



Clinical Study Protocol

NCT Number: NCT04844073

Title: A Phase 1/2, First-in-Human, Open-Label, Dose-Escalation Study of TAK-186 (Also Known as MVC-101), An EGFR x CD3 COnditional Bispecific Redirected Activation (COBRA) Protein in Patients With Unresectable Locally Advanced or Metastatic Cancer

Study Number: CP-MVC-101-01

Document Version and Date: Amendment 8.0, 08 Aug 2024

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PROTOCOL

A Phase 1/2, First-in-Human, Open-Label, Dose-Escalation Study of TAK-186 (also known as MVC-101), An EGFR x CD3 COnditional Bispecific Redirected Activation (COBRA) Protein in Patients with Unresectable Locally Advanced or Metastatic Cancer

Phase 1/2, First-in-Human study of TAK-186 (also known as MVC-101) in Patients with Unresectable Locally Advanced or Metastatic Cancer

Sponsor: Takeda Development Center Americas, Inc.
500 Kendall St,
Cambridge, MA 02142 USA

Study Number: CP-MVC-101-01 (ClinicalTrials.gov ID: NCT04844073)

EudraCT Number: Not Applicable

Universal Trial Number: Not Applicable

Compound: TAK-186 * (MVC-101)
* The name after Takeda's acquisition of the compound is hereafter used in this protocol.

Date: 08 August 2024 **Amendment Number:** 8

Amendment History:

Date	Amendment Number	Amendment Type	Region
08 August 2024	8	Substantial	Global
01 July 2024	7 GB v1	Substantial	United Kingdom
01 December 2023	7	Substantial	Global
02 November 2023	6 UK v1	Non substantial	United Kingdom
08 February 2023	6	Substantial	Global
12 August 2022	5	Substantial	Global
07 March 2022	4	Substantial	Global
01 August 2021	3	Substantial	Global
25 May 2021	2	Substantial	Global
23 March 2021	1	Substantial	Global
04 November 2020	Original 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), pregnancy, and other applicable safety 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 (R2) 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,	Date _____	_____, MS, PhD,	Date _____
_____, Oncology Clinical Sciences		_____, Oncology Biostatistics	

_____, PhD,	Date _____
_____, Quantitative Clinical Pharmacology	

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 patients in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation, E6 Good Clinical Practice: 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 E](#)).

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

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1.3 Protocol Amendment 8: Summary of Changes and Rationale

This section describes the changes in reference to the protocol incorporating Amendment 8.

The primary purpose of this amendment is to add immune effector cell-associated neurotoxicity syndrome (ICANS) to the list of potential risks associated with TAK-186; add guidance on the management of ICANS; and add stopping rules for ICANS.

Additional changes based on emerging safety data include updates to the eligibility criteria for patients with central nervous system metastases, pulmonary embolism, noninfectious pneumonitis, pulmonary compromise or hypotension; add requirements for absolute neutrophil count, oxygen saturation level, hypotension, hypertension and afebrile to receive TAK-186 dose; add criteria for [REDACTED] after a dose interval of >14 days; add antiemetics to the list of premedications; add new section on postinfusion dexamethasone; clarify instructions on patient-reported outcome (PRO) assessments and clarify language for optional biopsy in dose escalation and backfill cohorts.

The stopping criteria for cytokine release syndrome (CRS) have also been revised to allow adequate time for patients experiencing Grade 3 or higher CRS to improve to Grade 2 or less. This allows more time for patients to wean-off from less aggressive supportive measures such as intravenous (IV) fluids and lower flow oxygen that are necessary to effectively manage CRS that has improved in severity.

Changes and revised text in the body of the protocol are also applied to the synopsis, where applicable.

Minor grammatical, editorial, formatting, and administrative changes that do not affect study conduct are applied throughout the document for clarification and administrative purposes.

Protocol Amendment 8		
Summary of Changes Since the Last Version of the Approved Protocol		
New Section Number and Title	Summary of Changes	Rationale
2.0 STUDY SUMMARY: Study Design 6.1 Overview of Study Design 6.1.1.1 [REDACTED] [REDACTED] 8.4 Dose Escalation Rules Appendix A Schedule of Events Appendix B PK, Immunogenicity, and Pharmacodynamic Biomarkers	Removed details of [REDACTED] dosing regimen.	To simplify protocol for effective study conduct and focus on the established study dosing regimen as [REDACTED] is no longer used.

Protocol Amendment 8		
Summary of Changes Since the Last Version of the Approved Protocol		
New Section Number and Title	Summary of Changes	Rationale
2.0 STUDY SUMMARY: Study Design 6.1 Overview of Study Design 9.5.15.3 Tumor Biopsy	Updated to clarify fresh paired tumor biopsy samples optional for patients in the dose-escalation phase and backfill cohorts.	Updated for clarity.
2.0 STUDY SUMMARY: Main Criteria for Inclusion 7.1 Inclusion Criteria	Inclusion criterion #13 updated for patients with symptomatic central nervous system metastases.	To further clarify enrollment requirements for patients with central nervous system lesion(s) to ensure that patients with new central nervous system metastasis are treated and stable prior to enrollment.
2.0 STUDY SUMMARY: Main Criteria for Exclusion 7.2 Exclusion Criteria	Exclusion criterion #7 updated definition of uncontrolled hypertension: systolic blood pressure >160 mmHg.	To make criteria consistent with Common Terminology Criteria for Adverse Events grading.
	Exclusion criterion #7 updated to exclude patients with pulmonary embolism requiring treatment occurring <3 months before initiation of TAK-186.	Updated to allow patients with non-acute pulmonary embolism (defined as >3 months) that is treated to be enrolled on study.
	Exclusion criterion #7 added hypotension Grade ≥ 2.	Revised to ensure adequate vital signs for enrollment due to potential for worsening with cytokine release syndrome.
	Exclusion Criterion #9 updated to state that patients with any history of Grade 2 or higher noninfectious pneumonitis should be excluded and patients with any radiation-induced pneumonitis or Grade 1 noninfectious pneumonitis that has resolved may be enrolled. Exclusion Criterion #10 updated to exclude patients with oxygen saturation ≤92% on room air or who require any supplemental oxygen.	Updated to further clarify exclusion criteria for pneumonitis and requirements for clinically significant pulmonary compromise.
4.3 Potential Risks and Benefits	Added immune effector cell-associated neurotoxicity syndrome to list of potential risks.	Revised to include as a potential risk based on recent events of immune effector cell-associated neurotoxicity syndrome seen on study.

Protocol Amendment 8		
Summary of Changes Since the Last Version of the Approved Protocol		
New Section Number and Title	Summary of Changes	Rationale
6.1.1.1 [REDACTED] [REDACTED]	[REDACTED] [REDACTED]	[REDACTED]
6.1.2 Cohort-Expansion Phase	Added study stopping rules for immune effector cell-associated neurotoxicity syndrome.	Revised to reflect immune effector cell-associated neurotoxicity syndrome as a potential risk based on recent events of immune effector cell-associated neurotoxicity syndrome seen on study.
	Updated study stopping rules for cytokine release syndrome.	Revised to allow improvement to Grade 2 or less for cytokine release syndrome events that are Grade 3 or higher. This allows more time for weaning of less aggressive supportive measures, such as intravenous fluids and lower flow oxygen, required to effectively manage cytokine release syndrome that has improved in severity.
6.3.2 End of Study/Study Completion Definition and Planned Reporting 9.5.15.3 Tumor Biopsy	Added statement about stopping the collection of samples at the end of study.	Added for clarity.
6.4 Posttrial Access 6.4.1 Duration of Posttrial Access	Updated language for posttrial access of TAK-186.	Included different mechanism options for posttrial access that can be pursued if posttrial access is warranted after study completion/termination.
8.5.1 Criteria for Beginning a Subsequent Treatment Cycle	Added requirements for absolute neutrophil count, oxygen saturation level, afreble, hypotension and hypertension, to receive TAK-186 dose.	Revised to include the requirement for continuing dosing to ensure adequate neutrophil count prior to dosing to allow for potential administration of tocilizumab and adequate vital signs prior to dosing due to the potential for worsening with cytokine release syndrome.
8.5.2 Additional Criteria to Start a Delayed Subsequent Dose	Added language for restarting dosing with TAK-186 after intervals of >14 days.	Updated for clarity.

Protocol Amendment 8		
Summary of Changes Since the Last Version of the Approved Protocol		
New Section Number and Title	Summary of Changes	Rationale
8.5.4 Criteria for Discontinuation of TAK-186	Added language to allow patients who continue to receive clinical benefit and tolerate therapy well after 7 cycles, and have no alternative treatment options the opportunity to continue on study treatment.	Updated for clarity.
8.6 Prohibited Concomitant Medications and Procedures	Criteria for prohibition of radiation therapy has been updated.	Updated for clarity.
8.7 Permitted Concomitant Medications and Procedures	Use of alcohol and other precautions has been revised and moved from Section 8.6 Prohibited Concomitant Medications and Procedures.	Updated for clarity.
8.9.1 CRS and Infusion-related reactions (IRRs) 10.1.5 SAE Definition	Added language that in circumstances where tocilizumab is not available, other anti-IL-6 agents (eg, siltuximab) or tocilizumab biosimilars may be used to treat cytokine release syndrome.	Updated for clarity.
8.9.1.1.2 Before Dose on Cycle 1 Days 1, 8, 15, 22	Added antiemetics to list of premedications	Updated for clarity and patient safety.
8.9.1.1.2 Before Dose on Cycle 1 Days 1, 8, 15, 22 8.9.1.1.3 Postinfusion Dexamethasone:	Added information on premedication dosing with dexamethasone and added a new section for postinfusion dexamethasone use.	Updated for clarity and patient safety.
8.9.1.1.4 Postinfusion Fluid Support on Cycle 1 Days 1, 8, 15, 22*:	Added statement about reducing or discontinuing postinfusion fluid support.	Updated for clarity and enhanced patient safety.
8.9.1.2 Management of CRS	Added information for management of Grade 1 events of cytokine release syndrome and dose range of dexamethasone for Grade 2 and Grade 3 events.	Updated for clarity on management of cytokine release syndrome.
8.9.2.1 Transaminase Elevations	Criteria for management of transaminase elevations re-ordered and updated.	Updated for clarity.
8.9.2.2 Bilirubin Elevations	Added levels to define Grade 1, Grade 2, and Grade 3 and 4 elevations; added criteria for discontinuation if event meets Hy's law.	Updated for clarity and enhanced patient safety.

Protocol Amendment 8		
Summary of Changes Since the Last Version of the Approved Protocol		
New Section Number and Title	Summary of Changes	Rationale
8.9.3.1 Management Guidelines for Patients Experiencing Dermatologic Toxicity	Updated criteria for discontinuation of TAK-186 after Grade 3 skin reaction.	Revised in the interest of enhanced patient safety.
0 BID: twice daily. Management of Neurologic Adverse Events (ICANS) Appendix A Schedule of Events, Table A1 and Table A2 Appendix J ASTCT ICANS Consensus Grading for Adults	New section and appendix added.	Information added to provide information on the management of immune effector cell-associated neurotoxicity syndrome.
9.5.14 Disease Assessment Appendix A Schedule of Events	Added information for the collection of magnetic resonance imaging scans of the brain at screening and on study for patients with lung cancer and as clinically indicated for other patients.	Revised for enhanced patient safety due to the high incidence of brain metastasis in patients with non-small cell lung cancer.
9.5.18 Patient-Reported Outcomes Assessments	Re-ordered text in section. Added instructions for patients who do not complete baseline patient-reported outcome assessments; clarified timing of the patient-reported outcome assessments.	Updated for clarity.
Appendix A Schedule of Events, Table A1 and Table A2: abbreviations and footnotes.	Added neurologic examination to physical examination assessments at baseline and after first symptoms of immune effector cell-associated neurotoxicity syndrome are suspected. Updated window for collection of vital signs. Specified that all patients must have brain scan with contrast at baseline and clarified criteria for repeat brain scans. Clarified timing of patient-reported outcome assessments.	Revised to reflect management of potential risk of immune effector cell-associated neurotoxicity syndrome.
Appendix B PK, Immunogenicity, and Pharmacodynamic Biomarkers, Table B1: abbreviations and footnotes.	Added pharmacokinetic and cytokine sampling times for events of immune effector cell-associated neurotoxicity syndrome.	Revised to clarify the timing and pharmacokinetic/pharmacodynamic markers collection related to immune effector cell-associated neurotoxicity syndrome.
Appendix I Clinical Chemistry, Hematology and Urinalysis	Updated chemistry panel: bicarbonate (HCO ₃) or carbon dioxide (CO ₂), and urinalysis tests: protein or albumin.	Revised for clarity.

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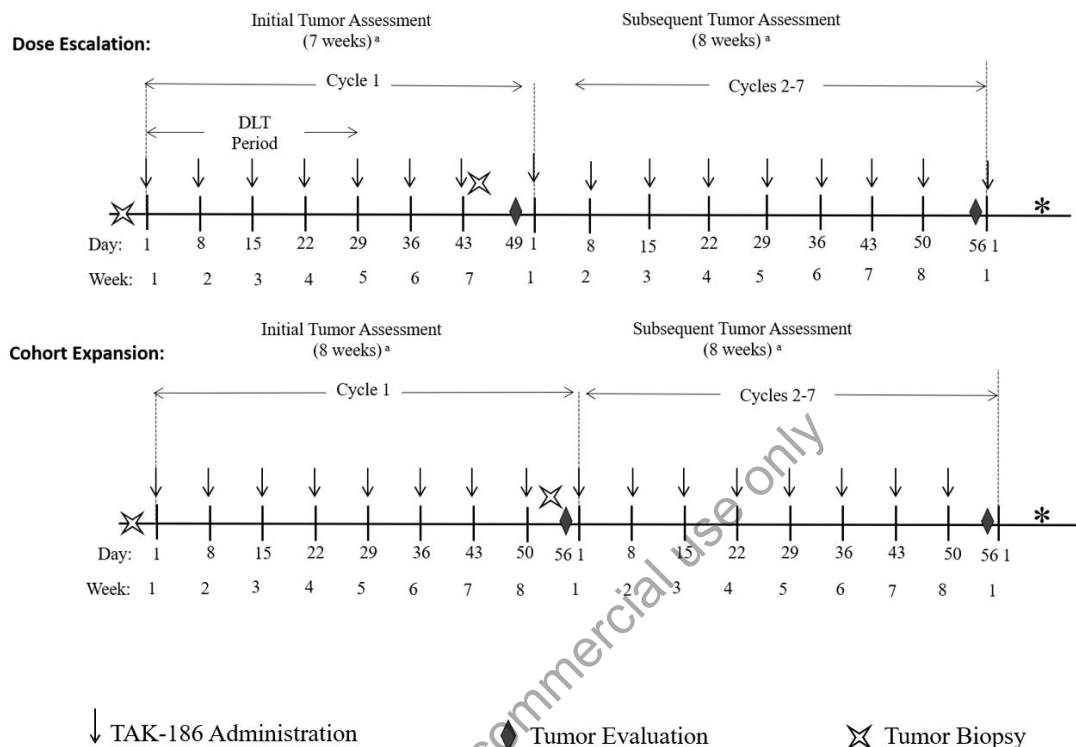
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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc.	Compound: TAK-186
Title of Protocol: A Phase 1/2, First-in-Human, Open-Label, Dose-Escalation Study of TAK-186 (also known as MVC-101), An EGFR x CD3 COnditional Bispecific Redirected Activation (COBRA) Protein in Patients with Unresectable Locally Advanced or Metastatic Cancer	EudraCT No.: Not applicable
Study Number: CP-MVC-101-01	Phase: 1/2
Study Design: This is a phase 1/2, open label, dose escalation and cohort expansion study designed to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, immunogenicity, and preliminary antitumor activity of TAK-186 administered by intravenous (IV) infusion once weekly (QW) in patients with unresectable, locally advanced or metastatic cancer. The study consists of a dose-escalation phase to determine the maximum tolerated dose (MTD). The dose-escalation phase will be followed by a cohort-expansion phase to assess efficacy and safety of TAK-186 as monotherapy in unresectable, locally advanced or metastatic solid tumors expressing epidermal growth factor receptor (EGFR), including non-small cell lung cancer (NSCLC), colorectal cancer (CRC), and head and neck squamous cell carcinoma (HNSCC) and may compare 2 different doses or regimens of TAK-186 during cohort expansion dose optimization in a 1:1 randomized fashion, if applicable. TAK-186 will be administered by IV infusion QW. Treatment will be continued until disease progression, completion of 7 cycles in the event of no radiologic evidence of tumor regression, withdrawal of consent, or death, whichever occurs first. For patients who continue to receive clinical benefit at the end of the 7 cycles, tolerate TAK-186 well, and have no alternative treatment options, the investigator may request to continue study treatment, after discussion with the sponsor's medical monitor. The study treatment schema is presented in Figure 1.	

Figure 1: Study Treatment Schema



^a For both the dose-escalation phase and cohort-expansion phase, tumor assessment will be performed at the end of each cycle and results should be reviewed before initiating the next treatment cycle with TAK-186.

* All patients will complete the end-of-treatment (EOT) visit 30 (+10) days after the last dose of study drug and then be followed for survival every 12 weeks (see [Appendix A](#)). The survival follow-up will be performed until the patient has died or is lost to follow-up or up to a maximum of 48 weeks after the last dose.

✕ Fresh paired tumor biopsy samples are optional for patients in the dose-escalation phase and backfill cohorts. For the cohort-expansion phase, patients will be required to consent to fresh paired tumor biopsies.

During dose escalation, TAK-186 infusion will be administered over 60 (±10) minutes for [REDACTED] the first cohort assigned dose, with all subsequent infusions administered over 30 (+10) minutes if the patient tolerates the first cohort-assigned dose well. If the patient experiences an infusion-related reaction during the 30-minute infusion, the duration of the infusion may be increased to 60 to 90 minutes in subsequent infusions. The duration of the initial TAK-186 infusion in cohort expansion will be based on the safety and PK evaluation in dose escalation but must be at least 30 minutes. Details on [REDACTED] are provided further below.

Patients will be monitored for signs and symptoms of cytokine release syndrome (CRS) and infusion-related reactions. During dose escalation with [REDACTED] patients will be monitored overnight for at least 24 hours following the [REDACTED] and the first cohort-assigned dose of TAK-186. Refer to Schedule of Events ([Appendix A](#)) for additional monitoring times. Starting with Cycle 2, investigators can monitor patients after each infusion for a length of time based on their clinical assessment of each patient. The monitoring schedule in the cohort-expansion phase may be modified based on the safety findings from dose escalation. Patients may be monitored overnight and admitted to the hospital upon development of symptoms suggestive of CRS during the in-clinic

observation period and otherwise, if clinically indicated. Tocilizumab must be available on-site where the patient is being monitored.

