must be conducted only after informed consent is obtained.

ⁱ One prebaseline tumor scan collected before screening is optional. The prebaseline tumor scan should have been collected at least 4 weeks prior to the baseline scan, and should use the same image modality and include the same anatomical regions as the baseline scan. Deidentified copies of these scans may be collected and transferred to the sponsor or designee (eg, central imaging vendor/imaging contract research organization) for storage and any future analysis.

^j Physical examination/directed physical examination: Complete physical examination including examination of skin, HEENT, lymph nodes, heart, chest, lungs, abdomen, extremities, and neurologic systems will be performed at screening, on Day 1 of each cycle. If the screening physical examination was completed within -7 to 0 days of C1D1, a complete physical examination does not need to be repeated. On all other days, a directed physical examination will be performed and focused on areas based on the patient's recent medical history and the investigator's clinical discretion. A basic neurologic examination using the ICE assessment tool will be conducted to evaluate neurologic status at baseline and repeated as clinically indicated after the first symptoms of ICANS are suspected until resolution.

^k Need not be repeated if performed during screening within 72 hours of C1D1.

^l ECGs at screening; on C1D1, C1D8, C1D15; and on Day 1 of each subsequent beginning with Cycle 2 will be obtained in triplicate (approximately 1 minute apart). ECGs obtained at other time points will be single evaluations unless triplicate ECGs are clinically indicated. If the infusion is interrupted, ECGs will be obtained and based on the time when infusion resumes.

Screening: ECG performed in triplicate at 1 time point within 28 days of the first dose of TAK-280.

Note: Predose ECG before initial dose of TAK-280 can be omitted if screening ECG is performed within 72 hours of SOI.

Cycle 1: Days 1, 8, 15, and 22: Preinfusion within -30 to 0 minutes of SOI, at EOI (within 0 to +30 minutes of EOI), and at 1 hour after EOI (within $\pm$ 30 minutes).

Days 2 and 9: 24 hours after EOI (within $\pm$ 3 hours).

Day 10: 48 hours after EOI (within $\pm$ 3 hours).

All other ECGs: Preinfusion (within -30 to 0 minutes) on TAK-280 infusion days.

^m Vital signs: These include temperature, pulse rate, blood pressure, respiratory rate, and oxygen saturation. If the infusion is interrupted, vital signs will be obtained and based on the time when infusion resumes.

Cycle 1 Days 1, 8, 15, and 22: Preinfusion (within -30 to 0 minutes); at 15 and 30 minutes after SOI (within ± 5 minutes for each time point); at EOI (within ± 5 minutes); and at 1, 2, 3, 4, 5 and 6 hours after EOI (within ± 10 minutes for each time point).

Days 2 and 9: 24 hours after EOI (within ± 3 hours).

Day 10: 48 hours after EOI (within ± 3 hours).

Cycle 2: Preinfusion (within -30 to 0 minutes), at EOI (within ± 5 minutes), and at 1 and 4 hours after EOI (within ± 15 minutes for each time point).

Starting with Cycle 3: Preinfusion (within -30 to 0 minutes) and at EOI (within ± 5 minutes). Post-EOI vital sign monitoring can be deferred if patient has been clinically stable and per the investigator's discretion.

ⁿ Register patient: Administration of the initial TAK-280 cohort dose to the first 3 patients treated in each dose-escalation cohort will be staggered by a minimum of 48 hours.

^o Through the end of Cycle 1, on nondosing days or when the patient is not hospitalized, patients will be asked to record their oral temperature BID (first in the morning and last in the evening) and any time the patient feels febrile in a patient diary, which should be brought to the site at each visit through C2D1. If a patient experiences a temperature $\geq 100.4^{\circ}\text{F}$ (38°C) at any time during the study, they will be instructed to call the investigator. Clinically significant fever will be reported as AEs according to CTCAE Version 5.0 guidelines.

^p Laboratory assessments: See [Appendix B](#) for the list of laboratory tests. Samples will be collected within 72 hours before dosing and analyzed by the local laboratory. Samples collected on treatment days will be before SOI.

^q Thyroid function tests, including TSH and FT₄, to be performed at screening, on Day 1 of every other cycle beginning at Cycle 3, and EOT.

^r Pregnancy test: A serum test for women of childbearing potential should be performed as indicated. Test results must be reviewed before study drug infusion. Testing should also be performed at the EOT visit if previous testing was completed >7 days before the EOT visit.

^s See [Appendix A](#) Tables A4 through A6 for specific time points and details.

^t PK, ADA, and ctDNA: After Cycle 3, collection will occur only in Cycles 5, 7, 9, 11, and 13.

^u Tumor marker levels that are elevated at baseline or that have a history of being elevated will be followed. Perform this assessment at EOT only if the previous evaluation was >6 weeks before the EOT visit.

^v Tumor assessment time points will remain fixed by the C1D1 date regardless of subsequent delayed or missed doses of TAK-280. Perform these at baseline (within 28 days of the first dose), on Day 28 (-6 days) on even-numbered cycles (ie, Cycles 2, 4, 6, 8, 10, 12, and 14), and at EOT (perform only if the previous evaluation was >6 weeks before the EOT visit). Imaging should be done using contrast enhanced CT or MRI (unless contrast is contraindicated). The same technique with appropriate contrast usage (CT or MRI) used at screening should be used throughout the study. Imaging should include chest, abdomen and pelvis, as well as any other anatomical region appropriate for the participant's disease. Deidentified copies of all imaging scans (including those collected before screening scans, screening scans, and any unscheduled scans) may be collected and transferred to the sponsor or designee (eg, central imaging vendor/imaging contract research organization) for storage and any future analysis as needed.

^w Data are collected only for standard-of-care assessments. See [Section 9.4.15](#) for guidance on tumor assessments during the follow-up period.

^x Contrast enhanced CT or MRI of the brain (unless contrast is contraindicated) will be performed in cases where it is clinically indicated (eg, suspicion of brain metastases), and repeat brain scans will be performed only if the screening brain scan was positive or as clinically indicated. Perform at baseline (within 28 days of the first dose), on Day 28 (-6 days) on even-numbered cycles (ie, Cycles 2, 4, 6, 8, 10, 12, and 14), and at EOT (perform only if the previous evaluation was >6 weeks before the EOT visit).

^y Patients must allow acquisition of an existing FFPE tumor tissue sample. Tissue sample(s) may be submitted to the central laboratory by C1D15. Refer to the laboratory manual for specific instructions.

^z Pretreatment and on-treatment biopsies are strongly encouraged for patients in dose-escalation DLT-evaluable cohorts, and are required for the first 6 backfill patients enrolled at cohort-assigned dose levels [REDACTED]. During the cohort-expansion phase, similar paired tumor biopsies, preferably from the same lesion, will be required. The pretreatment biopsy sample should be obtained within 28 days of first dose of TAK-280. The on-treatment tumor biopsy should be performed within 7 days before the C3D1 infusion. If the pretreatment biopsy sample is deemed inadequate for testing and evaluation, the planned on-treatment biopsy will not be required. See [Section 9.4.16.2](#) for additional guidance on tumor biopsies. The requirement for this biopsy may be removed once endpoint criteria are met.

^{aa} All patients will enter a survival follow-up period after the last dose of study drug is given, to be followed every 12 weeks for at least 48 weeks for survival. Survival information and death details may be collected by methods that include, but are not limited to, telephone, email, mail, or retrieval from online or other databases (eg, Social Security indexes).

^{bb} A safety check of patients will be performed by the site staff approximately 48 hours after EOI for each TAK-280 dose administered in Cycles 1, 2, and 3. In-person or remote safety check (eg, via telephone) is allowable.

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Table A3 Schedule of Events With [REDACTED]

Evaluation/Procedure	Screening (Within 28 Days of First Dose)	Cycle 1 ^a ([REDACTED])								Cycle 2						Cycle 3				Cycle 4 and Beyond					EOT ^b	Immune- mediated AE Follow- up ^c	Survival Follow- up/EOS ^d
	Day	1	2	8	9	15	16	17	22	1	2	8	15	22	28	1	8	15	22	1	8	15	22	28			Q12W
Visit window (±) days ^e		0	0	3	0	3	0	0	3	3		3	3	3	-6	3	3	3	3	3	3	3	3	-6	+10	+7	7
Administer TAK-280 ^f		X		X		X			X	X		X	X	X		X	X	X	X	X	X	X	X				
Postinfusion observation ^g		X		X		X			X	X		X	X	X		X	X	X	X	X	X	X	X				
ICF ^h	X																										
Medical history ⁱ	X																										
Physical examination/directed physical examination ^j	X	X ^k		X		X			X	X		X	X	X		X	X	X	X	X	X	X	X		X		
ECOG performance status	X	X								X						X				X					X		
ECG ^l	X	X ^k	X	X	X	X	X	X	X	X						X				X							
Vital signs ^m	X	X	X	X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	X	X	X		X		
Height	X																										
Weight	X	X ^k		X		X			X	X		X	X	X		X	X	X	X	X	X	X	X		X		
Eligibility checklist and Patient Registration ⁿ	X																										
Patient diary review ^o				X		X			X	X																	
LABORATORY ASSESSMENTS																											
Comprehensive chemistry panel ^p	X	X ^k	X	X	X	X	X		X	X			X			X		X		X					X		
Special chemistry ^p	X	X ^k		X		X			X	X						X				X					X		
Hematology ^p	X	X ^k		X		X			X	X			X			X		X		X		X			X		
Coagulation ^p	X	X ^k		X		X			X	X						X				X					X		
Endocrine tests ^{p, q}	X															X				X ^q					X ^q		
Urinalysis ^p	X	X ^k							X	X						X				X					X		
Pregnancy test ^{p, r}	X	X ^k								X						X				X					X ^r		

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	Screening (Within 28 Days of First Dose)	Cycle 1 ^a ()								Cycle 2						Cycle 3				Cycle 4 and Beyond					EOT ^b	Immune-mediated AE Follow-up ^c	Survival Follow-up/EOS ^d
Evaluation/Procedure	Day	1	2	8	9	15	16	17	22	1	2	8	15	22	28	1	8	15	22	1	8	15	22	28			Q12W
Visit window (±) days ^e		0	0	3	0	3	0	0	3	3		3	3	3	-6	3	3	3	3	3	3	3	3	-6	+10	+7	7
PK ^s		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X ^t					X		
ADA ^s		X				X			X	X		X	X	X		X		X		X ^t					X		
Flow cytometry (subset) ^s		X	X	X		X	X	X	X	X	X		X			X											
EFFICACY ASSESSMENTS																											
Tumor marker ^u	X									X						X				X					X ^u		
ctDNA ^s		X														X				X ^t					X		
Cytokine sampling ^s		X	X	X	X	X	X	X	X	X	X					X	X										
Tumor assessment (CT/MRI) ^v	X														X									X	X ^v		X ^w
Brain MRI/CT, if applicable ^x	X														X									X	X ^x		X ^w
Archival tissue ^y	X																										
Fresh Biopsy ^z	X															X											
Survival follow-up contact ^{aa}																											X
SAFETY ASSESSMENTS																											
Safety check ^{bb}		X		X		X			X	X		X	X	X		X	X	X	X								
Concomitant medications		Continuous																									
Assessment for AEs		Continuous																									
Immune-mediated AEs		Continuous																								X	

ADA: antidrug antibody; AE: adverse event; BID: twice daily; CRS: cytokine release syndrome; CT: computed tomography; CTCAE: Common Terminology Criteria for Adverse Events; ctDNA: circulating tumor DNA; CxDx: Cycle x Day x; DLT: dose-limiting toxicity; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOI: end of infusion; EOS: end of study; EOT: end of treatment; FFPE: formalin-fixed paraffin-embedded; hCG: human chorionic gonadotropin; HEENT: head, eyes, ears, nose, and throat; ICANS: immune effector cell-associated neurotoxicity syndrome; ICE: Immune Effector Cell-associated Encephalopathy; ICF: informed consent form; IRR: infusion-related reaction; MRI: magnetic resonance imaging; PK: pharmacokinetic(s); Q: every; SOI: start of infusion; W: week(s).