Tocilizumab is to be administered at the dose of 8 mg/kg at the onset of any sign potentially indicative of Grade 2 CRS, per American Society of Transplantation and Cell Therapy (ASTCT) CRS consensus grading, defined by fever (a temperature of $\geq 38^{\circ}\text{C}$) with hypotension not requiring vasopressors, and/or hypoxia requiring low-flow nasal cannula or blow-by oxygen. The maximum dose administered at one 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, provision of oxygen, and other supportive measures are recommended, according to institutional practice. Early administration of tocilizumab is advised to mitigate against more severe CRS.

Please refer to [Appendix H](#) for a more detailed description of ASTCT CRS consensus grading for CRS and [Table 8.a](#) for the general guidelines pertaining to management of patients who experience CRS.

The severity of adverse events (AEs) will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0) for non-CRS AEs. CRS will be graded according to ASTCT CRS consensus grading (Lee et al. 2019).

Dose-Escalation Phase:

Dose escalation will begin with 2 single-patient cohort escalation steps ([Figure 2](#), Table 1) and then be converted to a conventional 3+3 design (Table 1). The following dose escalation rules will be applied:

1. Dose increments will be limited to 100% for [REDACTED] full treatment doses up to the first [REDACTED] dose levels [REDACTED]
2. Maximum dose increments for the next dose cohort will be limited to 50% after the [REDACTED] dose for [REDACTED] full treatment doses if patients in a given dose cohort experience 2 or more Grade ≥ 2 CRS during the dose-limiting toxicity (DLT)-evaluation period.
3. Maximum dose increments will be limited to 30% for the next dose cohort for [REDACTED] full treatment doses if patients in a given dose cohort experience 2 DLTs during the DLT-evaluation period.

Intermediate doses may be explored during the dose-escalation phase of the study, based on review of the cumulative safety data and upon agreement between the investigators and the sponsor. Any decision to implement an intermediate dose will be documented and submitted to participating institutional review boards (IRBs)/independent ethics committees (IECs) and regulatory authorities, as appropriate, according to local requirements.

The highest dose of TAK-186 administered in the study will not exceed [REDACTED]. Administration of the initial TAK-186 dose to the first 3 patients treated in each subsequent dose escalation cohort will be staggered by a minimum of 48 hours.

Dose-Limiting Toxicity:

The DLT-evaluation period is defined as the time between the initial TAK-186 dose and Cycle 1 Day 28 in the dose-escalation phase. Patients are DLT-evaluable if they receive at least 3 target doses in a dose cohort without [REDACTED] or at least 2 target doses with [REDACTED] or experience a DLT within the first 28 days of treatment.

DLTs will be defined separately for hematologic, hepatic, and other nonhematologic events regardless of relationship except those events that are clearly due to extraneous causes, occurring during the DLT-evaluation period:

Hematologic DLT:

- Grade 4 neutropenia lasting >5 days.

- Grade ≥ 3 febrile neutropenia lasting >48 hours or Grade ≥ 3 febrile neutropenia associated with hemodynamic instability or infection.
- Grade 4 thrombocytopenia.
- Grade 3 thrombocytopenia and clinically significant bleeding.
- Grade ≥ 3 hemolysis.

The following events are excluded from the definition of hematologic DLT:

- Grade ≥ 3 lymphopenia.
- Grade 3 or higher anemia without associated clinically significant events.

Nonhematologic Hepatic DLTs:

Hepatic DLTs are defined as follows:

- Grade 3 aspartate aminotransferase (AST) or alanine aminotransferase (ALT), defined by increase of $>10.0 \times$ upper limit of normal (ULN).
- Grade 3 AST or ALT increase, defined by >5.0 to $10.0 \times$ ULN not resolving to Grade 2 (ie, >3.0 - $5.0 \times$ ULN) within 7 days and Grade 1 (ie, ULN to $3.0 \times$ ULN) within 14 days (unless patient enrolled with elevated transaminases secondary to metastases, then must resolve to baseline). Steroids must be tapered to ≤ 10 mg of prednisone or equivalent per day by Day 14.
- Grade 3 bilirubin increase, defined by an increase $>5.0 \times$ ULN.
- Grade 3 bilirubin increase, defined by an increase >3.0 to $5.0 \times$ ULN and not resolving to Grade 2 (ie, >1.5 - $3.0 \times$ ULN) within 7 days and Grade 1 (ie, $>ULN$ to $1.5 \times$ ULN) within 14 days. Steroids must be tapered to ≤ 10 mg of prednisone or equivalent per day by Day 14.
- Any event meeting the criteria for Hy's law as follows (all 3 features):
 - AST and/or ALT $>3 \times$ ULN.
 - Concurrent elevation of total bilirubin $>2 \times$ ULN $\pm$ signs of cholestasis.
 - No alternative etiology can be identified.

Other Nonhematologic DLTs:

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

- Grade 3 electrolyte abnormality lasting <72 hours without associated clinical complications and response to therapy.
- 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 diarrhea, constipation, or abdominal pain 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.
- Grade 3 skin toxicity resolving to Grade ≤ 2 within 7 days of initiation of oral or topical corticosteroids.
- Grade 3 inflammatory reaction in skin or soft tissue secondary to antitumor response (eg, metastatic disease, lymph nodes) resolving to Grade ≤ 1 within 7 days.

Safety data from dose escalation cohorts will be reviewed and all dose escalation decisions will be made jointly

by the investigators and sponsor.

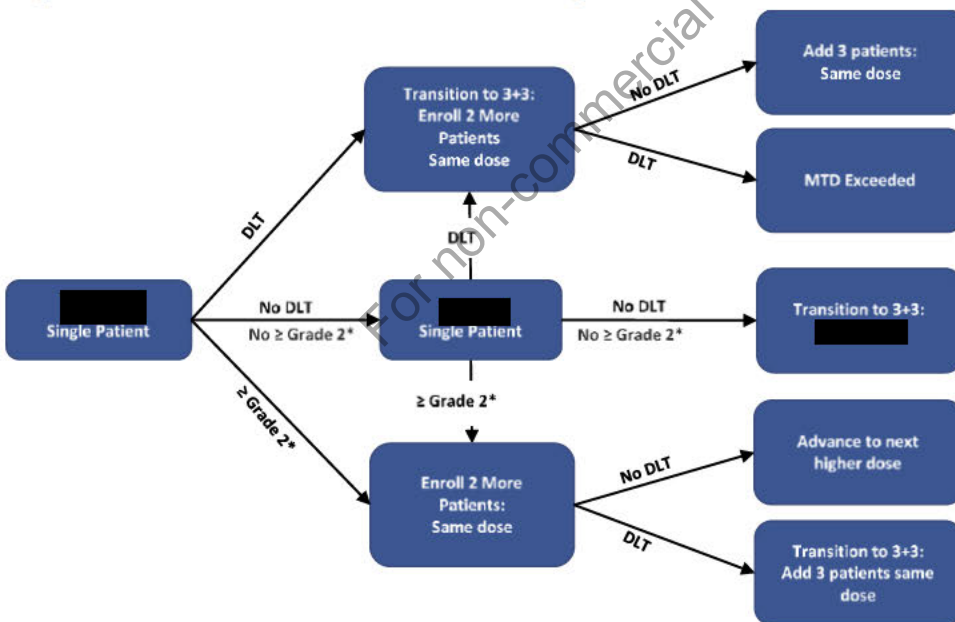
Patients who experience infusion delays of >14 days between 2 infusions during the DLT-evaluation period for any reasons other than DLT may remain on treatment, but will not be considered evaluable for DLT, and will be replaced in that dose cohort. In addition, patients who do not complete the full DLT-evaluation period and do not experience a DLT will be replaced in the same dose cohort.

In 3+3 dose escalation, if a DLT is observed in patients enrolled in the dose cohort, 3 additional patients will be added to the cohort to receive the assigned dose administration sequence. The decision to transition to the next cohort will be based on review of the aggregate safety, available PK, and pharmacodynamic data on all patients participating in the cohort through the DLT-evaluation period. The MTD is the highest dose level at which <33% of patients experience a drug-related DLT during the DLT-evaluation period.

Backfill in Dose Escalation Cohorts:

Any dose escalation cohort not exceeding the MTD can be expanded with additional patients for further evaluation of safety, PK, pharmacodynamics, and preliminary antitumor activity of TAK-186 after discussion between the investigators and sponsor.

Figure 2: Dose Escalation Plan in Single-Patient Dose Cohorts



AE: adverse event; DLT: dose-limiting toxicity; MTD: maximum tolerated dose; NCI CTCAE v5.0: National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

* Only select Grade 2 AEs, per CTCAE v5.0 trigger moving to a 3+3 design. See Section 8.3, Drug-Related Grade 2 AEs That Will Not Trigger Expansion to 3 Patients in the Single-Patient Cohorts.

Cohort-Expansion Phase:

During the initial cohort-expansion phase, approximately 30 patients with unresectable, locally advanced or metastatic NSCLC will be enrolled in a single arm cohort to receive TAK-186 with a dose determined from the dose-escalation phase of the study. Tumor assessment will be performed every 8 weeks (8 week/cycle) for patients enrolled in cohort expansion. An interim futility analysis is planned based on objective response rate (ORR) when the first 15 patients in the cohort become evaluable for efficacy by having at least 3 postbaseline scans or having discontinued therapy, whichever occurs earlier. Detailed futility boundaries are described in Section 13.2.

Based on the observed efficacy and safety data from the initial expansion cohort, more cohorts may be opened to assess different doses/regimens of TAK-186 in other EGFR expressing tumors, such as CRC and HNSCC, with approximately 30 patients in each tumor type.

The goals of the cohort-expansion phase are as follows:

- Provide additional information on the efficacy and safety of TAK-186, contributing to the determination of the recommended dose for pivotal study.
- Obtain additional data on the PK, pharmacodynamics, and immunogenicity of TAK-186.
- Assess the antitumor activity of TAK-186 in patients in selected EGFR expressing advanced solid tumors.

Survival Follow-up Period:

All patients will be followed for survival every 12 weeks for 48 weeks after end of treatment (EOT) visit by methods that include, but are not limited to, email, mail, telephone communication, or retrieval from online or other databases (eg, Social Security indexes) until the patient has died or is lost to follow-up. If EOT visit is not performed, patients will be followed for 48 weeks after the last dose of study drug.

Safety Reporting:

All hospitalizations for the sole purpose of drug administration and observations are considered planned for the purpose of the study and should not be considered serious adverse events (SAEs/AEs that occur during such planned hospitalization that meet the usual indication of hospitalization or prolongation of hospitalization by the investigator's medical judgement should be reported as SAEs. Hospitalization following the onset of symptoms suggestive of CRS for the purpose of close monitoring and supportive treatment should also be considered an SAE.

Rules for Patient Discontinuation/Continuation of Study Therapy:

Patients can continue to receive TAK-186 until any of the following conditions is met:

- Patient meets criteria for objective progression by modified Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 ([Appendix D](#)) ie, progression that is confirmed by a second scan after receiving one more cycle of TAK-186. *
- Occurrence of drug-related DLT during the DLT-evaluation period in dose-escalation phase. **

• Occurrence of intolerable toxicity at any time during treatment. • Completion of 7 cycles of TAK-186 without radiologic evidence of tumor regression. *** • Pregnancy. • Sponsor, investigator, or regulatory agency terminates the study. • Withdrawal of patient consent. * Patients showing unequivocal worsening of cancer-related signs and symptoms at first assessment of radiologic progressive disease (PD) by RECIST v1.1 may discontinue the study drug without waiting for confirmation of disease progression. Patients meeting the criteria of PD by RECIST v1.1 but otherwise experiencing substantial clinical benefit with acceptable toxicity may continue therapy based on investigator opinion, on a case-by-case basis with sponsor agreement. ** Patients in the dose-escalation phase with clinical benefit may resume TAK-186 after complete recovery from the DLT, per investigator request on a case-by-case basis with sponsor agreement. *** For patients who continue to receive clinical benefit at the end of the 7 cycles, tolerate TAK-186 well, and have no alternative treatment options, the investigator may request the sponsor in writing to continue study treatment.	
Primary Objectives: The primary objective of the study is to characterize the safety, tolerability, and DLTs of TAK-186 when administered IV QW to patients with unresectable, locally advanced or metastatic cancer.	
Secondary Objectives: The secondary objectives of the study are to: • Determine the recommended phase 2 dose (RP2D) of TAK-186 when administered IV QW to patients with unresectable, locally advanced or metastatic cancer. • Characterize the PK and immunogenicity of TAK-186. • Evaluate the preliminary antitumor activity of TAK-186 in patients with unresectable, locally advanced or metastatic cancer. • Compare TAK-186 antitumor activity efficacy endpoints using conventional RECIST version 1.1 (Eisenhauer et al. 2009) (Appendix C) versus modified RECIST v1.1 (Wolchok et al. 2009) (Appendix D).	
Patient Population: Patients aged ≥18 years or local legal adult age with unresectable, locally advanced or metastatic cancer.	
Number of Patients: For dose escalation, the number of patients can be up to approximately 48 patients. More than 48 patients may be enrolled depending on results during the study and the number of TAK-186 doses evaluated. This number does not account for replacement of non-evaluable patients or the backfill patients. Approximately 30 patients with NSCLC will be enrolled during the cohort-expansion phase. Additional patients with EGFR expressing solid tumors, such as CRC and HNSCC, may be enrolled with approximately 30 patients per tumor type. Further, patients may be enrolled to allow comparison between 2 different doses or regimens of TAK-186 for the selected tumor type(s) by 1:1 randomization to each dose/regimen (eg, 40 patients randomized 1:1 for NSCLC). Therefore, the total sample size of the cohort-expansion phase of the study is	Number of Sites: Estimated total: Up to 35 sites in Australia, South Korea, United Kingdom, and the United States

estimated to be up to approximately 210 patients.	
Dose Level(s): The starting dose of TAK-186 is [REDACTED] followed by sequential escalation up to a maximum of [REDACTED]	Route of Administration: TAK-186 is to be administered by IV infusion QW with a commercially available syringe pump over 60 (±10) minutes for [REDACTED] and the first cohort-assigned dose, and 30 (+10) minutes for all subsequent infusions (unless modified as outlined in study procedures).
Duration of Treatment: Patients will be treated with TAK-186 until disease progression, intolerable toxicity, completion of 7 cycles of therapy without radiologic tumor regression, withdrawal of consent, or death, whichever occurs first.	Period of Evaluation: Total time is expected to be approximately up to 25 months for each patient and approximately up to 5 years for the study.
Main Criteria for Inclusion: General - Age ≥18 years or local legal adult age. - Eastern Cooperative Oncology Group (ECOG) performance status of ≤1 (Appendix G). - Ability to provide informed consent and documentation of informed consent before initiation of any study-related tests or procedures that are not part of standard of care for the patient's disease. Patients must also be willing and able to comply with study procedures, including the acquisition of specified research specimens. - Life expectancy ≥12 weeks. - Measurable disease as per RECIST v1.1 criteria (Appendix C) and documented by computed tomography (CT) and/or magnetic resonance imaging (MRI). The definitions for measurable lesions are the same whether conventional and modified RECIST criteria are applied. Cutaneous or subcutaneous lesions must be measurable by calipers. Lesions to be used as measurable disease for the purpose of response assessment must either not reside in a field that has been subjected to prior radiotherapy or have demonstrated clear evidence of radiographic progression since the completion of prior radiotherapy and before study enrollment or have been radiated at least 6 months before study enrollment. Tumor Histology Types - Patients with pathologically proven, unresectable, locally advanced or metastatic solid tumors that based on literature reports are considered to express EGFR. During cohort expansion, patients with locally advanced or metastatic solid tumors expressing EGFR including advanced or metastatic NSCLC, CRC, and HNSCC are eligible for enrollment. For cohort expansion only: No more than 4 prior lines of systemic therapy for locally advanced or metastatic disease are allowed. Archival Tissue: - Patients must allow acquisition of existing formalin-fixed paraffin-embedded (FFPE) archival tumor sample, either a block or unstained slides. Patients who provide fresh pretreatment biopsy samples will not be required to submit archival tumor samples. Tumor Biopsy - Patients enrolling in cohort expansion must be willing to consent to mandatory pretreatment (during screening) and on-treatment fresh tumor biopsies. Once the target number of biopsies has been collected, additional paired pretreatment and on-treatment biopsies will not be required; sample collection will be optional after this time point.	

For fresh tumor biopsies, the lesion must be accessible (those occurring outside the brain or those that are accessible by an interventional or endoscopic procedure) for a low-risk biopsy procedure that does not place the patient at an unjustifiable risk in the opinion of the investigator.

Patients who have an archived biopsy specimen available that was obtained up to 90 days prior to treatment initiation and have received no other treatment from the time of biopsy until the start of treatment with TAK-186, may submit that archived specimen in lieu of a pre-treatment biopsy upon agreement from the sponsor.

Laboratory Features

9. Acceptable laboratory parameters as follows:

- Albumin ≥ 3.0 g/dL.
- Platelet count $\geq 75 \times 10^3/\mu\text{L}$.
- Hemoglobin ≥ 9.0 g/dL.
- Absolute neutrophil count $\geq 1.0 \times 10^3/\mu\text{L}$.
- ALT/AST $\leq 3.0 \times \text{ULN}$; for patients with hepatic metastases, ALT and AST $\leq 5 \times \text{ULN}$.
- Total bilirubin $\leq 1.5 \times \text{ULN}$, except patients with Gilbert's syndrome, who may enroll if the conjugated bilirubin is within normal limits.
- Creatinine clearance ≥ 30 mL/minute using Cockcroft-Gault equation.

Reproductive Features

10. 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 postmenopausal 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 postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

WOCBP must have a negative serum pregnancy test performed within 72 hours before the initiation of study drug administration. WOCBP must use 1 form of highly effective method and 1 additional effective (barrier) method of contraception at the same time throughout the study, starting at screening through 90 days after the last dose of TAK-186. 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 patient 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 patient).

11. Male patients with partners of childbearing potential must use barrier contraception during the entire study treatment period through 120 days after the last dose of study drug and must not donate sperm during this period. In addition, male patients should also have their partners use contraception (as documented for female patients) for the same period of time.

Previous Checkpoint Inhibitor Therapy

12. Patients who have previously received an immune checkpoint inhibitor (eg, anti-PD-L1, anti-PD-1, anti-CTLA-4) before enrollment must have checkpoint inhibitor immune-related toxicity resolved to either Grade ≤ 1 or baseline (before the checkpoint inhibitor) to be eligible for enrollment. Patients who experienced previous checkpoint inhibitor-related hypothyroidism are eligible for the study regardless of CTCAE grade resolution if well controlled on thyroid replacement hormones.
13. Central nervous system (CNS) metastases must have been treated and meet the following criteria at the time of enrollment:
 - Definitive therapy was completed at least 2 weeks prior to the first dose of TAK-186.
 - No evidence of radiographic CNS progression following definitive therapy and by the time of study screening.
 - Any CNS disease is asymptomatic for at least 7 days (unless symptoms are deemed irreversible by the investigator), the patient is off steroids for at least 7 days, and the patient is either off or on stable doses of anti-epileptic drugs for malignant CNS disease for at least 7 days.
 - No concurrent leptomeningeal disease or spinal cord compression.

Main Criteria for Exclusion:

1. Patients with a history of known autoimmune disease except for:
 - Vitiligo.
 - Psoriasis not requiring systemic treatment for >1 year before receiving TAK-186.
 - History of Graves' disease in patients now euthyroid for >4 weeks.
 - Hypothyroidism managed by thyroid replacement.
 - Alopecia.
 - Well-controlled diabetes type 1.
2. Major surgery or traumatic injury within 8 weeks before first dose of TAK-186.
3. Unhealed wounds from surgery or injury.
4. Radiation therapy <2 weeks before initiation of TAK-186.
5. Treatment with >10 mg per day of prednisone (or equivalent) or other immune-suppressive drugs within the 7 days prior to the initiation of study drug. Steroids for topical, ophthalmic, inhaled, or nasal administration are allowed.
6. Prior therapy within the following timeframe before the planned start of TAK-186 as follows:
 - Cytotoxic chemotherapy, small molecule inhibitors, radiation, interventional radiology procedure, or similar investigational therapies: ≤ 2 weeks or 5 half-lives, whichever is shorter.
 - Monoclonal antibodies, antibody-drug conjugates, radioimmunoconjugates, or similar investigational therapies: ≤ 4 weeks.
 - Concurrent use of hormones either to maintain castrate levels of testosterone in patients with castration-sensitive prostate cancer or for non-cancer-related conditions (eg, insulin for diabetes, hormone replacement therapy) is acceptable. Bisphosphonates are permitted for supportive care of bone metastases (eg, breast or prostate cancer) or osteoporosis.
7. Clinically significant cardiovascular/vascular disease including:
 - Myocardial infarction or unstable angina <6 months before the initiation of study drug.
 - Clinically significant cardiac arrhythmia (eg, with potential for hemodynamic instability).

- Uncontrolled hypertension: systolic blood pressure >160 mmHg, diastolic blood pressure >100 mmHg.
 - Stroke, or transient ischemic attack <6 months before initiation of TAK-186.
 - Pulmonary embolism requiring treatment occurring <3 months before initiation of TAK-186.
 - Fridericia's corrected QT interval (QTcF) prolongation >480 msec.
 - Congestive heart failure (New York Heart Association Class III or IV).
 - Pericarditis/clinically significant pericardial effusion.
 - Myocarditis.
 - Hypotension Grade ≥ 2 .
 - Vasculitis not resolved <6 months before TAK-186 initiation.
8. Clinically significant gastrointestinal disorders including:
- Gastrointestinal perforation <6 months before study drug administration. Patients must have documented evidence (eg, upper endoscopy, colonoscopy) of completely healed area of prior perforation.
 - Gastrointestinal bleeding <2 months before study drug administration. Patients must have documented evidence (eg, upper endoscopy, colonoscopy) of completely healed area of prior bleeding.
 - Pancreatitis <6 months before the initiation of study drug. Patients must have a CT scan negative for evidence of remaining disease or normal pancreatic enzyme levels for >4 weeks before the initiation of TAK-186.
 - Diverticulitis flare <2 months before study drug administration. Patients must have a CT scan negative for evidence of remaining disease before the initiation of TAK-186.
 - History of Crohn's disease or ulcerative colitis.
9. Inflammatory process that has not resolved for ≥ 4 weeks from the date of first study dose. Patients with any history of Grade 2 or higher noninfectious pneumonitis will be excluded. (Patients with any radiation-induced pneumonitis or Grade 1 noninfectious pneumonitis that has resolved may be eligible for enrollment.)
10. Clinically significant pulmonary compromise: oxygen saturation $\leq 92\%$ on room air and requirement for any supplemental oxygen at the time of enrollment).
11. Active viral, bacterial, or systemic fungal infection requiring parenteral treatment within 7 days before the initiation of study drug. Systemic antiviral, antifungal, or antibacterial therapy must be completed >1 week before the initiation of study drug. Antimicrobial prophylaxis (eg, for *Pneumocystis carinii* infection) may continue the antimicrobial for that purpose.
12. Vaccination with any live virus vaccine within 4 weeks before the initiation of study drug administration or vaccination with other vaccines 2 weeks before the initiation of study drug administration. Inactivated annual influenza vaccination is allowed.
13. Patients who are known to be HIV positive or who are known to be hepatitis B or hepatitis C positive. Patients treated for hepatitis C must have viral titers of 0 for ≥ 2 years to be eligible. Patients with hepatitis B having undetectable or ≤ 500 IU hepatitis B viral titers are eligible. Patients with hepatocellular carcinoma (HCC) and known history of hepatitis B are excluded, regardless of hepatitis B viral titers.
14. Second primary invasive malignancy not in remission for ≥ 3 years. Exceptions include non-melanoma skin cancer, cervical carcinoma in situ, resected melanoma in situ, or any malignancy considered to be indolent and never having required therapy, except for indolent lymphoid malignancies.
15. Any serious underlying medical or psychiatric condition that would preclude understanding and rendering of informed consent or impair the ability of the patient to receive or tolerate the planned treatment.
16. Known hypersensitivity to TAK-186 (or any excipient contained in the drug or diluent formulation) or known hypersensitivity to tocilizumab.
17. Investigative site personnel or sponsor personnel directly affiliated with this study.
18. Prisoners or other individuals who are involuntarily detained.
19. Any medical or non-medical issue that would contraindicate the patient's participation in the study or confound the results of the study.

20. Female patients who are breastfeeding.

Endpoints:

The primary study endpoints are:

- Non-CRS AEs, according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.
- CRS, according to ASTCT CRS consensus grading (Lee et al. 2019).
- DLTs during the dose-escalation phase

The secondary endpoints are:

- RP2D selected on the basis of comprehensive safety, PK, and efficacy data.

Statistical Considerations:

Analysis Populations

The populations that will be used for analysis of the study data are defined:

- **DLT-evaluable population:** all patients who receive at least 3 target doses of TAK-186 in a dose cohort [REDACTED] or at least 2 target doses of TAK-186 [REDACTED] or experience a DLT within the DLT-evaluation period.
- **Safety population (All-Treated):** all patients who receive at least 1 dose of TAK-186. The safety population will be used for safety and efficacy analyses. Patients who receive at least 1 dose of TAK-186 and have relevant blood sampling will be included in PK, immunogenicity, and pharmacodynamics analyses. Details are as follows:
 - **PK population:** all patients who receive at least 1 dose of TAK-186 and sufficient PK data to reliably estimate 1 or more PK parameters.
 - **Immunogenicity population:** all patients who receive at least 1 dose of TAK-186 and have a baseline immunogenicity sample and at least 1 postbaseline immunogenicity sample for assessment.
 - **Pharmacodynamics population:** all patients who receive at least 1 dose of TAK-186 and have sufficient dosing and pharmacodynamics data to reliably measure pharmacodynamics parameters.

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 response summaries will be provided by dose level and schedule, and/or by tumor type (NSCLC, CRC, HNSCC, etc). Response rates may be calculated for specific disease subgroups, if appropriate.

Efficacy:

Efficacy will be evaluated in all-treated population (equivalent to the safety population).

Response duration will be calculated for responders as the time from initial response (complete response or partial response) to the time of documented PD or death, whichever occurs first. Response rates will be determined using both conventional RECIST 1.1 ([Appendix C](#)) and modified RECIST v1.1 criteria ([Appendix D](#)). Two-sided exact 90% CIs will be constructed around the ORRs.

Kaplan Meier methods will be used to estimate duration of response (DoR), progression-free survival (PFS), and overall survival (OS).

The primary analysis of this study will be carried out when all patients have discontinued therapy or, if continuing therapy, have data available through approximately 6 months of follow-up.

Safety: AE/SAEs will be summarized by frequency and severity.

PK Analysis: Individual TAK-186 plasma concentrations will be listed by time point and summarized by dose level. Individual and mean TAK-186 plasma concentration-time profiles for each dose level will also be presented graphically. PK parameters will be listed and summarized using descriptive statistics, including

arithmetic and geometric mean, median, standard deviation, coefficient of variation (CV), geometric 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 proportion of patients who are negative for antidrug antibodies (ADAs) at baseline and become positive in this assay, the proportion of patients who are negative at baseline and remain negative, those who have positive ADAs at baseline that increase or decrease in titer over the course of treatment, and the proportion of patients with neutralizing ADAs among those with ADA-positive samples will be summarized.

Pharmacodynamic Analysis: Pharmacodynamic parameters such as, but not limited to, those listed under Pharmacodynamics/Biomarkers and corresponding changes from baseline, may be summarized and/or may also be presented graphically, as possible depending on the data. Possible associations between changes in pharmacodynamic measures of interest and TAK-186 dose and exposure may be explored.

Sample Size Justification:

Dose escalation will begin with 2 single-patient cohort escalation steps and then be converted to a conventional 3+3 design. The sample size for the dose-escalation phase is up to approximately 48 patients.

The cohort-expansion phase of this study is designed to provide additional data on efficacy and safety of TAK-186. The study design with planned sample size of approximately 30 patients per tumor type has reasonable operating characteristics. Two potential dose levels or regimens might be further studied with 1:1 randomization in approximately 20 patients at each dose level or regimen for the selected tumor type(s) to optimize dose selection. The estimated total sample size for the cohort expansion is up to approximately 210 patients.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of 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 Principal Investigator/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 and the study medication, 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 (CSR) 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
ADA	antidrug antibody
adTAK-186	TAK-186 active dimer
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC _{last}	area under the concentration-time curve from time 0 to last quantifiable concentration
BOR	best overall response
BRCA	breast cancer gene
CD3	cluster of differentiation 3
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
CL	clearance
cmTAK-186	cleaved monomer of TAK-186
CNS	central nervous system
COBRA	COnditional Bispecific Redirected Activation
CPS	combined positive score
CR	complete response
CRC	colorectal cancer
CRO	contract research organization
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
cTAK-186	cleaved TAK-186
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CV	coefficient of variation
CYP	cytochrome P450
DLT	dose-limiting toxicity
dMMR	deficient mismatch repair
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOI	end of infusion
EOT	end of treatment

Abbreviation	Definition
EXTREME	cetuximab + cisplatin or carboplatin + fluorouracil
FACT	Functional Assessment of Cancer Therapy
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HCC	hepatocellular carcinoma
HNSCC	head and neck squamous cell carcinoma
HNSTD	highest non-severely toxic dose
HPV	human papillomavirus
HR	hazard ratio
IB	investigator's brochure
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	immune effector cell-associated encephalopathy
ICF	informed consent form
ICH	International Council for Harmonisation
iCRO	imaging contract research organization
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IL	interleukin
IRB	Institutional Review Board
IRR	infusion-related reaction
IV	intravenous
LFT	liver function test
■	■
MABEL	minimum anticipated biological effect level
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MMP	matrix metalloproteinase
mNSCLC	metastatic non-small cell lung cancer
MRI	magnetic resonance imaging
MSI-H	microsatellite instability high
MSS	microsatellite stable
MTD	maximum tolerated dose
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not evaluable
NK	natural killer
NOAEL	no observed adverse effect level
NSCLC	non-small cell lung cancer
NSG	nonobese diabetic severe combined immunodeficient gamma
ORR	objective response rate
OS	overall survival
PARP	poly ADP ribose polymerase

Abbreviation	Definition
PD	progressive disease
PD-L1	programmed death ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency of Japan
PO	per os; by mouth
PR	partial response
PRO	patient-reported outcome
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
QTcF	QT interval by Fridericia correction
QW	once weekly
RBC	red blood cell
RCC	renal cell carcinoma
RDE	recommended dose for expansion
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
scFv	single chain variable fragment
SD	stable disease
sdAb	single domain antibody variable domains
SOC	System Organ Class
SOI	start of infusion
SUSAR	suspected unexpected serious adverse reaction
TAS-102	trifluridine and tipiracil
TCR	T-cell receptor
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
T _{max}	time to maximum plasma concentration
TME	tumor microenvironment
TNF α	tumor necrosis factor-alpha
UK	United Kingdom
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
V _H	heavy chain variable domain
V _L	light chain variable domain
WOCBP	woman of childbearing potential
WT	wild-type

3.4 Corporate Identification

TDC Americas Takeda Development Center Americas, Inc

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4.0 INTRODUCTION

4.1 Background

After Takeda's acquisition of Maverick Therapeutics, the sponsorship of this study was changed to Takeda. Takeda changed the name of its conditionally active epidermal growth factor receptor (EGFR)-targeting T-cell engaging bispecific recombinant protein from MVC-101 to TAK-186. The drug candidate will hereafter be described in this protocol as TAK-186 to reflect the sponsor's designated name. MVC-101 is retained in parenthesis to clarify the genealogy of the drug product.

4.1.1 Disease Background

Patients with unresectable, locally advanced or metastatic EGFR expressing tumors will be enrolled in this clinical study. Once the recommended doses for expansion (RDEs) are determined in the dose-escalation phase of the study, patients with unresectable locally advanced or metastatic EGFR-expressing solid tumors, which may include non-small cell lung cancer (NSCLC), colorectal cancer (CRC), and head and neck squamous cell carcinoma (HNSCC) will be enrolled in the cohort-expansion phase of the study. 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 EGFR expression observed in these cancers, and 3) the rapidly accumulating evidence (conclusive for NSCLC and HNSCC) that immune modulation with checkpoint inhibitors that enhance T cell activity towards cancer cells has substantial antitumor activity in these tumors.

4.1.1.1 *Non-Small Cell Lung Cancer*

In Australia, it is estimated 13,092 patients were diagnosed with lung cancer and the vast majority of these cases will be one of the NSCLC histologies in 2020 ([Sung et al. 2021](#)). The diagnosis of NSCLC is most often made when the disease is advanced or metastatic (Stage IIIB/IV), beyond the time when it can be controlled with localized therapies, leaving only systemic treatment options. The survival remains dismal in advanced disease as only 17% of patients survive at least 5 years. In 2020, lung cancer was expected to account for approximately 18% of all cancer-related deaths in Australia ([lung cancer/canceraustralia.gov.au/statistics](http://lungcancer/canceraustralia.gov.au/statistics), [Lung Cancer] Accessed 05 July 2022).

In the United States (US), approximately 236,740 new cases of lung cancer (117,910 in men and 118,830 in women) and approximately 130,180 deaths from lung cancer (68,820 in men and 61,360 in women) are estimated in 2022, according to the American Cancer Society ([American Cancer Society 2022](#)).

Lung cancer is expected to be the most commonly diagnosed cancer and the leading cause of cancer death in Canada in 2022. An estimated 30,000 new cases of lung cancer are expected with a similar proportion for men and women. The age-standardized incidence rate for lung cancer is estimated to be 61.0 per 100,000 with an age-standardized mortality rate of 48.6 per 100,000 for

men and an age-standardized incidence rate of 57.2 per 100,000 with an age-standardized mortality rate of 39.5 per 100,000 for women ([Brenner et al. 2022](#)).

In NSCLC, approved checkpoint inhibitors such as nivolumab and pembrolizumab have demonstrated substantial antitumor activity and are changing the treatment paradigm in driver mutation-negative NSCLC. Checkpoint inhibitor therapies are now approved as monotherapy or combination therapy with chemotherapy in first-line, and as monotherapy in second-line ([Keytruda \(pembrolizumab\) Injection for Intravenous Use 2021](#); [Opdivo \(nivolumab\) Injection for Intravenous Use 2021](#)).

Checkpoint inhibitors given after progression following platinum-based chemotherapy demonstrated an objective response rate (ORR) of approximately 15%, including patients with different PD-L1 status in driver mutation-negative NSCLC. The ORR in patients with a Tumor Proportion Score of 50% was approximately 30%. Of note, the ORR of the standard of care comparator, docetaxel, was approximately 9% in this trial ([Herbst et al. 2016](#)). Checkpoint inhibitor therapy is approved as first-line therapy in driver mutation-negative NSCLC, or in patients with EGFR mutation or anaplastic lymphoma kinase fusion who have progressed following relevant tyrosine kinase inhibitor (TKI); second-line therapy is anecdotal use of alternative chemo regimens as these treatments have not been rigorously evaluated after checkpoint inhibitor failures.

EGFR mutations play a significant role in driving tumor development and progression in approximately 20% of NSCLC adenocarcinomas (EGFR-mutant NSCLC). Unlike driver mutation-negative NSCLC, mNSCLC does not respond well to checkpoint inhibitor therapy after anti-EGFR therapy for unclear reasons. One theory for lack of checkpoint inhibitor efficacy is that mNSCLC does not carry as high a mutational load as driver mutation-negative NSCLC, making these tumors less amenable to native adaptive immune attack by T-cells ([Miura and Sunaga 2018](#)). Despite the significant advances in NSCLC treatment with checkpoint inhibitor therapy, advanced disease remains largely incurable. NSCLC is a very good candidate for evaluation of TAK-186 with a high percentage of tumors expressing EGFR and demonstrated susceptibility to immune modulation with monotherapy checkpoint inhibitors. EGFR mutation positive NSCLC represents an especially interesting opportunity for TAK-186 in that it may bring to bear a T-cell mediated attack on tumors that exhibit a lack of response to checkpoint inhibitor therapy.

4.1.1.2 CRC

CRC is the third most common cancer diagnosed and the third leading cause of cancer-related deaths in the US. Approximately 106,180 new cases of colon cancer and 44,850 new cases of rectal cancer are estimated and CRC is expected to cause approximately 52,580 deaths in 2022, according to the American Cancer Society ([American Cancer Society 2022](#)). Approximately 16,400 patients in Australia were diagnosed with CRC in 2019, with an estimated 6,000 deaths (Australian Institute of Health and Welfare, 2020).