^a For patients in the dose-escalation cohorts, the DLT-evaluation period is defined as the time between the initial TAK-280 dose and C1D28.

^b EOT visits will be conducted 30 days (+10 days) after last TAK-280 dose or before the start of subsequent systemic anticancer therapy, whichever occurs first.

^c Patients will attend a follow-up visit to assess immune-mediated AEs 90 days (+ 7 days) after last TAK-280 dose, unless subsequent systemic anticancer therapy is started before this time. Relevant laboratory tests and examinations may be required if immune-mediated AE is suspected.

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^d The EOS visit should be performed when the patient finishes the survival follow-up, withdraws consent, or is lost to follow-up or when the study is terminated. EOS information may be collected by methods that include, but are not limited to, telephone, email, mail, or retrieval from online or other databases (eg, Social Security indexes).

^e Visit and assessment windows are presented as guidance. Specific assessment window allowances are listed in the respective footnotes that follow. Out-of-window visits/time points will not be considered protocol deviations unless they affect patient safety or data integrity; these will be assessed by the medical monitor before database closure.

^f TAK-280 will be administered over 60 ($\pm$ 10) minutes. Based on emerging data (eg, severity of the IRRs), the infusion time may be adjusted to shorter or longer than 60 minutes on agreement with the sponsor and investigator; however, infusion time will not be less than 30 minutes. The start time and stop time of each TAK-280 infusion must be documented. After the DLT-evaluation period, a minimum of a 4-day interval should occur between doses of TAK-280.

^g Postinfusion observations: During the dose-escalation phase only, the following observations are required for Cycles 1 and 2:

Overnight observation: C1D1, C1D8, C1D15 (a minimum 24-hour observation period is required for all patients after the administration [REDACTED] and the first cohort dose. Refer to Table A1 [REDACTED] and Table A2 for [REDACTED]).

6-hour observation: C1D22.

4-hour observation: C2D1, C2D8, C2D15, and C2D22.

The sponsor strongly recommends overnight observation after all infusions in Cycles 1 and 2.

Starting with Cycle 3, investigators can monitor patients after each infusion for a duration based on their clinical assessment of each patient.

For all doses in all cycles, the patient can be monitored overnight if the patient develops symptoms suggestive of CRS during the postinfusion observation period.

^h Informed consent is to be obtained before enrollment. Study-specific procedures must be conducted only after informed consent is obtained.

ⁱ One prebaseline tumor scan collected before screening is optional. The prebaseline tumor scan should have been collected at least 4 weeks prior to the baseline scan, and should use the same modality and include the same anatomical regions as the baseline scan. Deidentified copies of these scans may be collected and transferred to the sponsor or designee (eg, central imaging vendor/imaging contract research organization) for storage and any future analysis.

^j Physical examination/directed physical examination: Complete physical examination including examination of skin, HEENT, lymph nodes, heart, chest, lungs, abdomen, extremities, and neurologic systems will be performed at screening, on Day 1 of each cycle. If the screening physical examination was completed within -7 to 0 days of C1D1, a complete physical examination does not need to be repeated. On all other days, a directed physical examination will be performed and focused on areas based on the patient's recent medical history and the investigator's clinical discretion. A basic neurologic examination using the ICE assessment tool will be conducted to evaluate neurologic status at baseline and repeated as clinically indicated after the first symptoms of ICANS are suspected until resolution.

^k Need not be repeated if performed during screening within 72 hours of C1D1.

^l ECGs at screening; on C1D1, C1D8, C1D15; and on Day 1 of each subsequent cycle beginning with Cycle 2 will be obtained in triplicate (approximately 1 minute apart). ECGs obtained at other time points will be single evaluations unless triplicate ECGs are clinically indicated. If the infusion is interrupted, ECGs will be obtained and based on the time when infusion resumes.

Screening: ECG performed in triplicate at 1 time point within 28 days of the first dose of TAK-280.

Note: Predose ECG before initial dose of TAK-280 can be omitted if screening ECG is performed within 72 hours of SOI.

Cycle 1: Days 1, 8, 15, and 22: Preinfusion within -30 to 0 minutes of SOI, at EOI (within 0 to +30 minutes of EOI), and at 1 hour after EOI (within $\pm$ 30 minutes).

Days 2, 9, and 16: 24 hours after EOI (within $\pm$ 3 hours).

Day 17: 48 hours after EOI (within $\pm$ 3 hours).

All other ECGs: Preinfusion (within -30 to 0 minutes) on TAK-280 infusion days.

^m Vital signs: These include temperature, pulse rate, blood pressure, respiratory rate, and oxygen saturation. If the infusion is interrupted, vital signs will be obtained and based on the time when infusion resumes.

Cycle 1 Days 1, 8, 15, and 22: Preinfusion (within -30 to 0 minutes); at 15 and 30 minutes after SOI (within ± 5 minutes for each time point); at EOI (within ± 5 minutes); and at 1, 2, 3, 4, 5 and 6 hours after EOI (within ± 10 minutes for each time point).

Days 2, 9, and 16: 24 hours after EOI (within ± 3 hours).

Day 17: 48 hours after EOI (within ± 3 hours).

Cycle 2: Preinfusion (within -30 to 0 minutes), at EOI (within ± 5 minutes), and at 1 and 4 hours after EOI (within ± 15 minutes for each time point).

Starting with Cycle 3: Preinfusion (within -30 to 0 minutes) and at EOI (within ± 5 minutes). Post-EOI vital sign monitoring can be deferred if patient has been clinically stable and per the investigator's discretion.

ⁿ Register patient: Administration of the initial TAK-280 cohort dose to the first 3 patients treated in each dose-escalation cohort will be staggered by a minimum of 48 hours.

^o Through the end of Cycle 1, on nondosing days or when the patient is not hospitalized, patients will be asked to record their oral temperature BID (first in the morning and last in the evening) and any time the patient feels febrile in a patient diary, which should be brought to the site at each visit through C2D1. If a patient experiences a temperature $\geq 100.4^{\circ}\text{F}$ (38°C) at any time during the study, they will be instructed to call the investigator. Clinically significant fever will be reported as AEs according to CTCAE Version 5.0 guidelines.

^p Laboratory assessments: See [Appendix B](#) for the list of laboratory tests. Samples will be collected within 72 hours before dosing and analyzed by the local laboratory. Samples collected on treatment days will be before SOI.

^q Thyroid function tests, including TSH and FT₄, to be performed at screening, on Day 1 of every other cycle beginning at Cycle 3, and EOT.

^r Pregnancy test: A serum test for women of childbearing potential should be performed as indicated. Test results must be reviewed before study drug infusion. Testing should also be performed at the EOT visit if previous testing was completed >7 days before the EOT visit.

^s See [Appendix A](#) Tables A4 through A6 for specific time points and details.

^t PK, ADA, and ctDNA: After Cycle 3, collection will occur only in Cycles 5, 7, 9, 11, and 13.

^u Tumor marker levels that are elevated at baseline or that have a history of being elevated will be followed. Perform this assessment at EOT only if the previous evaluation was >6 weeks before the EOT visit.

^v Tumor assessment time points will remain fixed by the C1D1 date regardless of subsequent delayed or missed doses of TAK-280. Perform these at baseline (within 28 days of the first dose), on Day 28 (-6 days) on even-numbered cycles (ie, Cycles 2, 4, 6, 8, 10, 12, and 14), and at EOT (perform only if the previous evaluation was >6 weeks before the EOT visit). Imaging should be done using contrast enhanced CT or MRI (unless contrast is contraindicated). The same technique with appropriate contrast usage (CT or MRI) used at screening should be used throughout the study. Imaging should include chest, abdomen and pelvis, as well as any other anatomical region appropriate for the participant's disease. Deidentified copies of all imaging scans (including those from scans collected prior to screening scans, screening scans, and any unscheduled scans) may be collected and transferred to the sponsor or designee (eg, central imaging vendor/imaging contract research organization) for storage and any future analysis as needed.

^w Data are collected only for standard-of-care assessments. See [Section 9.4.15](#) for guidance on tumor assessments during the follow-up period.

^x Contrast enhanced CT or MRI of the brain (unless contrast is contraindicated) will be performed in cases where it is clinically indicated (eg, suspicion of brain metastases), and repeat brain scans will be performed only if the screening brain scan was positive or as clinically indicated. Perform at baseline (within 28 days of the first dose), on Day 28 (-6 days) on even-numbered cycles (ie, Cycles 2, 4, 6, 8, 10, 12, and 14), and at EOT (perform only if the previous evaluation was >6 weeks before the EOT visit).

^y Patients must allow acquisition of an existing FFPE tumor tissue sample. Tissue sample(s) may be submitted to the central laboratory by C1D15. Refer to the laboratory manual for specific instructions.

^z Pretreatment and on-treatment biopsies are strongly encouraged for patients in dose-escalation DLT-evaluable cohorts, and are required for the first 6 backfill patients enrolled at cohort-assigned dose levels [REDACTED]. During the cohort-expansion phase, similar paired tumor biopsies, preferably from the same lesion, will be required. The pretreatment biopsy sample should be obtained within 28 days of first dose of TAK-280. The on-treatment tumor biopsy should be performed within 7 days before C3D1 infusion. If the pretreatment biopsy sample is deemed inadequate for testing and evaluation, the planned on-treatment biopsy will not be required. See Section 9.4.16 for additional guidance on tumor biopsies. The requirement for this biopsy may be removed once endpoint criteria are met.