Approximately 50% to 60% of patients afflicted with CRC have metastatic disease at diagnosis, with common sites of involvement including liver, lymph nodes, lung, peritoneum, and soft tissues (Lee et al. 2007; Van Cutsem 2006; Yoo et al. 2006), and about half of early-stage patients eventually develop metastatic or advanced disease (Martini et al. 2017). Survival outcomes for patients with metastatic CRC are dismal, with the 5-year survival rate approximately 14% (Bray et al. 2018). Patients with unresectable locally advanced or metastatic CRC most commonly receive combination regimens with one or more of the following agents: 5-FU/leucovorin, irinotecan, capecitabine, oxaliplatin with or without anti-vascular endothelial growth factor (VEGF) agents (bevacizumab, aflibercept) or anti-EGFR antibodies (cetuximab, panitumumab), or multi-specific TKIs (regorafenib). Common chemotherapy regimens include FOLFOX (folinic acid, 5-fluorouracil, and oxaliplatin), FOLFIRI (folinic acid, 5-fluorouracil, and irinotecan), FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin), or CapeOx (oxaliplatin and capecitabine), administered with a biological agent depending on K-Ras mutation status and contraindications. The most common biologic agent used in the first-line setting is the VEGF inhibitor, bevacizumab (National Comprehensive Cancer Network 2022). For the roughly 50% to 60% of patients who have K-Ras wild-type (WT), the biologic agent may consist of an EGFR inhibitor, such as cetuximab or panitumumab. In K-Ras-mutant CRC, the EGFR inhibitors, panitumumab, or cetuximab are not used, and biologic therapy is limited to bevacizumab.

Trifluridine and tipiracil (TAS-102) (Mayer et al. 2015) and regorafenib (Grothey et al. 2013) are approved as third-line therapy in the US. While these agents provide statistical improvements in overall survival (OS), the benefit is relatively small. In a phase 3 trial of TAS-102, the median OS was 7.1 months (95% CI: 6.5, 7.8) with TAS-102, and 5.3 months (95% CI: 4.6, 6.0) with placebo, hazard ratio (HR 0.68 [95% CI: 0.58, 0.81; $p < 0.001$]). Regorafenib is approved in Australia for metastatic CRC previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, with an anti-VEGF therapy, and, if K-Ras WT, with an anti-EGFR therapy. In a phase 3 trial, prolongation of OS was observed with regorafenib (HR, 0.77; [95% CI: 0.64, 0.94]; $p = 0.0102$). The median survival was 6.4 months (95% CI: 5.8, 7.3) with regorafenib and 5.0 months (95% CI: 4.4, 5.8) with placebo.

Compared with HNSCC and NSCLC, patients with CRC have had only modest improvement in survival with new therapies, and this is largely due to the lack of efficacy with checkpoint inhibitor therapy, outside of the small group of patients with microsatellite instability high (MSI-H) CRC. The exact way in which microsatellite stable (MSS) CRC evades immune detection and destruction is yet to be fully understood. MSS CRC can be classified into 2 patterns representative of noninflamed tumors. The first is through immunological ignorance, in which tumors are poorly infiltrated by lymphocytes; and second, through an immunosuppressive microenvironment created to evade immune surveillance by recruiting myeloid-derived suppressor cells or by secreting factors including TGF β , to suppress chemokines and cytokines required to facilitate T-cell infiltration into tumors (Hegde et al. 2016).

TAK-186 has the potential to bring T-cells to tumors and induce T-cell infiltration and attack in tumors that are naturally noninflamed. Theoretically, TAK-186 would be able to overcome either

immune ignorance or immune-suppressive environments that may be in part responsible for CRC immune evasion. In addition, because a high percentage of both left- and right-sided CRC tumors express EGFR, TAK-186 will employ EGFR to essentially “hook” T-cells to the tumor. Because the drug is delivered systemically, all CRC tumors should be equally amenable to TAK-186. This mechanism should apply equally well to K-Ras-mutant CRC.

Because of the relatively high percentage of tumors that express EGFR, TAK-186 promises to offer substantial clinical benefit in patients with immunologically quiescent CRC.

4.1.1.3 *Head and Neck Squamous Cell Cancer*

Cancers of the head and neck constitute a collection of tumors that begin in the squamous cells lining the mucosal surfaces of the head and neck, referred to as HNSCC, and are categorized by the area of the head or neck in which they begin: oral cavity, pharynx (includes nasopharynx, oropharynx, and hypopharynx), paranasal sinuses, nasal cavity, and salivary glands. Infection with human papillomavirus (HPV), specifically HPV-16 and HPV-18, are risk factors for developing HNSCC, particularly oropharyngeal cancers involving the tonsils or the base of the tongue ([Chaturvedi et al. 2011](#)).

Head and neck cancers account for about 4% of all cancers in the US, and an estimated 66,470 people (48,520 men and 17,950 women) will be diagnosed with head and neck cancer in 2022. Worldwide, an estimated 562,328 people were diagnosed with head and neck cancer in 2020 ([American Cancer Society 2022](#)).

Although cancers originating in the salivary glands are usually classified as part of head and neck cancers, salivary gland cancers can arise from multiple types of cells within a gland and therefore have a heterogeneous histological pathology compared to the other head and neck cancers. Therefore, patients with salivary gland cancers will not be evaluated in this study.

When HNSCC is detected in its earliest stages and treated, it is curable with excellent long-term OS. However, once patients develop locally recurrent or metastatic disease, HNSCC remains essentially incurable and 5-year survival is less than 50% ([American Cancer Society 2019](#)). Monoclonal antibodies targeting the T-cell immune checkpoint inhibitors have recently demonstrated substantial antitumor activity in patients with advanced HNSCC. Pembrolizumab received accelerated approval based on response rate and durability of response in patients with recurrent or metastatic HNSCC whose disease had progressed after platinum-containing chemotherapy (2nd-line), irrespective of the HPV status. The ORR following pembrolizumab in this population was approximately 16% ([Chow et al. 2016](#)).

Pembrolizumab also recently demonstrated substantial antitumor activity in a phase 3 trial relative to standard of care (EXTREME: cetuximab + cisplatin or carboplatin + fluorouracil) in patients with untreated (first-line) recurrent or metastatic HNSCC ([Burtneess et al. 2018](#); [Rischin et al. 2019](#)). Patients with a high (≥ 20) or any level (≥ 1) of combined positive score (CPS) who received pembrolizumab had a statistically significant improvement in OS versus EXTREME regimen: HR of 0.61 (0.45-0.83) $p=0.0007$ and HR of 0.78 (0.64-0.96) $p=0.0086$, respectively.

The ORRs with pembrolizumab in the CPS ≥ 20 and ≥ 1 groups were 23% and 19%, respectively (Kulangara et al. 2019).

Taken together, these data demonstrate that strong antitumor activity against HNSCC can be achieved by stimulating T-cells targeting tumor cell surface antigens. HNSCC is one of the more amenable solid tumors to immune attack. In fact, with a strong likelihood of pembrolizumab moving into first-line treatment for HNSCC, the role of chemo-based regimens such as EXTREME is in flux, as such therapies have not been evaluated after failure with checkpoint inhibitor therapy.

One of the most striking characteristics of HNSCC is the extremely high percentage of tumors ($\geq 90\%$) overexpressing EGFR (Wheeler et al. 2015), a marker that is inversely correlated with survival (Ang et al. 2002; Pectasides et al. 2011; Zimmermann et al. 2006). EGFR overexpression and the resultant increase in proliferative signaling is considered to be one of the drivers of HNSCC (Feldman et al. 2016); however, EGFR mutations are rare and escape from EGFR inhibitors is generally through alternative pathway signaling (Perisanidis 2017; Temam et al. 2007).

Although the recent advances in therapy for advanced HNSCC have increased the OS for patients, the disease remains incurable and pembrolizumab did not increase the response rate over EXTREME. The constitutively high level of EGFR expression in HNSCC, and strong antitumor activity of therapies that enhance T-cell activity, leading to substantial antitumor activity, make HNSCC a highly suitable candidate to target with TAK-186.

4.1.2 Background on EGFR and CD3

4.1.2.1 EGFR

EGFR is a receptor tyrosine kinase in the ErbB family. Overexpression of EGFR is frequently observed in multiple human cancers, including HNSCC, CRC and NSCLC (Jin et al. 2018; Mendelsohn and Baselga 2000). The percentage of HNSCC cancers overexpressing EGFR is considered to be $>90\%$ (Byeon et al. 2019). EGFR overexpression is more variable in CRC (35%-75%) and NSCLC (43%-89%) compared with HNSCC (Scagliotti et al. 2004; Swinson et al. 2004).

However, EGFR immunohistochemistry (IHC) has been shown to be a poor marker in predicting effectiveness of cetuximab in CRC and thus EGFR IHC testing is generally considered an inadequate indicator of patient exclusion for treatment with an anti-EGFR targeting monoclonal antibody (Chung et al. 2005; Kang et al. 2012). Similarly, a lack of a consistent method of evaluating EGFR expression in NSCLC has caused a disparity in reporting the EGFR across studies evaluating expression, however some studies report EGFR, at any level of expression, in $>90\%$ of tumors (Scagliotti et al. 2004; Shepherd et al. 2005).

Two distinct therapeutic strategies used to block EGFR in cancer treatment (monoclonal antibodies [eg, cetuximab, panitumumab] and small molecule TKIs [eg, gefitinib, osimertinib]) have demonstrated clinical benefit. Unfortunately, mutations in EGFR and downstream signaling

molecules are associated with poor clinical response to current EGFR-targeted therapy (Sequist et al. 2007). Oncogene aberrations such as K-Ras mutations are one of the most commonly occurring aberrations and found in 25% of NSCLC and 40% to 50% of CRC (Maus et al. 2014). K-Ras mutations play a critical role in primary resistance to EGFR-targeted therapy among EGFR-positive cancers. An effective treatment using EGFR-targeting therapy in cancers with K-Ras mutations is not currently available (Califano et al. 2012).

In addition to the high percentage of EGFR-expressing HNSCC, CRC and NSCLC's (with a substantial percentage of overexpression), increased matrix metalloproteinase (MMP) activity has been shown to be increased with higher expression of EGFR in these tumors (Cox et al. 2000; Jimenez et al. 2015; O-Charoenrat et al. 2000; Swinson et al. 2004; Zuo et al. 2017).

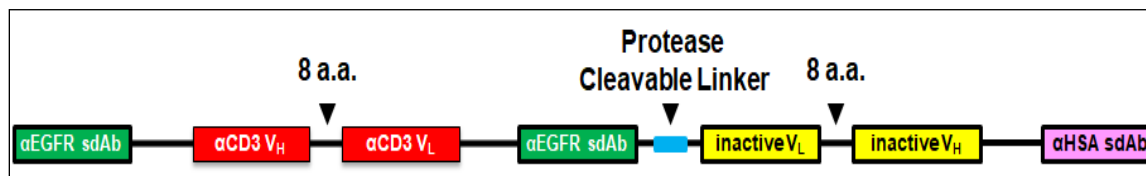
4.1.2.2 CD3

Cluster of differentiation 3 (CD3) is an invariant complex of proteins that is required for expression of and signaling through the antigen-specific T-cell receptor (TCR) on T-cells. CD3 is a transmembrane complex with four distinct subunits (CD3 γ , CD3 δ , CD3 ϵ , and CD3 ζ) non-covalently linked to the TCR. The TCR:CD3 complex is responsible for signal transduction in T-cells, including activation during immune response (Guy and Vignali 2009; Smith-Garvin et al. 2009). CD3 is expressed almost exclusively by T-cells and is present in all stages of T-cell development (Chetty and Gatter 1994).

4.1.3 TAK-186 Background

TAK-186 is a conditionally-active EGFR-targeting T-cell engaging bispecific recombinant antibody being developed for the treatment of cancer. TAK-186 is a polypeptide composed of 895 amino acids (94.7 kilodalton). The amino acid sequence of TAK-186 has homology to known structural domains. TAK-186 has 3 single domain antibody variable domains (sdAb), 2 heavy chain variable domains (V_H), and 2 light chain variable domain (V_L) regions (Figure 4.a).

Figure 4.a TAK-186 Construct Design



a.a.: amino acid; α : anti; CD3: cluster of differentiation 3; EGFR: epidermal growth factor receptor; HSA: human serum albumin; sdAb: single domain antibody variable domains; V_L: light chain variable domain; V_H: heavy chain variable domain.

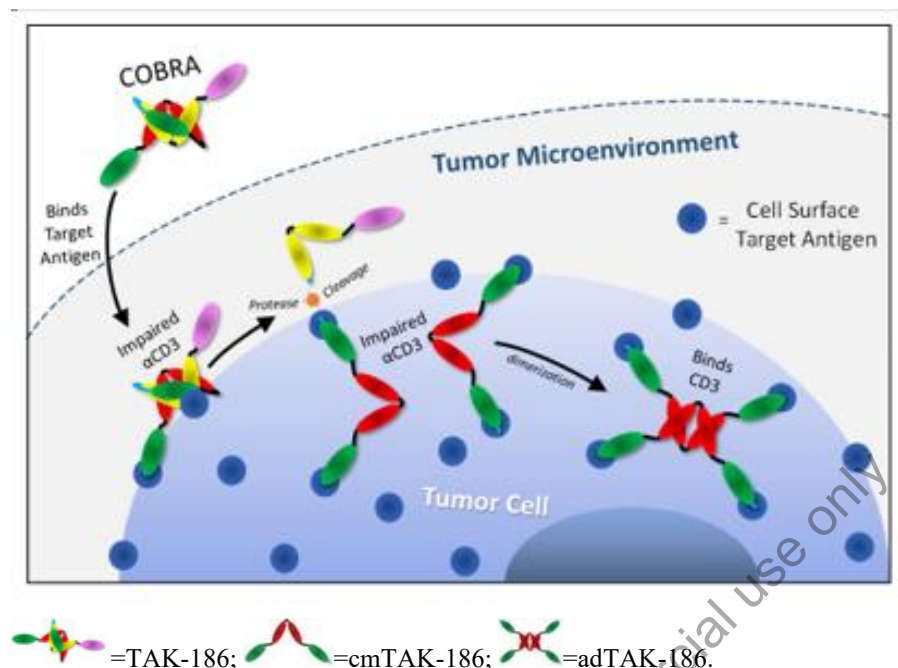
Two sdAbs recognize and bind EGFR. The third sdAb recognizes and binds human serum albumin. Each V_H and V_L are parts of the CD3 ϵ -binding single chain variable fragment (scFv) but have been constrained to prevent formation of an scFv by joining them with a short (8 amino

acid) linker. One of the V_H and V_L pairs has inactivating mutations in the complementarity-determining region 2 (inactive V_L and inactive V_H) and interaction between the mutated and non-mutated pairs of V_H and V_L prevents CD3 ϵ binding by TAK-186 in its intact form. Following the second EGFR-binding sdAb is a sequence of amino acids that can be cleaved by human proteases, including MMP9 and MMP2.

MMP activity is increased in the tumor microenvironment (TME) relative to healthy tissues (Dudani et al. 2018); thus, COnditional Bispecific Redirected Activation (COBRA) mediated T-cell activation is promoted by linker cleavage within the tumor setting, relative to levels of activation expected in healthy tissues that may also express EGFR. When the linker is cleaved by a protease in the presence of EGFR-expressing cells, TAK-186 active moieties are released, consisting of the anti-EGFR sdAbs and anti-CD3 V_H and V_L domains, that can dimerize on the cell surface of EGFR⁺ cells and co-engage T-cells to deliver a cytotoxic response (see Figure 4.b).

TAK-186 is designed to bind to EGFR upon administration, and both EGFR and CD3 ϵ following activation in the TME. Due to the linker length constraints, TAK-186 is folded into a compact structure where 2 pairs of scFvs come together (V_H -inactive V_L ; V_L -inactive V_H) preventing CD3 ϵ binding of TAK-186. Active T-cell engagement via the CD3 ϵ binding domain only occurs after protease-mediated cleavage of TAK-186 in the cleavable linker. Upon cleavage, the inactivating domain is released from the fragment containing V_H , V_L and 2 EGFR-binding sdAbs. The resulting activated fragment forms a dimer in the TME where each V_H and V_L pairs with its partner V_L and V_H (respectively) in an identical molecule to form a dimer comprising 2 fully active CD3 ϵ binding domains and four EGFR-binding sdAbs. Protease cleavage, and therefore CD3 ϵ -mediated activation of T-cells, outside of the TME is expected to be minimal. The half-life of TAK-186 is extended via binding to serum albumin in circulation; this albumin-binding domain containing the inactive V_H and V_L is removed from the target-binding moiety upon activation, thereby reducing exposure and subsequent toxicity to any normal target-expressing healthy tissue outside of the tumor (Figure 4.b).

Figure 4.b TAK-186 Mechanism of Action



adTAK-186: TAK-186 active dimer; CD3: cluster of differentiation 3; COBRA: COnditional Bispecific Redirected Activation; cmTAK-186: TAK-186 cleaved monomer; EGFR: epidermal growth factor receptor; TAK-186: drug product.

TAK-186 binds EGFR in prodrug form but does not bind CD3ε. TAK-186 is cleaved by proteases in the tumor microenvironment, resulting in formation of CD3ε-binding active dimer. Concurrent loss of the albumin-binding half-life extension domain allows rapid clearance of any active dimer which exits the tumor.

In its intact prodrug state, TAK-186 can only bind EGFR and albumin. However, once activated by MMP-mediated linker cleavage, 2 TAK-186 cleaved monomer fragments (cmTAK-186) on the cell surface interact to form an active dimer of TAK-186 (adTAK-186), which can then co-engage EGFR and CD3ε, while releasing the inactivating domains that includes the half-life extending albumin-binding domain (see [Figure 4.b](#)). The ability of adTAK-186 to bind both EGFR and CD3ε simultaneously was confirmed by recombinant protein binding, as well as cell culture binding studies.

4.1.3.1 TAK-186 Pharmacology

A brief summary is provided of TAK-186 nonclinical pharmacology data; please refer to the TAK-186 Investigator's Brochure (IB) for a more detailed description.

Both in vitro and in vivo studies supported the mechanism of action of TAK-186 and its ability to bind tumor cells, and upon MMP-mediated linker cleavage, activate and elicit T-cell mediated tumor cell killing. CD3ε positive T-cells incubated with a panel of EGFR-expressing cancer cell lines in the presence of increasing concentrations of cleaved TAK-186 (cTAK-186, pre-cleaved via incubation of TAK-186 with MMP-9) showed potent cytotoxic activity. Efficient, target cell-

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dependent, redirected killing activity by TAK-186 was demonstrated utilizing both human and cynomolgus monkey peripheral blood mononuclear cells.

In vivo, TAK-186 demonstrated tumor regressions in several established human tumor xenograft models in mice including HT29 (CRC), LoVo (CRC) and SCC25 (HNSCC). TAK-186 administration intravenously (IV) every 3 days for a total of 7 doses resulted in dose-dependent antitumor activity when EGFR-expressing human tumor cells were implanted subcutaneously in nonobese diabetic severe combined immunodeficient gamma (NSG) mice with adoptively transferred human T-cells administered IV. Activity of TAK-186 in vivo correlated with relative in vitro target cell surface EGFR expression levels. Administration of the noncleavable form of TAK-186 (Pro214), at [REDACTED] resulted in no antitumor activity in LoVo-, HT29-, or SCC25-bearing mice.

Central nervous system (CNS), cardiovascular, and respiratory effects of TAK-186 were evaluated as part of the 5-week Good Laboratory Practice (GLP)-compliant toxicology study. No noteworthy CNS, cardiovascular, or respiratory findings were observed.

4.1.3.2 TAK-186 Pharmacokinetics and Toxicology

A brief summary is provided of nonclinical pharmacokinetic (PK) and toxicology data with TAK-186; please reference the TAK-186 IB for a more detailed description.

The in vivo toxicologic profile of TAK-186 was evaluated in a 2-week non-GLP and a 5-week GLP-compliant toxicity study in cynomolgus monkeys, the only pharmacologically relevant species.

In the 2-week non-GLP study, TAK-186 was administered IV (60-minute infusion) to cynomolgus monkeys following a 2-week dose administration phase (2 doses total) [REDACTED] with the same dose each [REDACTED]

[REDACTED] Findings were consistent with the expected pharmacology of TAK-186, with T-cell activation concomitant with EGFR targeting and associated cytokine release. At tolerated doses, clinical observations and clinical pathology changes were mostly mild and generally not adverse. These effects were partially or fully reversible at the time of euthanasia.

Two controls, cTAK-186 and Pro214 (the pre-cleaved and noncleavable forms of TAK-186, respectively), used in the 2-week non-GLP toxicology study confirmed the mechanism of action of TAK-186, showing increased T-cell activity occurring only in the presence of cTAK-186. It also showed that physiological changes and clinical signs were due to cleavage of TAK-186 and were not an inherent property of the uncleaved intact molecule.

The PK and pharmacodynamic studies demonstrated cytokine release-mediated responses with cTAK-186 along with rapid blood clearance (CL) due to the loss of the half-life extension domain.

The GLP-compliant toxicity study included a 5-week dose administration phase (5 doses total)

██████████ TAK-186 or a vehicle control was administered by 30-minute IV infusion to cynomolgus monkeys at ██████████. TAK-186 treatment-related clinical observations were generally dose related in incidence, severity, and duration. Changes in the skin and mucocutaneous junctions were noted at ██████████. The changes consisted of red/dry skin, swollen face or periorbital area, and red and/or swollen penis/prepuce/scrotum, some with discharge and paraphimosis. At the highest dose, ██████████ ulcerations, swelling, and crust formation with discharge from the mucocutaneous junctions (ie, lips, eyelids, anus, prepuce, and nares) were observed. Dexamethasone mitigated the skin findings, and all resolved or were nearly resolved at the 4-week recovery period. One monkey receiving ██████████ was found dead on Day 30. This animal experienced the most severe adverse reactions of all of the animals, requiring the only dose interruption in the study. The death was considered secondary to immune-related pulmonary effects possibly associated with antidrug antibody (ADA) formation or infusion reaction.

Transient, TAK-186-related dose-dependent decreases were noted in a majority of absolute cell counts for lymphocyte subpopulations at the end of weekly dose administration. Most of the lymphocytes recovered to baseline levels by the end of the recovery period. Dose-dependent increases in MCP-1, IL-1RA, MIP1 β , and IL-10 occurred in the majority of TAK-186 dosed animals. ██████████

██████████ Most of the changes in lymphocytes and cytokines were related to the TAK-186 mechanism of action.

Hematologic changes were transient and consisted of attenuated reticulocyte count, decreased red cell mass, and decreased mean corpuscular hemoglobin concentration. Frequent blood sampling and secondary effects of cytokine elevations may have contributed to the decreases.

Systemic exposure to TAK-186, based on area under the concentration-time curve from time 0 to last quantifiable concentration (AUC_{last}), increased with increasing doses in an approximately dose-proportional manner at doses lower than ██████████ and greater than dose proportional at doses higher than ██████████.

In conclusion, the highest non-severely toxic dose (HNSTD) was established as ██████████ and the no observed adverse effect level (NOAEL) as ██████████ in the GLP-compliant study.

In summary, the nonclinical program for TAK-186 fully supports the initiation of a phase 1/2 study for this novel agent in the treatment of patients with unresectable locally advanced or metastatic cancer who have exhausted standard medical therapy.

4.1.4 First-in-Humans Dose Selection

Typically, CD3 bispecific constructs follow a minimum anticipated biological effect level (MABEL) approach to setting the first-in-humans (FIH) dose due to their immune agonistic

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properties (Saber et al. 2017). However, TAK-186 is a prodrug that is conditionally activated, and the traditional MABEL approach would assume a TAK-186 dose is already at full pharmacologic activity rather than its conditionally activated state that first requires cleavage of the prodrug. Since complete cleavage of TAK-186 is not expected in vivo, a MABEL-based FIH starting dose would result in an unacceptably low starting dose with negligible potential for pharmacological activity. Therefore, the FIH approach was shifted to an HNSTD with extended safety margin.

The cynomolgus monkey was determined to be the only pharmacologically relevant toxicology model for TAK-186 based on interspecies target homology and/or specificity to human EGFR, CD3ε, and serum albumin. The HNSTD for the 5-week GLP-compliant toxicology study in cynomolgus monkeys was an [REDACTED] based on lack of lethality (ie, tolerability) at this dose, relatively mild clinical and anatomic pathology findings, and reversibility of toxicologic findings following the recovery period. Instead of the standard 1/6th HNSTD scaling by body weight or body surface area, an extended safety margin of 1/100th HNSTD scaled by body weight was selected to yield a FIH starting dose of TAK-186 at [REDACTED].

In a mouse xenograft model of EGFR expressing human tumor cells implanted subcutaneously in NSG mice with adoptively transferred human T-cell, dose-dependent antitumor activity (ie, tumor regression) was observed at [REDACTED] when TAK-186 was administered every 3 days for 7 doses. The proposed FIH starting dose of [REDACTED] is approximately 10-fold lower than the estimated pharmacologic dose, which will limit risk of exposure to subtherapeutic doses. It further supports the proposed FIH starting dose.

The FIH starting dose of [REDACTED] based on an HNSTD with extended safety margin provides a conservative approach while still being acceptably close to the estimated pharmacologic dose level. Additionally, the FIH dosing scheme utilizes [REDACTED] comparable to that in the GLP-compliant toxicology study in cynomolgus monkeys to effectively mitigate the occurrence and severity of cytokine release syndrome (CRS) (see Section 6.1.1.1).

4.2 Rationale for the Proposed Study

The study is designed to determine the recommended phase 2 dose (RP2D) of TAK-186 when administered as a single agent to adult patients aged ≥18 years or local legal adult age with locally advanced or metastatic solid tumors expressing EGFR. The study consists of a dose-escalation phase designed to determine maximum tolerated dose (MTD) followed by a cohort-expansion phase to assess efficacy and safety of TAK-186 in solid tumors expressing EGFR, including NSCLC, CRC, and HNSCC and may compare 2 different doses or regimens of TAK-186 during cohort expansion dose optimization in a 1:1 randomized fashion, if applicable.

NSCLC, CRC, and HNSCC are good candidates for evaluation of TAK-186 anticancer activity. All tumor types have been shown to express membranous EGFR in the majority of cases and all have demonstrated susceptibility to immune modulation with monotherapy checkpoint inhibitors. In addition, evidence is well documented that in these cancers increased EGFR expression is

associated with increased MMP activity (Section 4.1.2.1). Nonetheless, the majority of patients with these tumor types do not respond to treatment with checkpoint inhibitors and, despite recent advances in the treatment of each disease, an unmet need remains for better therapy in these patients.

4.3 Potential Risks and Benefits

TAK-186 is currently being evaluated in this phase 1/2 study in patients with unresectable locally advanced or metastatic cancer who have experienced failure of or are intolerant to standard therapies.

The potential and identified adverse effects listed are based on the findings from nonclinical studies with TAK-186 and clinical experience with TAK-186 to date. It is possible that the administration of TAK-186 to patients with cancer will result in adverse events (AEs) that were not observed or predicted from the completed nonclinical studies conducted with animals.

The potential and identified risks of TAK-186 include:

- CRS
- Immune effector cell-associated neurotoxicity syndrome (ICANS).
- Infusion-related reactions.
- Liver function test (LFT) abnormalities.
- Dermatologic toxicity.
- Immune-related AEs.

These risks are described in detail in the IB.

This clinical study protocol for TAK-186 includes mitigations and monitoring for potential AEs specified for this compound by using close clinical monitoring and laboratory and imaging evaluations, including disease assessment. The timing of these tests and evaluations is detailed in the Schedule of Events (Appendix A).

Guidelines for the management of these clinical events are provided in Section 8.9.

Further details for TAK-186 administration, safety events, and management can be found in Section 8.0 and the Guidance for Investigator section of the IB.

4.3.1 Potential Effects Based on Nonclinical Studies

Potential risks of TAK-186 were evaluated in a 2-week non-GLP-compliant study and a 5-week GLP-compliant toxicity study in male and female cynomolgus monkeys and are summarized below. Additional details can be found in Section 4.1.3.2 and the Guidance for Investigator section of the IB.

4.3.1.1 *Clinical Observations Related to EGFR*

In the GLP-compliant study, TAK-186 treatment-related clinical observations were generally dose related in incidence, severity, and duration of effect and resolved by the end of the recovery phase. For a description of these findings see Section 4.1.3.2 and the IB. These findings are consistent with the EGFR target distribution and were mitigated with the use of dexamethasone and resolved or were reduced following the 4-week recovery period. Current Food and Drug Administration (FDA)-approved anti-EGFR targeted therapies also demonstrate dermatological-related side effects, with the most common being acneiform rash, which was not observed with TAK-186, but also include redness, dry skin, and ulceration, which were observed with TAK-186.

4.3.1.2 *Immune System Effects*

Immune system effects included TAK-186 dose-dependent decreases in a majority of absolute cell counts, including natural killer (NK) cells, B lymphocytes, total T lymphocytes, and Tc, Th, and regulatory T lymphocytes at 24 hours end of infusion (EOI), with transient dose-dependent increases in relative percentages of CD25+ activated and Ki67+ proliferating populations. Dose-dependent increases in MCP-1, IL-1RA, MIP-1 β , and IL-10 were observed for a majority of TAK-186-dosed animals at all dose levels. These changes are generally consistent with the mechanism of action of TAK-186 and indicative of expected levels of activity in the periphery. Changes in the lymphocytes were recovered or tended toward recovery to baseline levels by the end of the recovery period.

Additional details can be found in the IB.

4.3.1.3 *Hematological Effects*

Other hematologic changes following TAK-186 administration were mostly transient and consisted of attenuated reticulocyte count, decreased red blood cell (RBC) mass values, minimally to moderately decreased mean corpuscular hemoglobin concentrations, increased basophils, increased large unstained cells, and increased eosinophil counts. Frequent protocol-specified blood sampling may have contributed to the decreases in RBC mass parameters. The hematologic effects may represent a secondary effect of elevated cytokines. Additional details can be found in the IB.

4.3.1.4 *Reproductive Effects*

Reproductive studies with TAK-186 have not been conducted because TAK-186 is not cross-reactive with rodent targets.

Clinical observations, and macroscopic and microscopic changes were observed in male and female reproductive organs in the non-GLP- and GLP-compliant, repeat-dose toxicity studies. Clinical observations included swollen prepuce/red skin on penis, abrasion on penis, discharge from penis, and paraphimosis. Macroscopic and microscopic changes included red foci/depressions in mucocutaneous junctions of the genital areas and rectum that correlated with

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apoptosis of the basal epithelium, basal cleft formation, and ulceration in the squamous epithelium of the vagina, vulva, clitoris, prepuce, penis, and scrotum. TAK-186 affects the epithelium of reproductive organs and as such may represent a reproductive hazard, although direct effects on reproduction were not assessed. Additional details can be found in the IB.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

The primary objective of this study is:

- To characterize the safety, tolerability, and dose-limiting toxicities (DLTs) of TAK-186 when administered IV once weekly (QW) to patients with unresectable, locally advanced or metastatic cancer.

5.1.2 Secondary Objectives

The secondary objectives of the study are to:

- Determine the RP2D of TAK-186 when administered IV QW to patients with unresectable, locally advanced or metastatic cancer.
- Characterize the PK and immunogenicity of TAK-186.
- Evaluate the preliminary antitumor activity of TAK-186 in patients with unresectable, locally advanced or metastatic cancer.
- Compare TAK-186 antitumor activity efficacy endpoints using conventional Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) (see [Appendix C](#)) versus modified RECIST v1.1 (see [Appendix D](#)).

5.1.3 Exploratory Objectives

The exploratory objectives of the study are to:

- Explore the relationships between PK, pharmacodynamics, patient safety, and TAK-186 antitumor activity.
- Evaluate the relationship between tumor EGFR expression at baseline (pretreatment) and TAK-186 antitumor activity.
- Evaluate the relationship between tumor PD-L1 expression and TAK-186 antitumor activity.
- Evaluate the impact of tumor T-cell infiltration following TAK-186 administration.
- Evaluate the dose-response impact on tumor T-cell infiltration following TAK-186 administration.

- Evaluate the impact of TAK-186 on circulating immune cells and cytokines following TAK-186 administration.
- 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.
- Evaluate circulating tumor DNA (ctDNA) pre- versus on-treatment and correlation with patient response data.
- Explore the tolerability of TAK-186 through collection of patient-reported symptomatic AEs and the overall patient-reported burden of these symptomatic AEs.

5.2 Estimands

Not applicable.

5.3 Endpoints

5.3.1 Primary Endpoints

The primary study endpoints are:

- Non-CRS AEs, according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.
- CRS, according to American Society for Transplantation and Cellular Therapy (ASTCT) CRS consensus grading ([Lee et al, 2019](#)).
- DLTs during the dose-escalation phase.

5.3.2 Secondary Endpoints

The secondary endpoints are:

- RP2D selected on the basis of comprehensive safety, PK, and efficacy data.

PK and Immunogenicity:

- Single- and multiple-dose PK parameters.
- ADAs, ADA titers; neutralizing ADAs (ADA-positive samples).

Efficacy:

- ORR: the proportion of patients achieving complete response (CR) or partial response (PR) according to RECIST v1.1 (both confirmed and unconfirmed) and modified RECIST v1.1.
- Duration of response (DoR): the time in weeks from initial confirmed objective response (CR or PR) to the time of documented progressive disease (PD) or death from any cause, whichever occurs first. Objective response will be determined using both RECIST v1.1 and modified RECIST v1.1 response criteria.
- Progression-free survival (PFS): the time from the date of the first dose of study drug to the date of any documented confirmed PD, using both RECIST v1.1 and modified RECIST v1.1, or the date of death from any cause.
- OS: the time from the first dose of study drug until the date of death due to any cause.

5.3.3 Exploratory Endpoints

The exploratory endpoints are:

- EGFR expression in tumors.
- PD-L1 expression in tumors.
- Determination of fold change of immune cell markers including but not limited to total T cells, CD8+ and CD4+ T cell infiltration in pretreatment versus on-treatment biopsy specimens.
- Baseline assessment of biomarkers in the TME such as but not limited to tumor mutational burden and MSI-H status as well as immune cell infiltration of different immune cell populations, including but not limited to, CD4 and CD8 T-cells, NK cells, macrophages.
- Changes from baseline in peripheral blood immune cell markers assessed by flow cytometry (including but not limited to activation [CD8+, CD25+] or proliferation [CD8+, Ki67] markers).
- Changes from baseline in peripheral cytokine concentrations.
- Evaluation of changes in ctDNA levels pretreatment versus on-treatment.
- Description of patient-reported symptomatic AEs experienced over the course of the study, as measured by selected items from the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) item library and Functional Assessment of Cancer Therapy (FACT) item bank.
- Description of patient-reported overall side-effect burden, as measured by the single item FACT-GP5.

6.0 STUDY DESIGN

6.1 Overview of Study Design

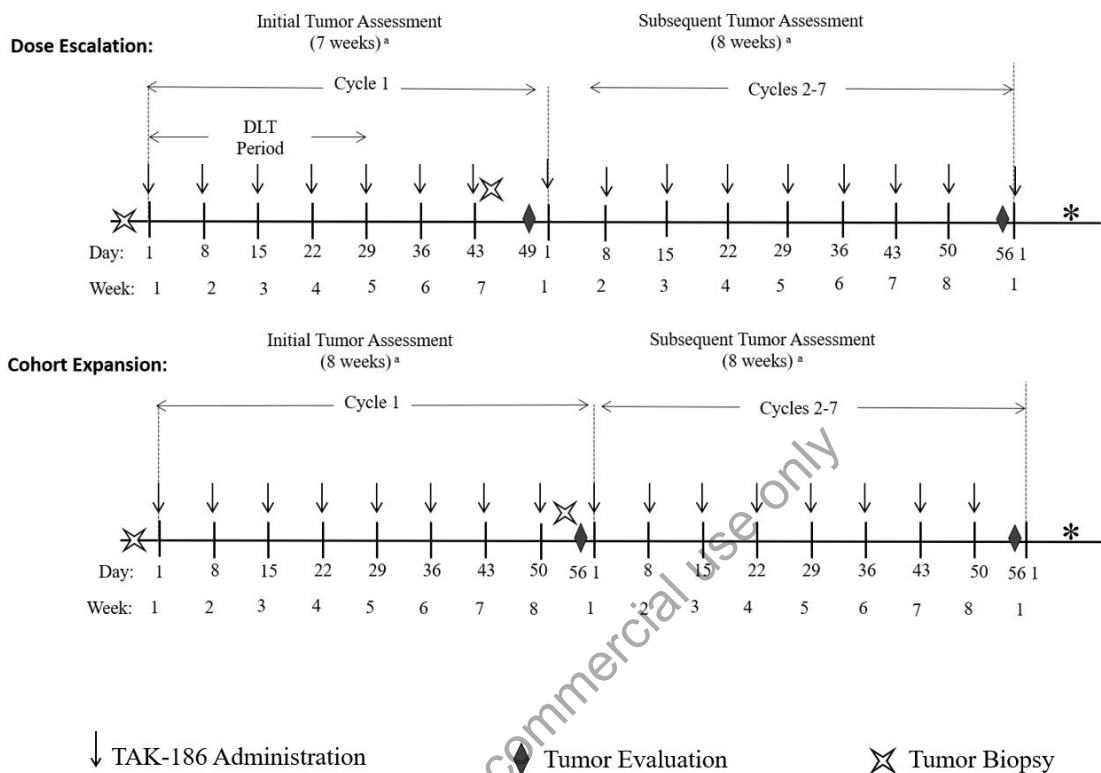
This is a phase 1/2, open-label, dose escalation and cohort expansion study designed to characterize the safety, tolerability, PK, pharmacodynamics, immunogenicity, and preliminary antitumor activity of TAK-186 administered by IV infusion QW in patients with unresectable, locally advanced, or metastatic cancer. The study consists of a dose-escalation phase to determine the MTD. The dose-escalation phase will be followed by a cohort-expansion phase to assess efficacy and safety of TAK-186 as monotherapy in unresectable, locally advanced or metastatic solid tumors expressing EGFR, including NSCLC, CRC, and HNSCC and may compare 2 different doses or regimens of TAK-186 during cohort expansion dose optimization in a 1:1 randomized fashion, if applicable.