^{aa} All patients will enter a survival follow-up period after the last dose of study drug is given, to be followed every 12 weeks for at least 48 weeks for survival. Survival information and death details may be collected by methods that include, but are not limited to, telephone, email, mail, or retrieval from online or other databases (eg, Social Security indexes).

^{bb} A safety check of patients will be performed by the site staff approximately 48 hours after EOI for each TAK-280 dose administered in Cycles 1, 2, and 3. In-person or remote safety check (eg, via telephone) is allowable.

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Table A4 PK, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling, [REDACTED]

Cycle	TAK-280 Dosing	Cycle Day	PK Sampling Time (hours) ^a	ADA Sampling Time (hours)	Cytokine Sampling Time (hours) ^b	Flow Cytometry Subset (hours)	ctDNA
1	X	1	Predose ^c	Predose ^c	Predose ^c	Predose ^c	Predose ^c
			EOI				
			2		2		
			4			4	
			6		6		
		2	24		24	24	
		3	48		48	48	
	X	8	Predose ^c		Predose ^c	Predose ^c	
			EOI				
			6		6		
	X	15	Predose ^c	Predose ^c	Predose ^c	Predose ^c	
			EOI				
			6		6		
	X	22	Predose ^c	Predose ^c	Predose ^c	Predose ^c	
			EOI				
			6		6		

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Cycle	TAK-280 Dosing	Cycle Day	PK Sampling Time (hours) ^a	ADA Sampling Time (hours)	Cytokine Sampling Time (hours) ^b	Flow Cytometry Subset (hours)	ctDNA
2	X	1	Predose ^c	Predose ^c	Predose ^c	Predose ^c	
			EOI				
		2	24		24	24	
	X	8	Predose ^c	Predose ^c			
			EOI				
	X	15	Predose ^c	Predose ^c		Predose ^c	
			EOI				
	X	22	Predose ^c	Predose ^c			
			EOI				
3	X	1	Predose ^c	Predose ^c	Predose ^c	Predose ^c	Predose ^c
			2				
			4				
	X	8	Predose ^c		Predose ^c		
			EOI				
	X	15	Predose ^c	Predose ^c			
			EOI				
	X	22	Predose ^c				
			EOI				
5 and beyond ^{d,e}	X	1	Predose ^c	Predose ^c			
			EOI				
CRS			As required		As required		
EOT			No specific time	No specific time			No specific time

ADA: antidrug antibody; CRS: cytokine release syndrome; ctDNA: circulating tumor DNA; eCRF: electronic case report form; EOI: end of infusion; EOT: end of treatment; PK: pharmacokinetic; SOI: start of infusion.

Actual SOI and EOI times and PK and ADA sample collection times will be recorded on the eCRFs. All sample time points are hours after EOI unless otherwise specified. EOI is defined as the end of flushing.

The 24- and 48-hour samples will be collected on Cycle 1 Days 2 and 3, respectively, and can be collected ± 3 hours of the EOI. Time windows are presented as guidance. Out-of-window time points will not be considered protocol deviations unless they affect data integrity; these will be assessed by the medical monitor before database closure.

^a Do not collect PK samples from the infusion port. PK samples are to be collected within 10 minutes of the EOI and ± 10 minutes for 2, 4, and 6 hours after EOI, as listed in the table. PK samples obtained on noninfusion days should be collected at approximately the same time each sampling day.

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^b Additional samples may be obtained selectively at additional time points in patients who experience signs and symptoms of CRS. This includes the full cytokine panel obtained at scheduled time points and as soon as CRS is expected and, at minimum, at 4 and 24 hours after the initial sample is obtained.

^c All predose blood draws will be collected before the start of the infusion of TAK-280.

^d Collection is only during Cycles 5, 7, 9, 11, and 13.

^e PK, ADA, and ctDNA: After Cycle 3, collection will occur only in Cycles 5, 7, 9, 11, and 13.

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Table A5 PK, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling

Cycle	TAK-280 Dosing	Cycle Day	PK Sampling Time (hours) ^a	ADA Sampling Time (hours)	Cytokine Sampling Time (hours) ^b	Flow Cytometry Subset (hours)	ctDNA
1	X	1	Predose ^c	Predose ^c	Predose ^c	Predose ^c	Predose ^c
			EOI				
			2		2		
			6		6		
	X	2	24		24	24	
		8	Predose ^c		Predose ^c	Predose ^c	
			EOI				
			2		2		
			4			4	
			6		6		
		9	24		24	24	
		10	48		48	48	
	X	15	Predose ^c	Predose ^c	Predose ^c	Predose ^c	
			EOI				
			6		6		
	X	22	Predose ^c	Predose ^c	Predose ^c	Predose ^c	
			EOI				
			6		6		

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Cycle	TAK-280 Dosing	Cycle Day	PK Sampling Time (hours) ^a	ADA Sampling Time (hours)	Cytokine Sampling Time (hours) ^b	Flow Cytometry Subset (hours)	ctDNA
2	X	1	Predose ^c	Predose ^c	Predose ^c	Predose ^c	
			EOI				
		2	4		4		
			24		24	24	
	X	8	Predose ^c	Predose ^c			
			EOI				
	X	15	Predose ^c	Predose ^c		Predose ^c	
			EOI				
	X	22	Predose ^c	Predose ^c			
			EOI				
3	X	1	Predose ^c	Predose ^c	Predose ^c	Predose ^c	Predose ^c
			EOI				
			2				
			4		4		
	X	8	Predose ^c		Predose ^c		
			EOI				
	X	15	Predose ^c	Predose ^c			
			EOI				
	X	22	Predose ^c				
			EOI				
5 and beyond ^{d, e}	X	1	Predose ^c	Predose ^c			Predose ^c
			EOI				
CRS			As required		As required		
EOT			No specific time	No specific time			No specific time

ADA: antidrug antibody; CRS: cytokine release syndrome; ctDNA: circulating tumor DNA; eCRF: electronic case report form; EOI: end of infusion; EOT: end of treatment; PK: pharmacokinetic; SOI: start of infusion.

Actual SOI and EOI times and PK and ADA sample collection times will be recorded on the eCRFs. All sample time points are hours after EOI unless otherwise specified.

EOI is defined as the end of flushing.

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The 24- and 48-hour samples will be collected on Cycle 1 Days 9 and 10, respectively, and can be collected ± 3 hours of the EOI. Time windows are presented as guidance. Out-of-window time points will not be considered protocol deviations unless they affect data integrity; these will be assessed by the medical monitor before database closure.

^a Do not collect PK samples from the infusion port. PK samples are to be collected within 10 minutes of the EOI and ± 10 minutes for 2, 4, and 6 hours after EOI, as listed in the table. PK samples obtained on noninfusion days should be collected at approximately the same time each sampling day.

^b Additional samples may be obtained selectively at additional time points in patients who experience signs and symptoms of CRS. This includes the full cytokine panel obtained at scheduled time points and as soon as CRS is expected and, at minimum, at 4 and 24 hours after the initial sample is obtained.

^c All predose blood draws will be collected before the start of the infusion of TAK-280.

^d Collection is only during Cycles 5, 7, 9, 11, and 13.

^e PK, ADA, and ctDNA: After Cycle 3, collection will occur only in Cycles 5, 7, 9, 11, and 13.

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Table A6 PK, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling

Cycle	TAK-280 Dosing	Cycle Day	PK Sampling Time (hours) ^a	ADA Sampling Time (hours)	Cytokine Sampling Time (hours) ^b	Flow Cytometry Subset (hours)	ctDNA
1	X	1	Predose ^c	Predose ^c	Predose ^c	Predose ^c	Predose ^c
			EOI				
			2		2		
			6		6		
		2	24		24	24	
	X	8	Predose ^c		Predose ^c	Predose ^c	
			EOI				
			2		2		
			6		6		
		9	24		24	24	
	X	15	Predose ^c	Predose ^c	Predose ^c	Predose ^c	
			EOI				
			2		2		
			4			4	
			6		6		
		16	24		24	24	
		17	48		48	48	
	X	22	Predose ^c	Predose ^c	Predose ^c	Predose ^c	
			EOI				
			6		6		

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Cycle	TAK-280 Dosing	Cycle Day	PK Sampling Time (hours) ^a	ADA Sampling Time (hours)	Cytokine Sampling Time (hours) ^b	Flow Cytometry Subset (hours)	ctDNA
2	X	1	Predose ^c	Predose ^c	Predose ^c	Predose ^c	Predose ^c
			EOI				
			4		4		
		2	24		24	24	
	X	8	Predose ^c	Predose ^c			
			EOI				
	X	15	Predose ^c	Predose ^c		Predose ^c	
			EOI				
	X	22	Predose ^c	Predose ^c			
			EOI				
3	X	1	Predose ^c	Predose ^c	Predose ^c	Predose ^c	Predose ^c
			EOI				
			2				
			4		4		
	X	8	Predose ^c		Predose ^c		
			EOI				
	X	15	Predose ^c	Predose ^c			
			EOI				
	X	22	Predose ^c				
			EOI				
5 and beyond ^{d, e}	X	1	Predose ^c	Predose ^c			Predose ^c
			EOI				
CRS			As required		As required		
EOT			No specific time	No specific time			No specific time

ADA: antidrug antibody; CRS: cytokine release syndrome; ctDNA: circulating tumor DNA; eCRF: electronic case report form; EOI: end of infusion; EOT: end of treatment; PK: pharmacokinetic; SOI: start of infusion.

Actual SOI and EOI times and PK and ADA sample collection times will be recorded on the eCRFs. All sample time points are hours after EOI unless otherwise specified.

EOI is defined as the end of flushing.

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The 24- and 48-hour samples will be collected on Cycle 1 Days 16 and 17, respectively, and can be collected ± 3 hours of the EOI. Time windows are presented as guidance. Out-of-window time points will not be considered protocol deviations unless they affect data integrity; these will be assessed by the medical monitor before database closure.

^a Do not collect PK samples from the infusion port. PK samples are to be collected within 10 minutes of the EOI and ± 10 minutes for 2, 4, and 6 hours after EOI, as listed in the table. PK samples obtained on noninfusion days should be collected at approximately the same time each sampling day.

^b Additional samples may be obtained selectively at additional time points in patients who experience signs and symptoms of CRS. This includes the full cytokine panel obtained at scheduled time points and as soon as CRS is expected and, at minimum, at 4 and 24 hours after the initial sample is obtained.

^c All predose blood draws will be collected before the start of the infusion of TAK-280.