The data generated from this study will be used to support later phase registrational clinical studies.

TAK-186 will be administered by IV infusion QW. Treatment will be continued until disease progression, completion of 7 cycles in the event of no radiologic evidence of tumor regression, withdrawal of consent, or death, whichever occurs first. For patients who continue to receive clinical benefit at the end of the 7 cycles, tolerate TAK-186 well, and have no alternative treatment options, the investigator may request to continue study treatment, after discussion with the sponsor's medical monitor.

The study treatment schema is presented in [Figure 6.a](#).

Figure 6.a Study Treatment Schema



The DLT-evaluation period is defined as the time between the initial TAK-186 dose and Cycle 1 Day 28 in the dose-escalation phase.

a For both the dose-escalation phase and cohort-expansion phase, tumor assessment will be performed at the end of each cycle and results should be reviewed before initiating the next treatment cycle with TAK-186.

* All patients will complete the end-of-treatment (EOT) visit 30 (+10) days after the last dose of study drug and then be followed for survival every 12 weeks (see [Appendix A](#)). The survival follow-up will be performed until the patient has died or is lost to follow-up or up to a maximum of 48 weeks after the last dose.

✕ Fresh paired tumor biopsy samples are optional for patients in the dose-escalation phase and backfill cohorts. For the cohort-expansion phase, patients will be required to consent to fresh paired tumor biopsies.

During dose escalation, TAK-186 infusion will be administered over 60 (± 10) minutes for all [REDACTED] the first cohort assigned dose, with all subsequent infusions administered over 30 (+10) minutes if the patient tolerates the first cohort-assigned dose well. If the patient experiences an infusion-related reaction during the 30-minute infusion, the duration of the infusion may be increased to 60 to 90 minutes in subsequent infusions. The duration of the initial TAK-186 infusion in cohort expansion will be based on the safety and PK evaluation in dose escalation but must be at least 30 minutes. [REDACTED]

Patients will be monitored for signs and symptoms of CRS and infusion-related reactions throughout the study. During dose escalation [REDACTED] patients will be monitored overnight for at least 24 hours following [REDACTED] the first cohort-assigned dose of TAK-186. Refer to Schedule of Events ([Appendix A](#)) for additional monitoring times. Starting with Cycle 2, investigators can monitor patients after each infusion for a length of time based on their clinical assessment of each patient. The monitoring schedule in the cohort-expansion phase may be modified based on the safety findings from dose escalation. Patients may be monitored overnight and admitted to the hospital upon development of symptoms suggestive of CRS during the in-clinic observation period and otherwise, if clinically indicated. Tocilizumab must be available on-site where the patient is being monitored.

Tocilizumab is to be administered at the dose of 8 mg/kg at the onset of any sign potentially indicative of Grade 2 CRS, per ASTCT CRS consensus grading, defined by fever (a temperature of $\geq 38^{\circ}\text{C}$) with hypotension not requiring vasopressors, and/or hypoxia requiring low-flow nasal cannula or blow-by oxygen ([Lee et al. 2019](#)). The maximum dose of tocilizumab administered at one 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, provision of oxygen, and other supportive measures are recommended, according to institutional practice. Early administration of tocilizumab is advised to mitigate against more severe CRS.

Please refer to [Appendix H](#) for a more detailed description of ASTCT CRS consensus grading and [Table 8.a](#) for general guidelines pertaining to management of patients who experience CRS.

The severity of AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0) for non-CRS AEs. CRS will be graded according to ASTCT CRS consensus grading ([Lee et al. 2019](#)) ([Appendix H](#)). DLTs will be defined separately based on the hematologic, hepatic, and other nonhematologic AEs defined in the DLT Section [8.2](#).

6.1.1 Dose-Escalation Phase

Dose escalation will begin with 2 single-patient cohort escalation steps and then be converted to a conventional 3+3 design. The following dose escalation rules will be applied:

1. Dose increments will be limited to 100% for [REDACTED] full treatment doses up to the first [REDACTED] dose levels [REDACTED].

The highest dose of TAK-186 administered in the study will not exceed [REDACTED]. Administration of the initial TAK-186 dose to the first 3 patients treated in each subsequent dose escalation cohort will be staggered by a minimum of 48 hours.

6.1.1.1

6.1.1.2 *Backfill in Dose Escalation Cohorts*

Any dose escalation cohort not exceeding the MTD can be expanded using backfill cohorts with additional patients for further evaluation of safety, PK, pharmacodynamics, and preliminary antitumor activity of TAK-186 after discussion between the investigators and sponsor.

Starting at dose level 6, the backfill cohorts will only enroll patients with NSCLC, CRC, or HNSCC (see Section 7.1).

6.1.2 Cohort-Expansion Phase

During the initial cohort-expansion phase, approximately 30 patients with unresectable, locally advanced or metastatic NSCLC will be enrolled in a single arm cohort to receive TAK-186 with a dose determined from the dose-escalation phase of the study. Dose selection for the cohort-expansion phase will be based on the PK, pharmacodynamic, safety, and tolerability data from the dose-escalation phase of the study. This would include empirical modeling of exposure-safety analysis and biomarker response data.

Tumor assessment will be performed every 8 weeks (8 week/cycle) for patients enrolled in cohort expansion. An interim futility analysis is planned based on ORR when the first 15 patients in the cohort become evaluable for efficacy by having at least 3 postbaseline scans or having discontinued therapy, whichever occurs earlier. Detailed futility boundaries are described in Section 13.2.

Based on the observed efficacy and safety data from the initial expansion cohort, more cohorts may be opened to assess different doses/regimens of TAK-186 in other EGFR expressing tumors, such as CRC and HNSCC, with approximately 30 patients in each tumor type.

Up to approximately 210 patients could be treated during the cohort-expansion phase of the study. The RP2D will be determined at the end of the cohort-expansion phase on the basis of the assessment of safety, PK, and efficacy data, including exposure-response analyses.

The goals of the cohort-expansion phase are as follows:

- Provide additional information on the efficacy and safety of TAK-186, contributing to the determination of the recommended dose for pivotal study.
- Obtain additional data on the PK, pharmacodynamics, and immunogenicity of TAK-186.
- Assess the antitumor activity of TAK-186 in patients in selected EGFR expressing advanced solid tumors.

Key decisions on the implementation of cohort expansion will be documented and submitted to participating IRBs/IECs and regulatory authorities, as appropriate, per local requirements.

The sponsor may decide to stop administration of a TAK-186 dose for a particular tumor type on the basis of cumulative data from patients receiving the same dose for another tumor type.

During this phase, criteria for pausing enrollment based on unacceptable toxicity will also be defined using a Bayesian approach. Starting with the first 10 patients and then every 5 patients

up to a maximum of 30 patients in each dose cohort during the cohort-expansion phase, patient accrual to the study may be suspended under the following circumstances:

- Grade 3 or higher CRS that does not resolve to Grade 2 or lower within 24 hours meeting the stopping bounds of ≥ 1 of 10 patients, or ≥ 1 of 15 patients, or ≥ 2 of 20 patients, or ≥ 2 of 25 patients, or ≥ 3 of 30 patients.
- Grade 3 ICANS that does not resolve to Grade 1 or lower within 7 days or Grade 4 ICANS meeting the stopping bounds of ≥ 1 of 10 patients, or ≥ 1 of 15 patients, or ≥ 2 of 20 patients, or ≥ 2 of 25 patients, or ≥ 3 of 30 patients.

The stopping boundaries for the above-mentioned events are based on Bayesian strategy to monitor outcomes in clinical studies. If the stopping rules are met, the probability is 80% that the true rate of such events is greater than 5% with a prior beta distribution with parameters 1 and 1 for the binomially distributed toxicity rate.

If enrollment is halted due to triggering of the stopping rule, recruitment can only be restarted following review/communication/submission of a substantial protocol amendment by the regulatory authorities.

6.2 Number of Patients

Up to approximately 258 patients will be enrolled in this study from approximately 35 study centers in Australia, South Korea, United Kingdom (UK), and the US. Enrollment is defined in Section 9.5.11.

For dose escalation, the number of patients is up to approximately 48 patients. Patients who are DLT non-evaluable during the DLT evaluation period will be replaced. More than 48 patients may be enrolled depending on results during the study and the number of TAK-186 doses evaluated. This number does not account for replacement of non-evaluable patients or the backfill patients.

Approximately 30 patients with NSCLC will be enrolled during the cohort-expansion phase. Additional patients with EGFR expressing solid tumors, such as CRC and HNSCC, may be enrolled with approximately 30 patients per tumor type. Further, patients may be enrolled to allow comparison between 2 different doses or regimens of TAK-186 for selected tumor type(s) by 1:1 randomization to each dose/regimens (eg, 40 patients randomized 1:1 for NSCLC). Therefore, the total sample size of the cohort-expansion phase of the study is estimated to be up to approximately 210 patients.

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 no more than 25 months.

Treatment will be continued until disease progression, completion of 7 cycles in the event of no radiologic evidence of tumor regression, intolerable toxicity, withdrawal of consent, or death, whichever occurs first. For patients who continue to receive clinical benefit at the end of the 7 cycles, tolerate TAK-186 well, and have no alternative treatment options, the investigator may request to continue study treatment, after discussion with the sponsor's medical monitor.

Patients will be followed for 30 days after the last dose of TAK-186, or decision to discontinue patient from study treatment, as determined by the investigator, or the start of subsequent alternative anticancer therapy to permit the detection of any delayed treatment-related AEs. All patients will be followed for survival follow-up every 12 weeks for 48 weeks by methods that include, but are not limited to, email, mail, or telephone communication retrieval from online or other databases (eg, Social Security indexes) during the survival follow-up period until the patient has died, is lost to follow-up, or the follow-up has continued for a total of 48 weeks after the last dose of TAK-186.

Individual patients will be considered to have completed the study after completing 7 cycles and completion of continued follow-up for a total of 48 weeks after the last dose of TAK-186 or until death, whichever occurs first.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

The study will be considered as complete when all individual patients have completed the study (see Section 9.7. The results of the study's primary endpoints will be presented in a clinical study report (CSR) with any subsequent results presented in CSR addenda.

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 end-of-treatment (EOT) visit combined with the end-of-study (EOS) visit 30 (+10) days after the last dose or before the start of subsequent systemic anticancer therapy, whichever occurs first. The collection of PK, pharmacodynamic, biomarker, and ADA samples may be stopped immediately in ongoing patients. Patients previously discontinued from study treatment, who have not completed OS follow-up at the time of the end of the study will undergo the EOS visit at the next scheduled survival follow-up visit, if possible.

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

Refer to Table 6.a for disclosures information for all primary and secondary endpoints. The maximum time frame was estimated based on the estimated treatment duration of 13 months.

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
Primary		
Safety endpoints; TEAEs, SAEs, deaths within 30 days of last dose of study drug.	As defined in Section 10.1.	Up to approximately 13 months
DLTs	AEs described in the protocol reported during the DLT-evaluation period.	Up to approximately 13 months
Secondary		
RP2D determined from safety, PK, efficacy data	Dose determined during cohort expansion for investigation in later phase / registrational studies.	Up to approximately 13 months
Single- and multiple-dose PK parameters	AUC, CL, C_{max} , t_{max} , $t_{1/2}$, V_{ss} , other PK endpoints defined in Section 13.1.4.	Up to approximately 13 months
ADAs; ADA titers, neutralizing ADAs for ADA-positive samples	Proportion of patients with ADAs in plasma samples after receiving TAK-186.	Up to approximately 13 months
Antitumor activity; duration of tumor control	ORR using both RECIST v1.1 and modified RECIST v1.1; DOR, PFS, OS.	Up to approximately 13 months

ADA: antidrug antibody; AE: adverse event; AUC: area under the concentration time curve; C_{max} : maximum observed plasma concentration; observed plasma concentration at the end of a dosing interval; CL: clearance; DLT: dose-limiting toxicity; DOR: duration of response; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PK: pharmacokinetic(s); RECIST: Response Evaluation Criteria in Solid Tumors; RP2D: recommended phase 2 dose; SAE: serious adverse event; $t_{1/2}$: terminal half-life; TEAE: treatment-emergent adverse event; t_{max} : time to maximum plasma concentration; V_{ss} : volume of distribution at steady state.

6.3.4 Total Study Duration

The total time for conduct of the study is expected to be approximately up to 5 years (includes enrollment of all cohorts, 13 months of treatment, and approximately 12 months [48 weeks] of survival follow-up). These timing estimates for study conduct may vary from those observed during the actual study conduct.

6.4 Posttrial Access

At the conclusion or termination of the study, patients may be allowed to continue to receive TAK-186 as an extension phase of this study, in a separate open-label rollover study, or through a single-patient Investigational New Drug application or equivalent. The mechanism of access will depend on the number of patients who require TAK-186 and local laws and regulations. This access will be permitted only if the patients have, in the opinion of the investigator and confirmed by the sponsor, experienced a clinically important benefit from TAK-186 that they received in the trial, have no alternative therapeutic option, and would be harmed without continued access.

6.4.1 Duration of Posttrial Access

Continued access to TAK-186 for patients will be terminated for those individuals who no longer benefit from TAK-186 (eg, they have completed the recommended course of therapy or their disease has resolved or progressed), the benefit-risk no longer favors the individual, if TAK-186 becomes available either commercially or via another access mechanism, or when an alternative appropriate therapy becomes available. Posttrial access may be terminated in a country or geographical region where marketing authorization has been rejected, the development of TAK-186 has been suspended or stopped by the sponsor, TAK-186 can no longer be supplied, or after specific time frames or events as required by local regulations.

7.0 STUDY POPULATION

The inclusion and exclusion criteria define the target population for the study and identify those who may not be appropriate candidates based on prior therapies, comorbidities, and other clinicopathologic features. Patients must meet all the inclusion criteria and will be excluded if they meet any exclusion criterion.

7.1 Inclusion Criteria

Each patient must meet all the following inclusion criteria to be enrolled in the study:

General

1. Age ≥ 18 years or local legal adult age.
2. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1 ([Appendix G](#)).
3. Ability to provide informed consent and documentation of informed consent before initiation of any study-related tests or procedures that are not part of standard of care for the patient's disease. Patients must also be willing and able to comply with study procedures, including the acquisition of specified research specimens.
4. Life expectancy ≥ 12 weeks.
5. Measurable disease per RECIST v1.1 criteria ([Appendix C](#)) and documented by computed tomography (CT) and/or magnetic resonance imaging (MRI). The definitions for measurable lesions are the same whether conventional and modified RECIST criteria are applied. Cutaneous or subcutaneous lesions must be measurable by calipers. Lesions to be used as measurable disease for the purpose of response assessment must either a) not reside in a field that has been subjected to prior radiotherapy or b) have demonstrated clear evidence of radiographic progression since the completion of prior radiotherapy and before study enrollment or c) have been radiated at least 6 months before study enrollment.

Tumor Histology Types

6. Patients with pathologically proven, unresectable, locally advanced or metastatic solid tumors that based on literature reports are considered to express EGFR. During cohort expansion, patients with locally advanced or metastatic solid tumors expressing EGFR including advanced or metastatic NSCLC, CRC, and HNSCC are eligible for enrollment.

Patients with the following 18 tumor types will be included in the dose escalation cohorts:

Tumor Histologies During Dose Escalation:

- Urothelial cancer arising in the bladder, renal pelvis, ureter, or urethra that has progressed during or following treatment with a checkpoint inhibitor (PD-1 or PD-L1 therapy) and, if eligible, a platinum-containing regimen.
- Adrenocortical carcinoma that is unresectable, locally advanced or metastatic.
- Clear cell renal cell carcinoma (RCC) progressing during or following at least 2 approved therapeutic regimens (eg, small molecule inhibitors, checkpoint inhibitor therapy).
- Unresectable locally advanced or metastatic papillary RCC.
- Triple-negative breast cancer locally advanced or metastatic that is unresectable and refractory to standard first-line therapy, which may include cytotoxic chemotherapy alone and/or poly ADP ribose polymerase (PARP) inhibitors for breast cancer gene (BRCA) 1 or 2 mutations, and/or checkpoint inhibitor therapy in MSI-H/deficient mismatch repair (dMMR) positive tumors.
- HNSCC that has progressed during or following treatment with a checkpoint inhibitor and platinum-based chemotherapy (unless ineligible for platinum chemotherapy) for metastatic or recurrent disease.
- Gastric or gastro-esophageal junction adenocarcinoma, progressing during or after cytotoxic chemotherapy (eg, fluoropyrimidine, platinum agents) with or without trastuzumab (for adenocarcinoma).
- Esophageal squamous cell carcinoma progressing during or after cytotoxic chemotherapy.
- Skin squamous cell carcinoma in patients with metastatic or locally advanced disease who are not candidates for curative resection or radiation therapy.
- Pancreatic adenocarcinoma that is unresectable locally advanced or metastatic with at least 1 prior chemotherapy regimen (eg, gemcitabine or fluoropyrimidine based therapy).
- Cholangiocarcinoma locally advanced or metastatic that is unresectable in patients who have had ≥ 1 line of systemic chemotherapy.

- Hepatocellular carcinoma (HCC) progressing during or following at least 2 or more approved therapeutic regimens. First-line therapy includes sorafenib, lenvatinib, or checkpoint inhibitor + bevacizumab therapies. Second-line therapy includes regorafenib, cabozantinib, ramucirumab or checkpoint inhibitor therapies.
- **CRC:** locally advanced or metastatic CRC that has progressed after systemic therapies, including irinotecan, oxaliplatin, an anti-EGFR inhibitor (if K-RAS or N-RAS is WT), a checkpoint inhibitor (if MSI-H), and a VEGF inhibitor (if locally approved and accessible as a standard-of-care).
- Epithelial ovarian cancer progressing during or following at least 1 prior cytotoxic chemotherapeutic regimen, and subsequent PARP inhibitor therapy in BRCA mutation-positive patients (unless ineligible).
- Cervical cancer progressing during or following first-line cytotoxic chemotherapy and second-line cytotoxic chemotherapy or checkpoint inhibitor therapy in PD-L1 positive (CPS ≥ 1) or MSI-H/dMMR positive tumors.
- Endometrial cancer progressing on or following either cytotoxic chemotherapy ($\pm$ trastuzumab) or hormone therapy, and a checkpoint inhibitor therapy in MSI-H/dMMR-positive tumors.
- Thyroid cancer (follicular or papillary histology) that is iodine refractory and has progressed during or following at least 1 prior systemic antineoplastic regimen (eg, lenvatinib, sorafenib).
- NSCLC locally advanced or metastatic that has progressed during or following treatment with a platinum-based chemotherapy, a checkpoint inhibitor (unless known to be PD-L1 negative) or targeted therapy (for patients with a known actionable mutation).

Tumors During Cohort Expansion:

Patients with pathologically proven, unresectable, locally advanced or metastatic malignant solid tumors that based on prior literature reports are considered to express EGFR are eligible for enrollment:

- **NSCLC:** locally advanced or metastatic NSCLC that has progressed during or following treatment with platinum-based chemotherapy, a checkpoint inhibitor (unless known to be PD-L1 negative), or targeted therapy (for patients with a known actionable mutation).
- **CRC:** locally advanced or metastatic CRC that has progressed after systemic therapies, including irinotecan, oxaliplatin, an anti-EGFR inhibitor (if K-RAS or N-RAS is WT), a checkpoint inhibitor (if MSI-H), and a VEGF inhibitor (if locally approved and accessible as a standard-of-care).

- **HNSCC:** HNSCC that has progressed during or following treatment with a checkpoint inhibitor (unless ineligible, eg, PD-L1 negative) and platinum-based chemotherapy (unless ineligible for or intolerant to platinum-based chemotherapy) with or without cetuximab for metastatic or recurrent disease.

Patients with salivary gland tumors will not be considered as having HNSCC.

Patients who refuse surgery for potentially curable disease where the surgery or radiotherapy could result in severe morbidity are eligible. The reason for the refusal will be captured in the electronic case report forms (eCRFs).

No more than 4 prior lines of systemic therapy for locally advanced or metastatic disease are allowed.

Archival Tissue:

7. Patients must allow acquisition of existing formalin-fixed paraffin-embedded (FFPE) archival tumor sample, either a block or unstained slides. Patients who provide fresh pretreatment biopsy samples will not be required to submit archival tumor samples.

Tumor Biopsy

8. Patients enrolling in cohort expansion must be willing to consent to mandatory pretreatment (during screening) and on-treatment fresh tumor biopsies. Once the target number of biopsies has been collected, additional paired pretreatment and on-treatment biopsies will not be required; sample collection will be optional after this time point.

For fresh tumor biopsies, the lesion must be accessible (those occurring outside the brain or those that are accessible by an interventional or endoscopic procedure) for a low-risk biopsy procedure that does not place the patient at an unjustifiable risk in the opinion of the investigator.

Patients who have an archived biopsy specimen available that was obtained up to 90 days prior to treatment initiation and have received no other treatment from the time of biopsy until the start of treatment with TAK-186, may submit that archived specimen in lieu of a pretreatment biopsy upon agreement from the sponsor.

Laboratory Features

9. Acceptable laboratory parameters as follows:
 - Albumin ≥ 3.0 g/dL
 - Platelet count $\geq 75 \times 10^3/\mu\text{L}$
 - Hemoglobin ≥ 9.0 g/dL
 - Absolute neutrophil count $\geq 1.0 \times 10^3/\mu\text{L}$

- Alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) $\leq 3.0 \times$ upper limit of normal (ULN); for patients with hepatic metastases, ALT/AST $\leq 5 \times$ ULN
- Total bilirubin $\leq 1.5 \times$ ULN, except patients with Gilbert's syndrome, who may enroll if the conjugated bilirubin is within normal limits.
- Creatinine clearance of ≥ 30 mL/minute using Cockcroft-Gault equation.

Reproductive Features

10. 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 postmenopausal 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 postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

WOCBP must have a negative serum pregnancy test performed within 72 hours before the initiation of study drug administration. WOCBP must use 1 form of highly effective method and 1 additional effective (barrier) method of contraception at the same time throughout the study, starting at screening through 90 days after the last dose of TAK-186. 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 patient 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 patient).

A list of barrier methods is available in Section 8.8.

11. Male patients with partners of childbearing potential must use barrier contraception during the entire study treatment period through 120 days after the last dose of study drug and must not donate sperm during this period. In addition, male patients should also have their partners use contraception (as documented for female patients) for the same period of time.

Previous Checkpoint Inhibitor Therapy

12. Patients who have previously received an immune checkpoint inhibitor (eg, anti-PD-L1, anti-PD-1, anti-CTLA-4) before enrollment must have checkpoint inhibitor immune-related toxicity resolved to either Grade ≤ 1 or baseline (before the checkpoint inhibitor) to be eligible for enrollment. Patients who experienced previous checkpoint inhibitor-related hypothyroidism are eligible for the study regardless of CTCAE grade resolution if well controlled on thyroid replacement hormones.
13. CNS metastases must have been treated and meet the following at the time of enrollment:
 - Definitive therapy was completed at least 2 weeks prior to the first dose of TAK-186.
 - No evidence of radiographic CNS progression following definitive therapy and by the time of study screening.
 - Any CNS disease is asymptomatic for at least 7 days (unless symptoms are deemed irreversible by the investigator), the patient is off steroids for at least 7 days, and the patient is either off or on stable doses of anti-epileptic drugs for malignant CNS disease for at least 7 days
 - No concurrent leptomeningeal disease or spinal cord compression.

7.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study.

1. Patients with a history of known autoimmune disease with the exception of:
 - Vitiligo.
 - Psoriasis not requiring systemic treatment for >1 year before receiving TAK-186.
 - History of Graves' disease in patients now euthyroid for >4 weeks.
 - Hypothyroidism managed by thyroid replacement.
 - Alopecia.
 - Well-controlled diabetes type 1.
2. Major surgery or traumatic injury within 8 weeks before first dose of TAK-186.
3. Unhealed wounds from surgery or injury.

4. Radiation therapy <2 weeks before initiation of TAK-186.
5. Treatment with >10 mg per day of prednisone (or equivalent) or other immune-suppressive drugs within the 7 days before the initiation of study drug. Steroids for topical, ophthalmic, inhaled, or nasal administration are allowed.
6. Prior therapy within the following timeframe before the planned start of TAK-186 as follows:
 - Cytotoxic chemotherapy, small molecule inhibitors, radiation, interventional radiology procedure, or similar investigational therapies: ≤ 2 weeks or 5 half-lives, whichever is shorter.
 - Monoclonal antibodies, antibody-drug conjugates, radioimmunoconjugates, or similar investigational therapies ≤ 4 weeks.
 - Concurrent use of hormones either to maintain castrate levels of testosterone in patients with castration-sensitive prostate cancer or for non-cancer-related conditions (eg, insulin for diabetes, hormone replacement therapy) is acceptable. Bisphosphonates are permitted for supportive care of bone metastases (eg, breast or prostate cancer) or osteoporosis.
7. Clinically significant cardiovascular or vascular disease including:
 - Myocardial infarction or unstable angina <6 months before the initiation of study drug.
 - Clinically significant cardiac arrhythmia (eg, with potential for hemodynamic instability).
 - Uncontrolled hypertension: systolic blood pressure >160 mmHg; diastolic blood pressure >100 mmHg.
 - Stroke, or transient ischemic attack <6 months before initiation of TAK-186.
 - Pulmonary embolism requiring treatment occurring <3 months before initiation of TAK-186.
 - QT interval by Fridericia correction (QTcF) prolongation >480 msec.
 - Congestive heart failure (New York Heart Association Class III-IV).
 - Pericarditis or clinically significant pericardial effusion.
 - Myocarditis.
 - Hypotension Grade ≥ 2 .
 - Vasculitis not resolved <6 months before TAK-186 initiation.

8. Clinically significant gastrointestinal disorders including:
 - Gastrointestinal perforation <6 months before study drug administration. Patients must have documented evidence (eg, upper endoscopy, colonoscopy) of completely healed area of prior perforation.
 - Gastrointestinal bleeding <2 months before study drug administration. Patients must have documented evidence (eg, upper endoscopy, colonoscopy) of completely healed area of prior bleeding.
 - Pancreatitis <6 months before the initiation of study drug. Patients must have a CT scan negative for evidence of remaining disease or normal pancreatic enzyme levels for >4 weeks before the initiation of TAK-186.
 - Diverticulitis flare <2 months before study drug administration. Patients must have a CT scan negative for evidence of remaining disease before the initiation of TAK-186.
 - History of Crohn's disease or ulcerative colitis.
9. Inflammatory process that has not resolved for ≥ 4 weeks from the date of first study dose. Patients with any history of Grade 2 or higher noninfectious pneumonitis will be excluded. (Patients with any radiation-induced pneumonitis or Grade 1 noninfectious pneumonitis that has resolved may be eligible for enrollment.)
10. Clinically significant pulmonary compromise: oxygen saturation $\leq 92\%$ on room air and requirement for any supplemental oxygen at the time of enrollment).
11. Active viral, bacterial, or systemic fungal infection requiring parenteral treatment within 7 days before the initiation of study drug. Systemic antiviral, antifungal, or antibacterial therapy must be completed >1 week before the initiation of study drug. Antimicrobial prophylaxis (eg, for *Pneumocystis carinii* infection) may continue for that purpose.
12. Vaccination with any live virus vaccine within 4 weeks before the initiation of study drug administration or vaccination with other vaccines 2 weeks before the initiation of study drug administration. Inactivated annual influenza vaccination is allowed.
13. Patients who are known to be HIV positive or who are known to be hepatitis B or C positive. Patients treated for hepatitis C must have viral titers of 0 for ≥ 2 years to be eligible. Patients with hepatitis B having undetectable or ≤ 500 IU hepatitis B viral titers are eligible. HCC patients with known history of hepatitis B are excluded, regardless of hepatitis B viral titers.
14. 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 having required therapy, excluding indolent lymphoid malignancies.
15. Any serious underlying medical or psychiatric condition that would preclude understanding and rendering of informed consent or impair the ability of the patient to receive or tolerate the planned treatment.

16. Known hypersensitivity to TAK-186 (or any excipient [trehalose, histidine, arginine, or polysorbate-80] contained in the drug or diluent formulation) or known hypersensitivity to tocilizumab.
17. Investigative site personnel or sponsor personnel directly affiliated with this study.
18. Prisoners or other individuals who are involuntarily detained.
19. Any medical or nonmedical issue that would contraindicate the patient's participation in the study or confound the results of the study.
20. Female patients who are breastfeeding.

8.0 STUDY DRUG

Investigational medicinal product(s): TAK-186.

8.1 Study Drug Administration

All protocol-specific criteria for 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-186 should be administered under the supervision of a physician and/or staff experienced in the use of IV agents. Study drug is **not** to be administered as an IV push or bolus injection. Given the 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.

- Do not mix TAK-186 with other medicinal products.
- The infusion rate of the syringe pump should be adjusted to allow for a total infusion time of 60 ($\pm$ 10) minutes for [REDACTED] the first cohort assigned dose and 30 (+10) minutes for all subsequent infusions or directed by the sponsor if infusion time is modified.
- A minimum 4-day interval should elapse between doses of TAK-186.

Please see the pharmacy manual for detailed instructions on study drug administration.

Additional important details regarding study drug administration and preparation are addressed in Section 8.12.

8.2 Definitions of DLT

The DLT-evaluation period is defined as the time between the initial TAK-186 dose and Cycle 1 Day 28 in the dose-escalation phase. Patients are DLT-evaluable if they receive at least 3 target doses in a dose cohort [REDACTED] or at least 2 target doses [REDACTED] or experience a DLT within the first 28 days of treatment.

DLT criteria are defined as any of the events in Section 8.2.1, 8.2.2, and 8.2.3, regardless of relationship except those events that are clearly due to extraneous causes, occurring during the DLT-evaluation period.

TAK-186 dose administration should be withheld for patients who experience AEs potentially meeting criteria for a DLT, pending resolution of the event and TAK-186 attribution assessment.

Patients who experience infusion delays of >14 days between 2 infusions during the DLT-evaluation period for any reasons other than DLT may remain on treatment, but will not be considered evaluable for DLT, and will be replaced in that dose cohort. In addition, patients who do not complete the full DLT-evaluation period and do not experience a DLT will be replaced in the same dose cohort.

8.2.1 Hematologic DLTs

- Grade 4 neutropenia lasting >5 days.
- Grade ≥ 3 febrile neutropenia lasting >48 hours or Grade ≥ 3 febrile neutropenia associated with hemodynamic instability or infection.
- Grade 4 thrombocytopenia.
- Grade 3 thrombocytopenia and clinically significant bleeding.
- Grade ≥ 3 hemolysis.

The following events are excluded from the definition of hematologic DLT:

- Grade ≥ 3 lymphopenia.
- Grade 3 or higher anemia without associated clinically significant events.

8.2.2 Nonhematologic: Hepatic DLTs

Hepatic DLTs are defined as follows:

- Grade 3 ALT or AST, defined by an increase $>10.0\times$ the ULN.
- Grade 3 AST or ALT increase, defined by >5.0 to $10.0\times$ ULN and not resolving to Grade 2 (ie, >3.0 - $5.0\times$ ULN) within 7 days and Grade 1 (ie, $>ULN$ - $3.0\times$ ULN) within 14 days (unless patient enrolled with elevated transaminases secondary to metastases, then must resolve to baseline). Steroids must be tapered to ≤ 10 mg of prednisone or equivalent per day by Day 14.
- Grade 3 bilirubin, defined by an increase $>5.0\times$ ULN.
- Grade 3 bilirubin increase, defined by an increase of >3.0 to $5.0\times$ ULN and not resolving to Grade 2 (ie, >1.5 - $3.0\times$ ULN) within 7 days and Grade 1 (ie, $>ULN$ - $1.5\times$ ULN) within 14 days. Steroids must be tapered to ≤ 10 mg of prednisone or equivalent per day by Day 14.
- Any event meeting Hy's law criteria (all 3 features):

AST and/or ALT $>3 \times$ ULN.

Concurrent elevation of total bilirubin $>2 \times$ ULN with or without signs of cholestasis.

No alternative etiology can be identified.

8.2.3 Other Nonhematologic DLTs

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

- Grade 3 electrolyte abnormality lasting <72 hours without associated clinical complications and response to therapy.
- Grade 3 fever lasting <72 hours and not associated with hemodynamic instability.
- Grade 3 nausea or vomiting resolving to $\leq$ Grade 1 within 72 hours with or without medical intervention.
- Grade 3 amylase and/or lipase elevations not associated with either clinical or radiographic evidence of pancreatitis requiring hospitalization.
- Grade 3 diarrhea, constipation, or abdominal pain 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.
- Grade 3 skin toxicity resolving to Grade ≤ 2 within 7 days with oral or topical corticosteroids.
- Grade 3 inflammatory reaction in the skin or soft tissue secondary to antitumor response (eg, metastatic sites, lymph nodes) resolving to Grade ≤ 1 within 7 days.

8.2.3.1 Grade 2 Other Nonhematologic AEs That May be Considered DLTs

- Grade 2 AEs that are prolonged inordinately, based upon the medical judgment of the investigator, and/or lead to permanent discontinuation of TAK-186 due to patient intolerance.
- Any hepatic laboratory abnormalities meeting all three of Hy's law criteria (described in Section 8.2.2).

8.3 Drug-Related Grade 2 AEs That Will Not Trigger Expansion to 3 Patients in the Single-Patient Cohorts

The following drug-related AEs will not trigger expansion to 3 patients in single-patient dose escalation cohorts:

- Grade 2 anemia.
- Grade 2 endocrinopathies that are well controlled with hormone replacement.

- Grade 2 nausea, emesis or dyspepsia, diarrhea or constipation that resolves to Grade 1 or baseline with medical management within 48 hours.
- Grade 2 fatigue that resolves to Grade 1 or baseline within 4 days.
- Grade 2 fever or flu-like symptoms that resolve with medical management to Grade 1 or baseline within 24 hours.
- Grade 2 allergic reaction.
- Grade 2 CRS (by ASTCT CRS consensus grading) and infusion-related reaction(s) that resolve with medical management to Grade 1 or baseline within 24 hours.
- Grade 2 infections that resolve with medical management to Grade 1 or baseline within 72 hours.
- Grade 2 lymphocyte count or neutrophil count decrease.
- Grade 2 increase in lipase or amylase that resolves to Grade 1 or baseline in 72 hours.
- Grade 2 electrolyte abnormalities that resolve with medical management to Grade 1 or baseline within 72 hours.
- Grade 2 tumor pain.
- Grade 2 headache that resolves with medical management to Grade 1 or baseline in 24 hours.
- Grade 2 respiratory symptoms that resolve with medical management to Grade 1 or baseline within 24 hours.

Although DLTs may occur at any point during treatment, only DLTs occurring during the DLT evaluation period will necessarily influence decisions regarding dose escalation, expansion of a dose level, or evaluation of intermediate dose levels. Patients will be monitored through all cycles of therapy for treatment-related toxicities.

8.4 Dose Escalation Rules

Dose escalation is carried out in sequential cohorts of escalating doses ranging [REDACTED]. The initial 2 cohorts are single-patient cohort escalation steps [REDACTED] (Figure 8.a) and then converted to a conventional 3+3 design. The following dose escalation rules will be applied:

- Dose increments will be limited to 100% for [REDACTED] full treatment doses up to the first [REDACTED] dose levels [REDACTED].
- Maximum dose increments for the next dose cohort will be limited to 50% after the [REDACTED] dose for [REDACTED] full treatment doses if patients in a given dose cohort experience 2 or more Grade ≥ 2 CRS during the DLT-evaluation period.