^d Collection is only during Cycles 5, 7, 9, 11, and 13.

^e PK, pharmacodynamics, ADA, and ctDNA: After Cycle 3, collection will occur only in Cycles 5, 7, 9, 11, and 13.

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Appendix B Clinical Laboratory Tests

Pregnancy Test: Urine or serum (hCG) Hematology: Hct Hgb MCH mean MCHC MCV platelet count RBC count WBC count with differential counts Comprehensive Chemistry Panel: ALB ALP ALT AST Bicarbonate BUN/urea Calcium (Ca) Chloride (Cl) Creatinine GGT Glucose (nonfasting) Magnesium (Mg) Phosphorus (P) Potassium (K) Sodium (Na) Total protein Uric acid Bilirubin (total and direct)	Special Chemistry: Amylase Lipase ACTH Coagulation: aPTT INR PT Endocrine Tests: FT ₄ TSH Urinalysis: Appearance: color pH, Bilirubin, glucose, ketones, occult blood, protein, specific gravity, nitrite Microscopic examination of sediment Tumor Marker Tests: May include CA125, CA19-9, CEA, or other tumor markers that are relevant to the diagnosis.
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ACTH: adrenocorticotrophic hormone; ALB: albumin; ALP: alkaline phosphatase; ALT: alanine aminotransferase (formerly SGPT [serum glutamic-pyruvic transaminase]); aPTT: activated partial thromboplastin time; AST: aspartate aminotransferase (formerly SGOT [serum glutamic-oxaloacetic transaminase]); BUN: blood urea nitrogen; CA: cancer antigen; CEA: carcinoembryonic antigen; FT₄: free thyroxine; GGT: gamma glutamyl transferase; hCG: human chorionic gonadotropin; Hct: hematocrit; Hgb: hemoglobin; INR: international normalized ratio; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; PT: prothrombin time; RBC: red blood cell; TSH: thyroid-stimulating hormone; WBC: white blood cell.

Appendix C Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform study-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.
4. Ensure that study-related procedures, including study-specific (nonroutine/nonstandard panel) screening assessments, are NOT performed on potential patients before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to ICH and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to patients. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 12 weeks of study completion.
8. Ensure that requirements for informed consent, as outlined in ICH and local regulations, are met.
9. Obtain a valid signed ICF each patient who participates in the study, and document the date of consent in the patient's medical chart. The valid ICF is the most current version approved by the IRB/IEC. Each ICF should contain a patient authorization section that describes the uses and disclosures of a patient's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a patient authorization, then the investigator must obtain a separate patient authorization form from each patient or the patient's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years after notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
13. Report adverse reactions to the sponsor promptly. In the event of a serious adverse event, notify the sponsor within 24 hours.

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Appendix D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of the investigator, including his or her name, address, and other identifying personal information. In addition, the investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the UK, US, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- Institutional review boards and independent ethics committees.

The investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of the investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details, and results on publicly accessible clinical trial registries, databases, and websites.

The investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in the investigator's own country.

The investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described in this appendix.

Appendix E ECOG Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken et al, 1982 ([Oken et al. 1982](#)).

ECOG: Eastern Cooperative Oncology Group.

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Appendix F Operating Characteristics of the BOIN Design for Dose Escalation

The BOIN design ([Lin and Yin 2017](#); [Liu and Yuan 2015](#)) will be used to guide dose-escalation decisions. Dose-escalation rules are detailed in Section 8.3.

The operating characteristics of the BOIN design are evaluated with simulations based on assumptions of various distributions of toxicity across dose levels, as shown in [Table F1](#).

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Table F1 Simulation Scenarios

Dose Level (DL)	Dose	True DLT Rate							
		Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6	Scenario 7	Scenario 8
1 (starting dose)		0.30	0.13	0.05	0.06	0.05	0.05	0.03	0.01
2		0.48	0.30	0.15	0.10	0.07	0.07	0.04	0.02
3		0.50	0.48	0.30	0.11	0.08	0.09	0.05	0.03
4		0.52	0.51	0.45	0.30	0.10	0.11	0.06	0.04
5		0.56	0.56	0.49	0.48	0.30	0.12	0.07	0.05
6		0.60	0.60	0.53	0.53	0.48	0.30	0.08	0.06
7		0.63	0.65	0.57	0.61	0.57	0.48	0.30	0.07
8		0.67	0.70	0.62	0.69	0.70	0.70	0.48	0.30

DL; dose level; DLT: dose-limiting toxicity; MTD: maximum tolerated dose.

For simulation purpose, we consider all dose levels from DL1 to DL8. Initial cohort size is 1 DL1 and 2, and 3 for DL3 and above. The operating characteristics calculated from the simulations are shown in [Table F2](#). For example, in Scenario 4 where the true MTD is DL4, there is a 59.3% probability of selecting DL4 as the MTD. The expected total sample size for the dose escalation is around 22 patients with approximately 37% of patients treated at DL4.

The operating characteristics of the BOIN design based on 1,000 simulations of each scenario are presented in [Table F2](#).

Table F2 Operating Characteristics of the BOIN Design

	DL1	DL2	DL3	DL4	DL5	DL6	DL7	DL8		
									Number of Patients	% Early Stopping
Scenario 1:										
True DLT Rate	0.3	0.48	0.5	0.52	0.56	0.6	0.63	0.67		
Selection %	65	17.5	7.4	1.2	0	0	0	0		8.9
% Patients Treated	49.1	32.4	15.4	2.8	0.3	0	0	0	16.5	
Scenario 2:										
True DLT Rate	0.13	0.3	0.48	0.51	0.56	0.6	0.65	0.7		
Selection %	18.8	57.2	19.7	3.6	0.4	0	0	0		0.3
% Patients Treated	24.6	42	27	5.6	0.8	0.1	0	0	19.3	
Scenario 3:										
True DLT Rate	0.05	0.15	0.3	0.45	0.49	0.53	0.57	0.62		
Selection %	1	20	56.2	17.9	3.8	0.8	0.3	0		0
% Patients Treated	8.3	23	41.7	21.1	4.9	0.8	0.2	0	20	
Scenario 4:										
True DLT Rate	0.06	0.1	0.11	0.3	0.48	0.53	0.61	0.69		
Selection %	0.2	2.5	18.4	59.3	16.9	2.3	0.4	0		0
% Patients Treated	6.1	9.4	27.7	37	16.5	2.9	0.3	0	22	
Scenario 5:										
True DLT Rate	0.05	0.07	0.08	0.1	0.3	0.48	0.57	0.7		
Selection %	0	1.2	1.5	18.9	56.5	18.8	2.9	0.2		0
% Patients Treated	5.5	6.9	16.2	23.4	31.3	14.3	2.2	0.2	24.2	

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Table F2 Operating Characteristics of the BOIN Design

	DL1	DL2	DL3	DL4	DL5	DL6	DL7	DL8		
									Number of Patients	% Early Stopping
Scenario 6:										
True DLT Rate	0.05	0.07	0.09	0.11	0.12	0.3	0.48	0.7		
Selection %	0.4	1.3	2.5	4.5	19	52.6	19	0.7		0
% Patients Treated	5.5	6.6	16.1	16.6	20.4	24.1	9.8	1	25.1	
Scenario 7:										
True DLT Rate	0.03	0.04	0.05	0.06	0.07	0.08	0.3	0.48		
Selection %	0	0.1	1.1	0.9	1.7	19.6	57.1	19.5		0
% Patients Treated	4.5	5.1	13.8	13.4	14.2	18.2	22.1	8.7	26.3	
Scenario 8:										
True DLT Rate	0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.3		
Selection %	0	0	0.3	0.3	0.5	1.6	19.7	77.6		0
% Patients Treated	4	4.2	12.5	13	13.3	13.3	16.7	23	26.6	

DL: dose level; DLT: dose limiting toxicity; MTD: maximum tolerated dose.

% Early Stopping: early stopping due to excessive DLT.

Selection %: the percentage of selecting this dose as the MTD.

Appendix G Examples of Corrected QT Interval–Prolonging Agents

Use of the following drugs known to prolong the QTc may be permitted if patients rely on such medications and have used these chronically before their enrollment in this study and as long as the patient's baseline QTcF is <480 ms. Use of such medications should not be started on Cycle 1 Day 1; they may be started after the triplicate ECG assessments are completed on C1D2. If patients require such medications to treat other medical conditions during the study, these medications are permissible only after the C1D2 ECG assessments are completed. The list only provides examples and is not an exhaustive list of drugs that are known to prolong the QTc.

Drug Class	Examples of Drugs That Increase Risk of TdP, Name (Brand Name)
Antiarrhythmic	Amiodarone (Cordarone, Pacerone) Bepiridil (Vascor) Disopyramide (Norpace) Dofetilide (Tikosyn) Flecainide (Tambocor) Ibutilide (Corvert) Procainamide (Pronestyl, Procan) Quinidine (Cardioquin, Quinaglute) Sotalol (Betapace)
Antibiotic	Azithromycin (Zithromax) Clarithromycin (Biaxin) Erythromycin (Erythrocin, EES) Moxifloxacin (Avelox) Pentamidine (NebuPent, Pentam) Aparfloxacin (Zagam)
Anticancer	Arsenic trioxide (Trisenox) Vandetanib (Caprelsa)
Antidepressant	Citalopram (Celexa)
Antiemetic	Domperidone (Motilium) Droperidol (Inapsine)
Antihistamine	Astemizole (Hismanal) Terfenadine (Seldane)
Antilipemic/hypercholesterolemic	Probucol (Lorelco)
Antimalarial	Chloroquine (Aralen) Halofantrine (Halfan)
Antipsychotic	Chlorpromazine (Thorazine) Haloperidol (Haldol) Mesoridazine (Serentil) Pimozide (Orap) Thioridazine (Mellaril)
GI stimulant/heartburn agent	Cisapride (Propulsid)
Opiate agonist	Levomethadyl (Orlaam) Methadone (Dolophine, Methadose)

EES: erythromycin; GI: gastrointestinal; TdP: torsades de pointes.

Appendix H New York Heart Association Classification of Heart Failure

NYHA Class	Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea.
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

NYHA: New York Heart Association.

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Appendix I Statistical Considerations for Paired Biopsy Specimens

While biopsies are requested of patients with safely accessible nonirradiated/abscopal lesions (in the opinion of the investigator) during the dose-escalation phase, safely accessible biopsy specimens will be mandatory for the first 6 backfill patients enrolled in cohort-assigned dose levels [REDACTED] during the dose-escalation phase and all patients in the cohort-expansion phase.

After completion of the dose-escalation phase of the study, it is anticipated that additional patients will be evaluated in the cohort-expansion phase. During the cohort-expansion phase, the study is designed to demonstrate biologically and statistically meaningful increase in T cell infiltration into tumors after treatment with TAK-280. A certain number of paired patient biopsies (from a single indication and/or dose level) in the dose escalation and expansion cohorts may be needed to achieve our desired statistical confidence. To evaluate that, we surveyed the literature for the level of T-cell infiltration into tumors treated with immuno oncology agents in various tumor types ([Chalabi et al. 2020](#); [Ferrarotto et al. 2020](#); [Steele et al. 2018](#); [Tumeh et al. 2014](#)). Published results suggest that immuno oncology treatment-mediated T-cell infiltration can result in approximately 1.5- to 3 fold increases in CD8 T cells within the TME via the evaluation of pretreatment and posttreatment biopsies and yields an estimated %CV of 80% to 180% in most studies. Based on these data, we assumed a 2.0 fold increase and a %CV of 130% to project the minimum number of paired biopsies that are needed to achieve a 0.8 posterior probability of achieving a 1.5 fold increase in T cells after treatment with a probability of success of 80%. On the basis of these assumptions, it is projected that 15 pairs of biopsy specimens per indication and/or dose are required to achieve a minimum of 7 high quality and interpretable biopsies (assuming that 70% of biopsies at screening and on treatment will be evaluable and interpretable).

Appendix J ASTCT ICANS Consensus Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score ^a	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness ^b	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min) or repetitive clinical or electrical seizures without return to baseline in between
Motor findings ^c	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging ^d	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Source: (Lee et al. 2019).

CTCAE: Common Terminology Criteria for Adverse Events; ICANS: immune effector cell-associated neurotoxicity syndrome; ICE: immune effector cell-associated encephalopathy; ICP: intracranial pressure; NA: not applicable.

^a A patient with an ICE score of 0 may be classified as Grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as Grade 4 ICANS if unarousable.

ICE Categories:

- **Orientation:** orientation to year, month, city, hospital: 4 points (1 point each).
- **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points (1 point each).
- **Following commands:** ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point.
- **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point.
- **Attention:** ability to count backwards from 100 by 10: 1 point.

^b Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

^c Tremors and myoclonus associated with immune cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

^d Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Appendix K Management of ICANS

ICANS Grade	Sign or Symptom	Management		
		Diagnostic Work-Up	Supportive Care	Anti-IEC Therapies
Grade 1	Encephalopathy and/or depressed level of consciousness	- MRI imaging of the brain with and without contrast: CT of brain without contrast may be performed if MRI is not feasible: MRI spine if focal deficits are noted - Neurology consultation - ICE Score assessment every 6 hours or more frequently if clinically indicated - EEG - Consider diagnostic lumbar puncture if other causes of encephalopathy are suspected (eg, infections, autoimmune, leptomenigeal disease) - Add a meningitis-encephalitis panel from CSF in patients with neurologic symptoms that persist or worsen after ICANS therapy and/or if symptoms start after corticosteroids	- Vigilant supportive care; aspiration precautions; IV hydration - Withhold oral intake of food/medications/fluids and assess swallowing; convert all oral medications and/or nutrition to IV if swallowing is impaired - Avoid medications that cause central nervous system depression - Low doses of lorazepam after EEG is performed (0.25-0.5 mg IV every 8 hours) or haloperidol (0.5 mg IV every 6 hours) may be used with careful monitoring for agitated patients - If no seizures on EEG, continue prophylactic levetiracetam - If EEG shows focal or generalized convulsive or nonconvulsive seizure or convulsive status epilepticus, refer to further management as in Grade 3 or 4 ICANS	- Dexamethasone 10 mg IV for 1 dose (or methylprednisolone equivalent) and reassess in 6 hours or earlier if clinically indicated - If associated with concurrent CRS, add tocilizumab ^a
Grade 2	Encephalopathy and/or depressed level of consciousness	Neurological work-up as in Grade 1 ICANS	Supportive care as in Grade 1 ICANS	- Dexamethasone 10 mg IV every 12 hours (or methylprednisolone equivalent) - If associated with concurrent CRS, add tocilizumab ^a - Once ICANS improves to Grade 1 or less, taper and/or stop corticosteroids depending on clinical situation
Grade 3	Encephalopathy and/or depressed level of consciousness	- Neurological work-up as in Grade 1 ICANS - Consider repeat neuro-imaging (CT or MRI) every 2-3 days for persistent ≥Grade 3 encephalopathy - Consider diagnostic lumbar puncture if Grade 3 encephalopathy persists ≥2 days or earlier if other causes are suspected (eg, infections, autoimmune,	- Supportive care as in Grade 1 ICANS - Consider ICU transfer - If there are new abnormal findings on brain imaging ^b not related to primary malignancy, control hypertension with the goal of maintaining MAP within 20-25 mm Hg of baseline MAP, correct any uremia (dialysis if needed) and/or coagulopathy (transfuse to keep platelets >20-50 K/μL, fibrinogen >200 mg/dL and INR <1.5)	- Dexamethasone 10 mg IV every 6 hours (or methylprednisolone equivalent) - If associated with concurrent CRS, add tocilizumab ^a - If Grade 3 encephalopathy is persistent for >24 hours, increase dexamethasone to 20 mg IV every 6 hours (or methylprednisolone equivalent) - Once ICANS improves to

		leptomeingeal disease) ○ Add a meningitis-encephalitis panel from CSR in patients with neurologic symptoms that persist or worsen after ICANS therapy and/or symptoms start after corticosteroids		Grade 1 or less, taper and/or stop corticosteroids depending on clinical situation
	Seizure	• Neurological work-up as in Grade 1 ICANS • EEG if clinically indicated (eg, ongoing seizures, depressed level of consciousness) • Rule out other potential causes of seizure (beta-lactams, etc.)	• Transfer to ICU • Supportive care as in Grade 1 ICANS • For focal or generalized convulsive seizures, or nonconvulsive seizures, treat as summarized in Table K2	• Dexamethasone 20 mg IV every 6 hours (or methylprednisolone equivalent) ○ If associated with concurrent CRS, add tocilizumab ^a • Once ICANS improves to Grade 1 or less, taper and/or stop corticosteroids depending on clinical situation
	Focal cerebral edema	• Neurological work-up as in Grade 1 ICANS • Consider repeat neuro-imaging (CT or MRI) every 24 hours until edema resolves or more frequently if clinically indicated	• Transfer to ICU • Supportive care as in Grade 1 ICANS	• If focal edema is in brain stem or thalamus methylprednisolone 1000 mg/d in divided doses for IV for 3 days followed by taper depending on clinical situation ○ If associated with concurrent CRS, add tocilizumab ^a • If focal edema is in other areas of brain, methylprednisolone 1000 mg/d in divided doses IV for 1 day; assess daily and continue or taper depending on clinical situation • If associated with concurrent CRS, add tocilizumab ^a

ICANS Grade	Sign or Symptom	Management		
		Diagnostic Work-Up	Supportive Care	Anti-IEC Therapies
Grade 4	Encephalopathy and/or depressed level of consciousness	- Neurological work-up as in Grade 1 ICANS - Repeat neuro-imaging and lumbar puncture as in Grade 3 ICANS	- Transfer to ICU - Supportive care as in Grade 1 ICANS - Consider mechanical ventilation for airway protection - If there are new abnormal findings on brain imaging ^b not related to primary malignancy, control hypertension with the goal of maintaining MAP within 20-25 mm Hg of baseline MAP, correct any uremia (dialysis if needed) and/or coagulopathy (transfuse to keep platelets >20-50 K/μL, fibrinogen >200 mg/dL and INR <1.5)	- Methylprednisolone 1000 mg/d in divided doses IV for 3 days followed by taper as clinically indicated; if associated with concurrent CRS, add tocilizumab ^a - Continue corticosteroids until improvement to less than or equal to Grade 1 ICANS and then taper and stop corticosteroids depending on clinical situation - If Grade 4 ICANS is refractory for >24 hours or if patient is deteriorating rapidly, consider additional therapies ^a including activation of safety switches if applicable
	Seizure	- Neurological work-up as in Grade 1 ICANS - Rule out other potential causes of seizure (beta-lactams, etc.)	- Transfer to ICU - Supportive care as in Grade 1 ICANS - For focal or generalized convulsive seizures, or nonconvulsive seizures or convulsive status epilepticus, treat as in Table K2 or Table K3	- Methylprednisolone 1000 mg/d in divided doses IV for 3 days followed by taper as clinically indicated; if associated with concurrent CRS, add tocilizumab ^a - If Grade 4 ICANS is refractory for >24 hours or if patient is deteriorating rapidly, consider additional therapies ^a including activation of safety switches if applicable
	Motor Weakness	- Neurological work-up as in Grade 1 ICANS - MRI with and without contrast of the spine	- Transfer to ICU - Supportive care as in Grade 1 ICANS	- Methylprednisolone 1000 mg/d in divided doses IV for 3 days followed by taper as clinically indicated; if associated with concurrent CRS, add tocilizumab ^a - If Grade 4 ICANS is refractory for >24 hours or if patient is deteriorating rapidly, consider additional therapies ^a including activation of safety switches if applicable
	Diffuse Cerebral Edema or Raised Intracranial Pressure	- Neurological work-up as in Grade 1 ICANS - Consider repeat neuro-imaging as in focal cerebral edema from Grade 3 ICANS	- Transfer to ICU - Supportive care as in Grade 1 ICANS - For diffuse cerebral edema or signs of raised intracranial pressure, treat as in Table K4	- Methylprednisolone 1000 mg/d in divided doses IV for 3 days followed by taper as clinically indicated; if associated with concurrent CRS, add tocilizumab ^a - If Grade 4 ICANS is refractory for >24 hours or if patient is deteriorating rapidly, consider additional therapies ^a including activation of safety switches if applicable

^a See Table K1 for dosing of IL-6 antagonists and alternative agents.

^b Abnormal findings on imaging where correction of hypertension, uremia, and/or coagulopathy should be performed include changes suggestive of typical or atypical posterior reversible encephalopathy syndrome, temporal lobe and limbic system encephalitis (autoimmune or infection), acute disseminated encephalomyelitis, emboli, vasculitis, strokes, and/or seizure-related changes.

Table K1 Recommendations for Use of IL-6 Antagonists and Alternative Agents for Management of CRS and ICANS

Drug	Recommended Dose for CRS and/or ICANS	Maximum Dose	Mechanism of Action	Comments
Tocilizumab	8 mg/kg IV	Maximum 800 mg per dose	IL-6 receptor antagonist	- Maximum of 4 doses total over the entire course of CRS and ICANS - Dose may be repeated every 8 hours for up to 3 doses in a 24-hour period
Siltuximab	11 mg/kg IV once	--	IL-6 antibody	- Recommended primarily for patients who are intolerant to tocilizumab - No more than 1 dose in a 3-week period
Anakinra	100 mg subcutaneously daily for 7 days	--	IL-1 receptor antagonist	Renal dose adjustment may be needed for creatinine clearance <30 mL/minute
Cyclophosphamide	1500 mg/m ² IV for 1 dose	--	Alkylating agent	Give with mesna 1500 mg/m² IV over 24 hours for 1 dose
Anti-thymocyte globulin (rabbit)	1-2 mg/kg IV daily for 3 days	--	Immunosuppressant	- Hypersensitivity reactions can occur; premedicated with diphenhydramine and schedule dose of corticosteroid - Infuse over a minimum of 6 hours.

Table K2 Management of Focal or Generalized Convulsive or Non-Convulsive Seizures

- Assess CAB/consider airway protection/check blood glucose - Consult Neurology - For focal and generalized convulsive seizures, lorazepam 1-2 mg IV and repeat as needed (to a maximum cumulative dose of 4 mg) - For electrographical seizures, including nonconvulsive status epilepticus, lorazepam 0.5 mg IV and repeat every 5 minutes as needed (to a maximum cumulative dose of 2 mg) - Levetiracetam 500-1500 mg IV bolus (in addition to maintenance dose) - Replete with magnesium as needed to maintain magnesium level >2 mg/dL - Thiamine 100 mg IV every 8 hours for 5 days - If nonconvulsive seizures persist, transfer to ICU and add phenobarbital loading dose of 60 mg IV (monitor for respiratory depression, bradycardia and hypotension) - Maintenance doses after resolution of nonconvulsive status epilepticus - Lorazepam 0.5 mg IV every 8 hours for 3 doses - Levetiracetam 1000-1500 mg IV every 12 hours - Phenobarbital 30 mg IV every 12 hours (~0.5 mg/kg every 12 hours) - Monitor for respiratory depression, bradycardia, and hypotension - Assess for drug-drug interactions (ie, may induce metabolism of azole antifungals or other CYP3A4 substrates) and consider alternative therapy if drug interactions are significant - Target serum trough levels 15-40 µg/mL

Table K3 Management of Convulsive Status Epilepticus

- Assess CAB/consider airway protection/check blood glucose - Transfer to ICU - Consult Neurology - Lorazepam 0.1 mg/kg (maximum 4 mg/dose) given at a maximum rate of 2 mg/min; may repeat in 5 to 10 minutes - Levetiracetam 500-1500 mg IV bolus (in addition to maintenance dose) - Replete with magnesium as needed to maintain magnesium level >2 mg/dL - Thiamine 100 mg IV every 8 hours for 5 days - If seizures persist, add phenobarbital loading dose of 15 mg/kg IV (monitor for respiratory depression, bradycardia, and hypotension) - If refractory, consider additional therapies (see Table K1) - Maintenance doses after resolution of nonconvulsive status epilepticus - Levetiracetam 1000-1500 mg IV every 12 hours - Phenobarbital 0.5 mg/kg IV every 12 hours - Monitor for respiratory depression, bradycardia, and hypotension - Assess for drug-drug interactions (ie, may induce metabolism of azole antifungals or other CYP3A4 substrates) and consider alternative therapy if drug interactions are significant - Target serum trough levels 15-40 µg/mL - Continuous EEG monitoring if seizures are refractory to treatment

Table K4 Management of Diffuse Cerebral Edema and or Raised Intracranial Pressure

For papilledema without diffuse cerebral edema or other signs of raised intracranial pressure	- Acetazolamide 1000 mg IV followed by 250-1000 mg IV every 12 hours (monitor renal function and acid/base balance once or twice daily and adjust dose accordingly) - Dexamethasone 20 mg IV every 6 hours (or methylprednisolone equivalent) and start taper after resolution of papilledema
For diffuse cerebral edema on neuroimaging or signs of raised intracranial pressure such as decerebrate or decorticate posturing, cranial nerve VI palsy, or Cushing's triad	- Methylprednisolone 1000 mg/d in divided doses IV for 3 days followed by taper as clinically indicated - Elevate head end of patient's bed to an angle of 30 degrees - Hyperventilation to achieve target PaCO₂ of 28-30 mm Hg, but maintained for no longer than 24 hours - Hyperosmolar therapy with either mannitol (20 g/dL solution) or hypertonic saline (3% or 23.4% as detailed below) - Mannitol: initial dose 0.5-1 g/kg IV; maintenance dose 0.25-1 g/kg IV every 6 hours while monitoring metabolic profile and serum osmolality every 6 hours; and withhold mannitol if serum osmolality is ≥320 mOsm/kg or osmolality gap is ≥40) - Hypertonic 3% saline: initial dose 250 mL IV over 15 minutes, maintenance dose of 50-75 mL/hour IV while monitoring electrolytes every 4 hours; withhold infusion if serum sodium levels reach ≥155 mEq/L) - Hypertonic 23.4% saline (for patients with imminent herniation): dose to be administered by physician; initial dose of 30 mL IV; repeat after 15 minutes, if needed - If patient has Ommaya reservoir, drain CSF to target OP <20 mm Hg - Control hypertension with the goal of maintaining MAP within 20-25 mm Hg of baseline MAP; correct any uremia (dialysis if needed) and/or coagulopathy (transfuse to keep platelets >20-50 K/µL, fibrinogen >200 mg/dL and INR <1.5) - Consider neurosurgery consultation and IV anesthetics for burst-suppression pattern on EEG; transfuse to keep platelets ≥100 K/µL if possible and correct coagulopathy in case of surgical intervention - Consider additional therapies (See Table K1) - Metabolic profile every 6 hours and daily CT scans of head without contrast, with

Table K4 Management of Diffuse Cerebral Edema and or Raised Intracranial Pressure

	adjustments in usage of aforementioned medications to prevent rebound cerebral edema, renal failure, electrolyte abnormalities, hypovolemia, and hypotension
--	--

Adapted from IEC Therapy Toxicity Assessment and Management (also known as CARTOX) -Adult V4

mdanderson.org/documents/for-physicians/algorithms/clinical-management/clin-management-cytokine-release-web-algorithm.pdf

CAB: circulation, airway, breathing; CRS: cytokine release syndrome; CSF: cerebrospinal fluid; CT: computed tomography; CYP: cytochrome P450; EEG: electroencephalogram; ICANS: immune effector cell–associated neurotoxicity syndrome; IEC: immune effector cells; ICE: IEC-Associated Encephalopathy; ICU: intensive care unit; IEC: immune effector cell; IL: interleukin; INR: international normalized ratio; IV: intravenous; MAP: mean arterial pressure; MRI: magnetic resonance imaging; PaCO₂: partial pressure of carbon dioxide.

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Appendix L Protocol History

Amendment History:

Date	Amendment No.	Amendment Type	Region
19 December 2023	3 GB v1	Nonsubstantial	Great Britain
19 May 2023	3	Substantial	Global
08 March 2023	2	Substantial	Global
23 November 2021	1	Substantial	Global
18 October 2021	Initial protocol	Not applicable	Global

Protocol Amendment 3 GB v1 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 3 GB v1.

The primary reasons for this amendment are to update the contraception requirements, to add a requirement that an approved, substantial amendment is needed to restart recruitment after a halt in enrollment for study stopping rules, and to add clarifying language to the dose-escalation rules.

Protocol Amendment 3 GB v1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	Section Number and Title	Description of Each Change and Rationale	
	Location	Description	Rationale
1.	Section Error! Reference source not found. Error! Reference source not found. Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria Section Error! Reference source not found. Error! Reference source not found.	Updated contraception language to clarify the definition of women of childbearing potential (WOCBP) and updated acceptable methods of contraception.	Revised in response to regulatory (Medicines and Healthcare Products Regulatory Agency [MHRA]) feedback.
2.	Section 6.1.5 Study Stopping Rules	Added requirement for an approved substantial amendment before restarting recruitment after halt in enrollment.	Revised in response to regulatory (MHRA) feedback.
3.	Section 8.3 Dose-Escalation Rules	Added language to clarify dose-escalation rules for Bayesian Optimal Interval (BOIN) design.	Revised in response to regulatory (MHRA) feedback.

Protocol Amendment 3 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 3.

The primary purpose of this amendment is to add new sections for study stopping rules and the management of neurologic adverse events. In addition, this amendment adds thyroid function tests to the laboratory assessments, updates the criteria for discontinuation of TAK-280, adds requirements for restarting treatment with TAK-280 following on-study surgery, and updates the maximum number of prior systemic therapies allowed in patients with metastatic castration-resistant prostate cancer (mCRPC).

In addition, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are applied throughout the document for clarification and administrative purposes.

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	Section Number and Title	Description of Each Change and Rationale	
	Location	Description	Rationale
1.	Section 2.0 STUDY SUMMARY Main Criteria for Inclusion Section 7.1 Inclusion Criteria	Maximum number of prior systemic therapies allowed in patients with metastatic castration-resistant prostate cancer (mCRPC) has been extended from 3 to 4.	Updated to reflect the number of approved systemic therapies for patients with mCRPC.
2.	Section 2.0 STUDY SUMMARY Section 8.0 STUDY DRUG Section 10.2.1 Recording and Reporting AEs and SAEs Related to AxMPs	Removed information on auxiliary medicinal products.	To align with the requirements of a global study protocol.
3.	Section 2.0 STUDY SUMMARY	Removed Potential Risks and Benefits section.	To align with the requirements of a global study protocol.
4.	Section 6.1 Overview of Study Design	Added language from Section 2 Study Summary about the use of tocilizumab that was previously missing from the protocol body.	To align the text in the study summary and body of the protocol.
5.	Section 6.1.1.1 [REDACTED]	[REDACTED] [REDACTED] [REDACTED]	Added for clarity.
6.	Section 6.1.5 Study Stopping Rules	New section added to define criteria to suspend enrollment into the study and halt treatment of ongoing patients.	Revised in response to regulatory (United States Food and Drug Administration [US FDA]) feedback and in the interest of enhanced patient safety.

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	Section Number and Title	Description of Each Change and Rationale	
	Location	Description	Rationale
7.	Section 8.3 Dose-Escalation Rules	Text added to describe the maximum dose increments allowed for the next dose cohort.	Added for clarity.
8.	Section 8.4.2 Criteria for Beginning or Delaying the Next Dose of Study Drug	Text added to specify that the criteria to resume therapy with TAK-280 applies to both hematologic and nonhematologic toxicities.	Added for clarity in response to regulatory (US FDA) feedback.
9.	Section 8.4.3 Criteria for Dose Interruption During Infusion of TAK-280	Text added to specify when TAK-280 can be restarted after surgery.	Revised in response to regulatory (US FDA) feedback and in the interest of enhanced patient safety.
10.	Section 8.4.5 Criteria for Discontinuation of TAK-280	Criterion added to the list of reasons for the discontinuation of study drug: Recurrence of Grade ≥ 3 AE that previously led to drug interruption and is considered at least possibly related to TAK-280 treatment.	Revised in response to regulatory (US FDA) feedback and in the interest of enhanced patient safety.
11.	Section 8.4.6 Inpatient Dose Escalation	New section added; text moved from Section 8.4.4 Criteria for Dose Reduction.	Text moved for clarity and to include additional criteria for inpatient dose escalation.
12.	Section 8.6 Permitted Concomitant Medications and Procedures	Text added to monitor patients who receive sensitive cytochrome P450 enzyme substrates during the treatment period.	Revised in response to regulatory (US FDA) feedback and in the interest of enhanced patient safety.
13.	Section 8.7.3 Patient Activity Restrictions	Restriction window for breastfeeding was changed from 120 days to 90 days after the last dose of study drug.	To correct an error in the previous version of the protocol.

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	Section Number and Title	Description of Each Change and Rationale	
	Location	Description	Rationale
14.	Section 8.8.1.1 [REDACTED] Postinfusion Support	Text added to allow the use of [REDACTED] postinfusion treatment for cytokine release syndrome (CRS) prophylaxis.	Updated to allow additional medication [REDACTED] after the infusion of the study medication as CRS prophylaxis per investigator discretion after discussion with sponsor's medical monitor.
15.	Section 8.8.6 Management of Neurologic Adverse Events Appendix K Management of ICANS	New section added.	Revised in response to regulatory (US FDA) feedback and in the interest of enhanced patient safety.
16.	Section 10.5 Procedures for Reporting Product Complaints (Including Overdose)	Removed information on special situation reports.	To align with the requirements of a global study protocol.
17.	Appendix A Schedule of Events Table A1 Schedule of Events, [REDACTED], footnote i Table A2 Schedule of Events [REDACTED], footnote i Table A3 Schedule of Events [REDACTED], footnote i	Updated to include use of the Immune Effector Cell-associated Encephalopathy assessment tool to evaluate neurological status as part of the physical examination.	Revised in response to regulatory (US FDA) feedback and in the interest of enhanced patient safety.
18.	Appendix A Schedule of Events Table A1 Schedule of Events, [REDACTED] and footnote p Table A2 Schedule of Events [REDACTED] and footnote p Table A3 Schedule of Events [REDACTED] and footnote p Appendix B Clinical Laboratory Tests	Thyroid test assessments (thyroid-stimulating hormone and free thyroxine) added at screening, Day 1 of every other cycle beginning at Cycle 3, and end of treatment.	Revised in response to regulatory (US FDA) feedback and in the interest of enhanced patient safety.
19.	Appendix B Clinical Laboratory Tests	Updated to include blood urea nitrogen and urea.	Updated to account for differences in laboratory panels and clinical practice across sites and regions.

Protocol Amendment 2 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 2.

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The primary purpose of this amendment is to incorporate a modified dose optimization approach to more robustly determine an appropriate recommended phase 2 dose (RP2D) of single-agent TAK-280, when administered to patients with locally advanced or metastatic cancer.

The study design has been modified to identify 2 recommended doses for expansion (RDEs) during the dose-escalation phase of the study based on clinical safety and tolerability, and pharmacokinetic (PK), pharmacodynamic, and clinical efficacy data. During the cohort-expansion phase of the study, patients in the selected indication for randomization are to be randomized 1:1 to 2 RDEs (low and high), and patients in the remaining [REDACTED] indications will receive the high RDE of TAK-280. The RP2D will be determined at the end of the cohort-expansion phase based on the assessment of clinical efficacy, clinical safety and tolerability, and PK and pharmacokinetic data. A cohort using the low RDE 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.

In addition, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are applied throughout the document for clarification and administrative purposes.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	Section Number and Title	Summary of Changes	Rationale
	Location	Description	Rationale
1.	Section 2.0 STUDY SUMMARY, Study Design; Cohort-Expansion Phase Section 6.1.3 Cohort-Expansion Phase Section 9.3 Treatment Group Assignments	Revised to describe updated study design for the cohort-expansion phase; planned dosing with 2 recommended doses for expansion (RDEs) as determined in the dose-escalation phase in [REDACTED] indications: [REDACTED] metastatic castration-resistant prostate cancer (mCRPC), and [REDACTED]	The study design was updated to incorporate a dose optimization approach during the cohort-expansion phase.
2.	Section 2.0 STUDY SUMMARY, Study Design Section 8.8.1 Management of CRS/IRRs	Information added on the use of tocilizumab for the management of cytokine release syndrome (CRS) and infusion-related reactions.	To provide further clarity and details to manage the risk of CRS/infusion-related reaction (IRR).

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	Section Number and Title	Summary of Changes	Rationale
	Location	Description	Rationale
3.	Section 2.0 STUDY SUMMARY, Study Design 6.1 Overview of Study Design Section 6.1.4 Survival Follow-Up Period Section 6.3.1 Duration of an Individual Patient's Study Participation Appendix A Table A1 Schedule of Events, [REDACTED], Footnote x Appendix A Table A2 Schedule of Events [REDACTED], Footnote x Appendix A Table A3 Schedule of Events [REDACTED], Footnote x	Survival follow-up period updated from 52 weeks to 48 weeks from last dose of study drug.	To align with standard follow-up timelines across study programs.
4.	Section 2.0 STUDY SUMMARY, Dose-Escalation Phase Section 6.1.3 Dose-Escalation Phase	Statement added that patients who do not experience a dose-limiting toxicity (DLT) but are not DLT-evaluable will be replaced.	To clarify replacement criteria for patients during dose-escalation.
5.	Section 2.0 STUDY SUMMARY, Dose-Escalation Phase Section 8.1.1 General Administration Guidelines and Precautions Appendix A Table A1 Schedule of Events, [REDACTED], Footnote f Appendix A Table A2 Schedule of Events [REDACTED], Footnote f Appendix A Table A3 Schedule of Events [REDACTED], Footnote f	Updated requirements for overnight monitoring of patients after dosing updated.	To clarify how patients must be monitored postdose for potential CRS/IRR events.
6.	Section 2.0 STUDY SUMMARY, Number of Participants, Sample Size Justification Section 6.1 Overview of Study Design Section 6.2 Number of Patients Section 13.3 Determination of Sample Size	Number of study participants and study sites updated.	To align with changes to study design.
7.	Section 2.0 STUDY SUMMARY, Main Criteria for Inclusion Section 7.1 Inclusion Criteria	Criteria for eligibility updated with definitions of the 3 disease types to be enrolled during cohort-expansion phase.	To align with change in study design during the cohort-expansion phase.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	Section Number and Title	Summary of Changes	Rationale
	Location	Description	Rationale
8.	Section 2.0 STUDY SUMMARY, Main Criteria for Inclusion Section 7.1 Inclusion Criteria	Updated eligibility criteria for creatinine clearance level from 30 mL/min to 45 mL/min.	Updated per regulatory agency's recommendation to ensure that patients have adequate renal function.
9.	Section 2.0 STUDY SUMMARY, Main Criteria for Inclusion Section 7.1 Inclusion Criteria Section 9.4.16.1 Primary Specimen Collection Section 9.4.16.2 Tumor Biopsies Appendix A Table A1 Schedule of Events, [REDACTED], Footnote w Appendix A Table A2 Schedule of Events [REDACTED], Footnote w Appendix A Table A3 Schedule of Events [REDACTED], Footnote w	Updated requirements for the collection of tumor biopsy samples at screening and on study.	To provide clarity of timelines and support collection of biopsy samples.
10.	Section 2.0 STUDY SUMMARY, Main Criteria for Inclusion Section 7.1 Inclusion Criteria Section 8.7.3 Patient Activity Restrictions	Added requirement that male patients agree to refrain from donating sperm during the study and for 90 days after the last dose of TAK-280.	Updated per regulatory agency's recommendation to ensure adequate time between the receipt of study drug and sperm donation for fetal safety.
11.	Section 2.0 STUDY SUMMARY, Main Criteria for Exclusion Section 7.2 Exclusion Criteria	Added hypersensitivity to tocilizumab to list of exclusions.	Required exclusion for patient safety.
12.	Section 2.0 STUDY SUMMARY, Main Criteria for Evaluation and Analyses Section 5.2 Endpoints	Removed identification of maximum-tolerated dose (MTD) and RP2D as primary endpoint.	Identification of MTD and RP2D are part of the primary objective; these are not endpoints.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	Section Number and Title	Summary of Changes	Rationale
	Location	Description	Rationale
13.	Section 2.0 STUDY SUMMARY, Main Criteria for Evaluation and Analyses Section 5.2 Endpoints Section 6.3.3 Time Frames for Primary and Secondary Endpoints to Support Disclosures Section 13.1.3 Efficacy Analysis	Added definitions of efficacy endpoints. The following secondary endpoints have been added: disease control rate, prostate-specific antigen (PSA) response, duration of PSA response, time to PSA progression, PSA reductions of $\geq 50\%$ at 6 months, and immunogenicity characterization.	Definitions added for clarity. Disease control rate added to provide additional efficacy data. PSA endpoints added for patients with metastatic castration resistant prostate cancer (mCRPC).
14.	Section 2.0 STUDY SUMMARY, Statistical Considerations Section 13.1.1 Analysis Sets	Updates made to definitions of analysis sets; PSA response analysis set and immunogenicity analysis set added.	The DLT-evaluable analysis set and safety analysis set were updated to clarify the patient population to be used to determine RDEs for cohort-expansion. PSA analysis sets added to align with added efficacy endpoints for patients with mCRPC.
15.	Section 2.0 STUDY SUMMARY, Statistical Methods Section 13.1.3 Efficacy Analysis	Section updated with current statistical methods for general and efficacy analyses.	To reflect changes in study design and addition of efficacy endpoints.
16.	Section 2.0 STUDY SUMMARY, Potential Risks and Benefits	New section added.	To comply with new EU CTR guidelines and requirements.
17.	Section 4.1 Background Section 4.1.2 Nonclinical Background Section 4.2 Rationale for the Proposed Study	Updated with information from available nonclinical studies and edited for clarity.	To include current information from nonclinical studies and improved readability.
18.	Section 4.1.1 Disease Background and Unmet Clinical Need Section 4.1.1.1 mCRPC Section 4.1.1.2 [REDACTED] Section 4.1.1.3 [REDACTED]	Updated to include information [REDACTED] [REDACTED] [REDACTED] [REDACTED]	To reflect addition of [REDACTED] [REDACTED] [REDACTED] [REDACTED]

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	Section Number and Title	Summary of Changes	Rationale
	Location	Description	Rationale
19.	Section 4.2.2 FIH Dose Selection	Section removed.	The section was removed because it is not required for the protocol audience.
20.	Section 5.2.3 Exploratory Endpoints	Updated to include evaluation of cytokine levels and response per Immunotherapy Response Evaluation Criteria in Solid Tumors (iRECIST) criteria.	To enable an additional exploratory evaluation of cytokine levels and response per iRECIST criteria.
21.	Section 6.1.1 Dose-Escalation Phase	Added rules for maximum dose increments percentage allowed in subsequent dose cohorts.	Updated per regulatory agency's recommendation to ensure patient safety during dose exploration in the dose escalation phase.
22.	Section 6.1.1.1 [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
23.	Section 6.1.2 Backfill Patients in the Dose-Escalation Phase	New section added to describe the process for adding backfill patients during the dose-escalation phase.	To allow the option to enroll additional patients at individual dose level cohorts during the dose-escalation phase.
24.	Section 8.0 STUDY DRUG	Added information on auxiliary medicinal products (AxMPs) used in the study.	To comply with new EU CTR guidelines and requirements.
25.	Section 8.1 Study Drug Preparation	Updated to clarify drug preparation instructions.	Updated for clarity.
26.	Section 8.1.1 General Administration Guidelines and Precautions	Updated to clarify drug administration guidelines.	Updated for clarity.
27.	Section 8.2 Definitions of DLTs	Updated to include specific DLT criteria.	Updated for patient safety.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	Section Number and Title	Summary of Changes	Rationale
	Location	Description	Rationale
28.	Section 8.3 Dose-Escalation Rules	Section updated for clarity. Dose escalation/de-escalation rules updated.	Updated to align with Bayesian Optimal Interval (BOIN) design [REDACTED].
29.	Section 8.4 Dose-Modification Guidelines	Section updated for clarity. Added criterion that dose delays resulting in dosing interval of ≥ 21 days between doses will lead to permanent discontinuation of study drug.	Updated for clarity and to specify criterion for dose discontinuation.
30.	Section 8.8.3 Management of Thrombocytopenia	Added criterion for Grade 1 or Grade 2 event.	Updated for clarity and patient safety.
31.	Section 9.3 Treatment Group Assignments	Revised text to specify that the cohort-expansion phase patients in the selected indication will be randomized 1:1 to low/high RDE.	To reflect change in study design in cohort-expansion phase.
32.	Section 9.4.14 Disease Assessment	Updated to include the use of both Response Evaluation Criteria in Solid Tumors (RECIST) V1.1 and iRECIST; section also edited for clarity.	To include iRECIST as criteria for evaluating response.
33.	Section 9.4.18 Pharmacodynamic Measurements	Biomarkers to be evaluated updated.	To appropriately characterize pharmacodynamic activity for TAK-280.
34.	Section 9.7 Withdrawal of Patients From Study	Section removed.	Information in this section is provided in Section 6.3.1 Duration of an Individual Patient's Study Participation.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	Section Number and Title	Summary of Changes	Rationale
	Location	Description	Rationale
35.	Section 9.8 Immune-Mediated AE Follow-Up Section 10.3 Monitoring of AEs and Period of Observation Appendix A Table A1 Schedule of Events, [REDACTED], Footnote c Appendix A Table A2 Schedule of Events [REDACTED], Footnote c Appendix A Table A3 Schedule of Events [REDACTED], Footnote c	Added information for onsite follow-up visit 90 days after the last dose of study drug to assess immune-mediated adverse events (AEs).	Ensure collection of immune-mediated AEs occurring after treatment with TAK-280.
36.	Section 10.2.1 Recording and Reporting AEs and SAEs Related to AxMPs	New section with information on AEs and SAEs related to AxMPs.	Added to comply with new EU CTR guidelines and requirements.
37.	Section 10.5 Procedures for Reporting Product Complaints or Special Situation Reports (Including Overdose)	Updated to include information on special situation reports. Table of contacts removed and replaced with reference to the study manual.	Added to comply with new EU CTR guidelines and requirements. To ensure up-to-date contact information for reporting of complaints and errors.
38.	Section 13.1 Statistical and Analytical Plans	Updated time for conducting primary analysis.	To allow for sufficient collection of survival follow-up data.
39.	Section 13.1.6 PK/Pharmacodynamic Analysis	Added language about RDE selection and the potential to explore alternate dose levels.	Updated for clarity and to align with changes to the study design.
40.	Section 13.1.7 Immunogenicity Analyses	Added neutralizing antibody (NAb) titers to potential assessments.	Updated to align with planned immunogenicity analyses.
41.	Section 13.2 [REDACTED] [REDACTED]	Updated with statistical methods for analysis of patients in the cohort-expansion phase.	To align with changes in study design.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	Section Number and Title	Summary of Changes	Rationale
	Location	Description	Rationale
42.	Appendix F Conventional Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines Appendix G Modified Response Evaluation Criteria in Solid Tumors (Modified Response Evaluation Criteria in Solid Tumors) Guidelines	Removed Appendix F and G from list of appendices.	To align with the latest guidelines available in public without requiring a further protocol amendment if guidelines are updated.
43.	Appendix F (formerly Appendix H) Operating Characteristics of the Bayesian Optimal Interval Design for Dose Escalation	Data in tables updated to reflect current statistical plans.	Revised to align with changes in study design.
44.	Appendix I Statistical Considerations for Paired Biopsy Specimens	New appendix added.	To provide information on the statistical analysis of paired biopsy specimens.

Protocol Amendment 1 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 1.

Also updated are the length of monitoring period and the number of patients to be monitored after the initial dose of TAK-280. Other clarifications to the study inclusion/exclusion criteria and the study procedures were also made.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	Sections Affected by Change	Description of Each Change and Rationale	
	Location	Description	Rationale
1.	Section 2.0 STUDY SUMMARY Section 6.1.1 Dose-Escalation Phase Appendix A Schedule of Events, Table A1 (footnote '1')	Provided guidance that the initial TAK-280 doses in the first 3 patients be staggered by 48 hours in the dose-escalation cohorts.	The change refers to the time between first doses in the first 3 patients in each cohort to allow additional time for safety review between patients.

Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	Sections Affected by Change	Description of Each Change and Rationale	
	Location	Description	Rationale
2.	Section 2.0 STUDY SUMMARY Figure 6.a Study TAK-280-1501 Schema (including footnote) Section 6.1.1 Dose-Escalation Phase Section 8.2 Definitions of DLTs Appendix A Schedule of Events, Table A1 (footnote 'a')	Updated the definition of the DLT evaluation period.	[REDACTED]
3.	Section 2.0 STUDY SUMMARY Section 6.1 Overview of Study Design	Removed mention of "12 additional 28-day treatment cycles with TAK-280" and retained mention of total of 14 treatment cycles.	Change made to clarify the total number of treatment cycles.
4.	Section 2.0 STUDY SUMMARY Section 8.8.2.3 Postinfusion on Day 1 Appendix A Schedule of Events, Table A1 (footnote 'f')	Specified the 24-hour observation period for the first 3 patients at each dose level in the dose-escalation phase.	Change made to provide specific guidance for monitoring period.
5.	Section 2.0 STUDY SUMMARY Section 8.8.2.3 Postinfusion on Day 1	[REDACTED]	Change made to align visit days with the updates to the SOE.
6.	Section 2.0 STUDY SUMMARY Section 6.1.2 Cohort-Expansion Phase Section 13.2 [REDACTED] [REDACTED] Section 13.3 Determination of Sample Size Table 13.a Statistical Parameters Applied for Each Expansion Cohort (footnote 'e')	Removed evaluation of positive biomarker, translational, or other clinical data before enrollment into the second stage of each cohort.	Clarified that the second stage enrollment is only dependent on the response rate at the end of first stage based on Simon 2-stage design. Biomarker, translational, or other clinical data will not be used for this decision-making.

Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	Sections Affected by Change	Description of Each Change and Rationale	
	Location	Description	Rationale
7.	Section 2.0 STUDY SUMMARY, Inclusion Criteria Section 7.1 Inclusion Criteria	Specified that the creatinine clearance of ≥ 30 mL/min is acceptable as an inclusion criterion.	Clarified acceptable creatinine clearance values.
8.	Section 2.0 STUDY SUMMARY, Exclusion Criteria Section 7.2 Exclusion Criteria	Specified that vaccines (other than live vaccines) 2 weeks before the initiation of study drug are acceptable.	Change made to allow patients to be vaccinated before study start.
9.	Section 2.0 STUDY SUMMARY, Exclusion Criteria Section 13.1.1 Analysis Sets	Provided specific definition of DLT-evaluable analysis set.	Change made to increase clarity [REDACTED]
10.	Appendix A Schedule of Events, Table A1 (revised); Tables A2, A3, A4, A5, and A6 (new)	[REDACTED]	Simplified the SOE and sample collection schedules to streamline procedures.
11.	Section 6.1.1 Dose-Escalation Phase	Provided language for the measurement of vital signs and also patient discharge instructions.	Clarified patient safety monitoring instructions.
12.	Section 8.5 Excluded Concomitant Medications and Procedures	Included instructions for the collection of coronavirus disease 2019 (COVID-19) infection and vaccination data.	Clarified data collection procedures during COVID-19 pandemic.
13.	Section 8.7.2 Fluid and Food Intake Section 9.4.12 ECGs	Provided food intake restrictions before triplicate electrocardiograms (ECGs).	Clarified food intake limitations.
14.	Section 9.4.17.2 PK Measurements	Removed PK assay section.	PK assay information is provided in a separate document.
15.	Appendix A, Table A2 Laboratory Testing Blood Volumes (deleted) Section 9.4.13 Clinical Laboratory Evaluations	Deleted the appendix table with blood volumes.	Information not essential for the study conduct.
16.	Appendix B Clinical Laboratory Tests	Updated the urinalysis parameters.	Clarified the data to be collected for urinalysis.

Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	Sections Affected by Change	Description of Each Change and Rationale	
	<i>Location</i>	<i>Description</i>	<i>Rationale</i>
17.	Modified Response Evaluation Criteria in Solid Tumors (mRECIST) Guidelines	Updated the Modified Response Evaluation Criteria in Solid Tumors (mRECIST).	Provided the correct definition of unconfirmed progressive disease.
18.	Appendix H New York Heart Association Classification of Heart Failure (new)	Added the New York Heart Association Classification for the stages of heart failure.	Make the information readily available in the protocol.

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Signature Page for TAK-280-1501 Protocol Amendment 4

Title:

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