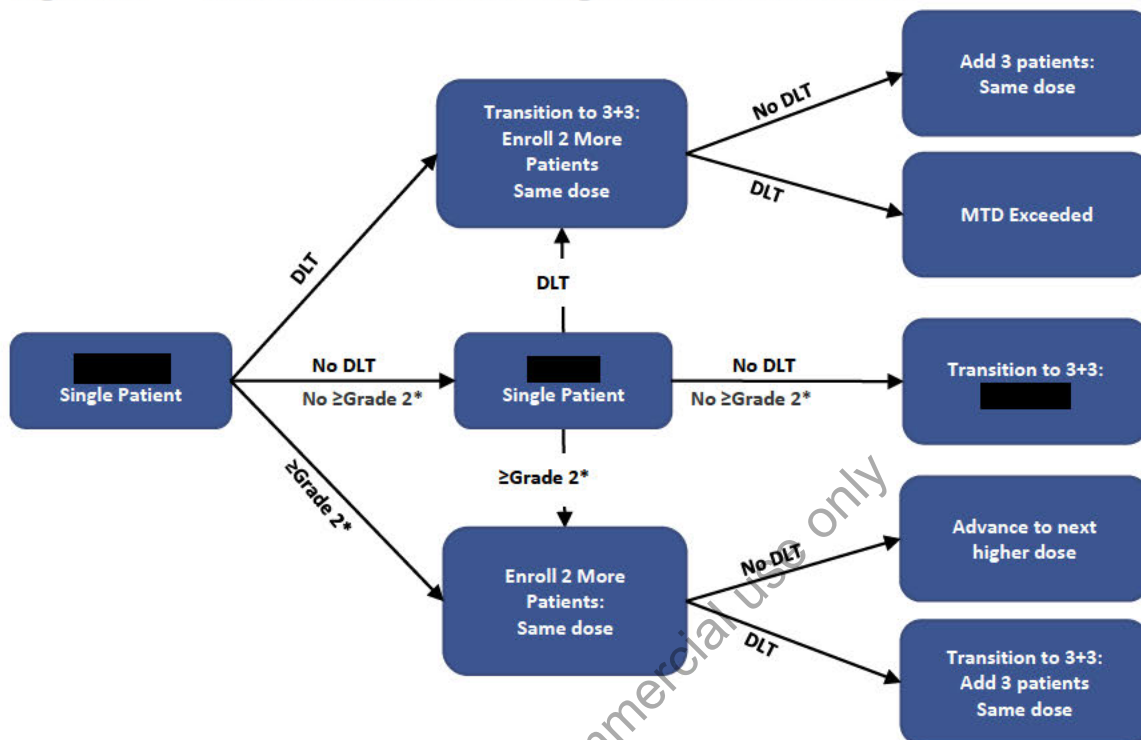
- Maximum dose increments will be limited to 30% for the next dose cohort for [REDACTED] full treatment doses if patients in a given dose cohort experience 2 DLTs during the DLT-evaluation period.

Intermediate doses may be explored during the dose-escalation phase of the study, based on review of the cumulative safety data and upon agreement between the investigators and the sponsor. Any decision to implement an intermediate dose will be documented and submitted to participating IRBs/IECs and regulatory authorities, as appropriate, according to local requirements.

The highest dose of TAK-186 administered in the study will not exceed [REDACTED]. Administration of the initial TAK-186 dose to the first 3 patients treated in each dose escalation cohort will be staggered by a minimum of 48 hours. [REDACTED]
[REDACTED]

The 2 single-patient dose cohorts will proceed as outlined (Figure 8.a). If no DLTs or drug-related Grade 2 AEs (with exceptions, see Section 8.2) occur in the [REDACTED] then a single patient will be enrolled into the [REDACTED]. If no DLTs or drug-related Grade 2 AEs (with exceptions, see Section 8.2) occur in the [REDACTED] then dose escalation transitions to a 3+3 design at the [REDACTED]. If a DLT occurs during the DLT-evaluation period for either the [REDACTED] escalation is transitioned to a 3+3 design enrolling 2 more patients at the dose at which the DLT occurred (ie, mimics the additional 3 patients enrolled in a 3+3 design). If a patient enrolled in a single-patient cohort experiences a drug-related Grade 2 AE (with exceptions listed in Section 8.2), the cohort will be expanded to 2 more patients at the same dose to achieve a total of 3 patients. If none of these 3 patients experience a DLT during the DLT-evaluation period, the dose will be escalated as depicted in Figure 8.a.

Figure 8.a Dose Escalation Plan in Single Patient Dose Cohorts



AE: adverse event; DLT: dose-limiting toxicity; MTD: maximum tolerated dose; NCI CTCAE v5.0: National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0.

* Only select Grade 2 AEs, per NCI CTCAE v5.0 trigger moving to 3+3 design; See Section 8.3 Drug-Related Grade 2 AEs that will not trigger expansion to 3 patients in the single-patient cohorts.

In the 3+3 dose escalation cohorts, if none of the 3 patients in the initial cohort experiences a DLT during the DLT-evaluation period, the dose will be escalated, and 3 patients will be enrolled at the next higher dose. If one of the first 3 patients treated at a given dose experiences a DLT, 3 additional patients will be enrolled at that dose (total of 6 patients in this cohort). If none of these 3 additional patients experiences a DLT, the dose will be escalated, and 3 patients will be enrolled at the next higher dose. If ≥ 2 patients of the first 3 patients or ≥ 2 of 6 patients treated at a given dose experience a DLT, then the MTD has been exceeded and the next lower dose is considered the MTD. Patients who are not DLT-evaluable (as defined in Section 8.2) will be replaced in the same dose cohort.

In this ongoing study, [Redacted] was implemented at Dose Levels 3 and 4. Starting at Dose Level 5, [Redacted] has been implemented with doses of [Redacted] based on emerging CRS data. The dose of [Redacted] is the first dose to be further assessed in the cohort-expansion phase.

Patients will be monitored for signs and symptoms of CRS and infusion-related reactions. Monitoring may occur in an in-patient setting if warranted by logistic procedures. During dose

escalation with a [REDACTED] patients will be monitored overnight for at least 24 hours following the [REDACTED] and the first cohort-assigned dose of TAK-186. Refer to Schedule of Events ([Appendix A](#)) for additional monitoring times. Starting with Cycle 2, investigators can monitor patients after each infusion for a length of time based on their clinical assessment of each patient. The monitoring schedule in the cohort-expansion phase may be modified based on the safety findings from dose escalation. Patients may be monitored overnight and admitted to the hospital upon development of symptoms suggestive of CRS during the in-clinic observation period and otherwise, if clinically indicated. All precautionary hospitalizations for the purpose of study drug administration and observation are considered planned for the purposes of the study and should not be considered serious adverse events (SAEs). For AEs that occur during such planned hospitalizations that meet the usual indication of hospitalization according to the investigator's medical judgement or AEs that prolong hospitalization should be reported as SAEs. Hospitalization following the onset of symptoms suggestive of CRS should also be considered SAEs.

Tocilizumab must be available on-site where the patient is being monitored.

8.5 Dose Modification Guidelines

Inpatient dose reductions during dose-escalation phase are not allowed, except for dose reductions for patients receiving TAK-186 at a dose that is subsequently determined to exceed the MTD. The total dose administered to a patient may be adjusted if the patient's weight changes by $\pm 10\%$ from the weight used at baseline (Cycle 1 Day 1) to calculate the dose.

The same dose modification guidelines will be used throughout the treatment period of the study.

8.5.1 Criteria for Beginning a Subsequent Treatment Cycle

The guidelines for pre- and postinfusion therapy for the second TAK-186 dose and subsequent TAK-186 doses will be re-evaluated after each dose escalation cohort by the investigators and sponsor's medical monitor. Beginning with the fourth dose of each cohort, premedications can either be reduced in dose or discontinued. Investigators may add therapy for CRS and infusion-related reactions based on clinical evaluation and institutional standards at any time during the study.

Dosing with TAK-186 will be weekly with 1 treatment cycle every 7 or 8 weeks (see [Figure 6.a](#)). To receive the next dose of TAK-186, the patient must meet the following criteria:

- Absolute neutrophil count $\geq 1,000/\text{mm}^3$ (Cycle 1 only).
- Afebrile
- Oxygen saturation of $>92\%$ on room air.
- Hypertension Grade <3 or hypotension Grade <2 .
- No ongoing toxicities precluding dosing per Section [8.9 Management of Clinical Events](#).

8.5.2 Additional Criteria to Start a Delayed Subsequent Dose

For dose administration intervals of >14 days, the following criteria should be used to restart dosing with TAK-186:

- In patients who are receiving a dose above the defined [REDACTED] dose administration should restart using the [REDACTED] as the initial dose(s) before returning to the higher dose a patient had been receiving before the dose delay.
- If dose delay occurred during Cycle 1, follow guidelines for Cycle 1 Day 1 dose administration, including premedication, postinfusion support, and patient monitoring.
- If dose delay occurred during Cycle 2 or beyond, consider following the supportive guidelines for Cycle 1 Day 1 based on patient tolerability, clinical status, and investigator discretion.

8.5.3 Infusion Interruption and Criteria for Resumption

Patients experiencing toxicity during infusion should have the study drug infusion held pending assessment, management, and resolution of the toxicity. If the toxicity is managed and does not meet DLT criteria, then infusion can be restarted at reduced speed upon resolution of the toxicity to Grade ≤ 1 or baseline (see Section 8.9.1.3).

8.5.4 Criteria for Discontinuation of TAK-186

Patients can continue to receive TAK-186 until any of the following conditions is met:

- Patient meets criteria for objective progression by modified RECIST v1.1 ([Appendix D](#)), ie, progression that is confirmed by a second scan after receiving one more cycle of TAK-186. *
- Occurrence of drug-related DLT during the DLT-evaluation period in dose-escalation phase. **
- Occurrence of intolerable toxicity at any time during treatment.
- Completion of 7 cycles of study without radiologic evidence of tumor regression. ***
- Pregnancy.
- Sponsor, investigator, or regulatory agency terminates the study.
- Withdrawal of patient consent.

* Patients showing unequivocal worsening of cancer-related signs and symptoms at first assessment of radiologic PD by RECIST v1.1 may discontinue the study drug without waiting for confirmation of disease progression. Patients meeting the criteria of PD by RECIST v1.1 but otherwise experiencing substantial clinical benefit with acceptable toxicity may continue therapy, based on investigator opinion on a case-by-case basis with sponsor agreement.

** Patients in the dose-escalation phase with clinical benefit may resume TAK-186 after complete recovery from the DLT, per investigator request on a case-by-case basis with sponsor agreement.

*** For patients who continue to receive clinical benefit at the end of the 7 cycles, tolerate TAK-186 well, and have no alternative treatment options, the investigator may request from the sponsor in writing to continue study treatment.

If a patient is withdrawn from the study or from TAK-186 dose administration for any reason other than PD, the investigator should make every effort to notify the sponsor within 24 hours.

8.6 Prohibited Concomitant Medications and Procedures

The following rules concerning concurrent treatment(s) will apply to this study:

- Other antineoplastic therapies including chemotherapy, small molecule inhibitors (eg, TKIs) or biologics, are not allowed. The exception is hormonal therapy to maintain castrate levels of testosterone in patients with castration-sensitive prostate cancer.
- Radiation therapy is prohibited, except for palliative radiotherapy and treatment of brain metastases. However, this treatment must not involve the lungs. Therapy with TAK-186 may be interrupted for up to 4 weeks. Palliative radiotherapy may not be given concurrently with TAK-186. Treatment with palliative therapy should be initiated at least 24 hours after receiving TAK-186, and reinitiation of TAK-186 can begin 7 days after the completion of palliative radiotherapy if it is not associated with complications. Palliative radiotherapy fields also should not overlap tumor lesions that have previously been designated as target lesions.
- Other investigational drugs during the treatment period of study are not allowed.
- Because TAK-186 has a mechanism of action dependent upon 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 daily of prednisone or equivalent is prohibited other than for the management of drug-related AEs. Steroids may be employed in the treatment of suspected TAK-186-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 an AE or as prophylaxis.
- Live vaccines should be avoided for 3 months after the last dose of TAK-186.

8.7 Permitted 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 eCRF.

Patients may receive the following concurrent therapy:

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- Use of bisphosphonates or receptor activator of nuclear factor kappa-B ligand inhibitors is allowed.
- Hormones to maintain castrate levels of testosterone in patients with castration-sensitive prostate cancer or for non-cancer-related conditions (eg, insulin for diabetes, hormone replacement therapy) are acceptable.

Elevated cytokines may modulate cytochrome P450 (CYP) enzyme activity. Therefore, patients who are administered sensitive CYP enzyme substrates (see examples on the US FDA website [<https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers>]) should be closely monitored for side effects. All changes in infusions, including interruptions and their duration, and reductions in rate and their duration must be recorded.

Alcohol, herbal supplements, and medications associated with potential hepatic injury should be used with caution. The sponsor's 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.

COVID-19 vaccination is not required but encouraged as patients with cancer receiving treatment are a vulnerable group. The following guidance is provided to coordinate the timing of vaccination and study treatment:

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

Deviation from the above guidelines should be discussed and agreed with the sponsor's medical monitor.

8.8 Precautions and Restrictions

It is not known what effects TAK-186 has on human pregnancy or development of the embryo or fetus; therefore, patients participating in this study should avoid becoming pregnant or avoid impregnating a partner. Nonsterilized patients of reproductive age with a uterus and/or ovaries and nonsterilized patients with testes/testis should use effective methods of contraception through defined periods during and after study treatment as specified below.

Reproductively female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, OR
- Surgically sterile (documented evidence of surgical sterilization at least 6 months before screening [eg, tubal ligation or hysterectomy]), OR
- If they are of childbearing potential, agree to practice 1 form of highly effective method and 1 additional effective (barrier) method of contraception, starting from the time of signing of the informed (e)consent form (ICF) through 90 days after the last dose of study drug. Examples of highly effective contraception are listed in the Inclusion Criteria (Section 7.1). Acceptable effective barrier methods include male or female condom with or without spermicide (female and male condoms should not be used together), and cap, diaphragm, or sponge with spermicide.
- Agree 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.)

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

- Agree to practice effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug, OR
- Agree 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.)

8.8.1 Prior Therapy

Prior therapy restrictions are described in the inclusion/exclusion criteria specified in Section 7.1 and 7.2.

8.8.2 Fluid and Food Intake

There are no requirements for fasting and no restrictions for fluid and food intake by the patients during the study, except intake to be restricted to bland snacks (eg, avoid food/beverage/condiment such as coffee, tea, or spice) before electrocardiogram (ECG) administration.

8.8.3 Patient Activity Restrictions

There are no restrictions on patient activities and no requirement for patient confinement during the study.

8.9 Management of Clinical Events

If dose alterations are necessary as a result of the events detailed below, please refer to Section 8.5.

8.9.1 CRS and Infusion-related reactions (IRRs)

The predicted mechanism of action of TAK-186 is the formation of an immunological synapse between the tumor target cells bearing EGFR and immune effectors bearing the T-cell-specific CD3 complex, leading to T-cell activation and killing of the tumor cell. Activation of T-cells is associated with the production of various cytokines.

As with other T-cell engaging and activating therapies, the occurrence of CRS is expected as an AE with TAK-186. CRS is defined as a supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Signs and symptoms can be progressive, must include fever at the onset, and may include hypotension, hypoxia, and end organ dysfunction (Stewart et al. 2022).

Patients who experience CRS should be managed according to the standard of care practice of medicine. General guidelines to manage CRS are provided in this section.

Tocilizumab is to be administered at the dose of 8 mg/kg at the onset of any signs potentially indicative of Grade 2 CRS, per ASTCT CRS consensus grading, defined by fever (a temperature of $\geq 38^{\circ}\text{C}$) with hypotension not requiring vasopressors, and/or hypoxia requiring low-flow nasal cannula or blow-by oxygen (Lee et al. 2019). The maximum dose of tocilizumab administered at one 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, provision of oxygen, and other supportive measures are recommended, according to institutional practice. Early administration of tocilizumab is advised to mitigate against more severe CRS. Severe reactions may require more intensive interventions including IV steroids, anti-tumor necrosis factor-alpha (TNF α) antibodies, or IL-1 inhibitors. Please refer to Table 8.a for general guidelines pertaining to the management of patients who experience CRS.

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

- Tocilizumab.
- Corticosteroids (eg, dexamethasone).
- IV fluids (normal saline).
- Vasopressors.
- Oxygen.
- Antipyretics.

In circumstances where tocilizumab is not available, other anti-IL-6 agents (eg, siltuximab) or tocilizumab biosimilars will be considered acceptable treatment of CRS, under the condition that this is consistent with local institutional guidelines/practice and that the availability of the anti-IL-6 agent(s) or tocilizumab biosimilars is(are) confirmed with the site investigator before patient enrollment.

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 cases, 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. Please refer to Section 8.9.1.2 for guidance on the management of CRS.

8.9.1.1 Premedication and Postinfusion Support

The following guidelines are either required (where noted) or recommended to avoid or minimize potential CRS and infusion-related reactions with TAK-186 administration.

8.9.1.1.1 Premedication and Postmedication

The guidelines for pre- and postinfusion therapy to the initial dose of TAK-186 will be re-evaluated after each dose escalation cohort by the investigators and sponsor's medical monitor. Investigators may add therapy for CRS and infusion-related reactions based on clinical evaluation and institutional standards at any time.

8.9.1.1.2 Before Dose on Cycle 1 Days 1, 8, 15, 22

Approximately 30 minutes before the infusion of TAK-186 the following premedications should be administered:

- Acetaminophen 650 mg or paracetamol 500 mg, or ibuprofen 400 mg by mouth (PO).
- Antiemetics (eg, ondansetron) will be given IV or PO at the institutional standard dose.
- Diphenhydramine 25 to 50 mg IV or PO or appropriate dose of equivalent H1 antagonist.
- H2 antagonist (eg, famotidine, cimetidine) or proton pump inhibitor (eg, esomeprazole, omeprazole) will be given IV or PO at the institutional standard dose.
- Dexamethasone [REDACTED].

[REDACTED]

[REDACTED]

[REDACTED]

Other pre-medications (such as antipyretics, H1 and H2 blockers, antiemetics) may be continued, discontinued, or reduced as clinically necessary after Cycle 1 Day 22.

8.9.1.1.3 Postinfusion Dexamethasone:

In addition to the premedication dexamethasone, dexamethasone [REDACTED] will be administered [REDACTED] after the completion of the TAK-186 infusion. Depending on the patient's tolerability and the investigator's judgement, post-medication dexamethasone may be also given after subsequent treatments. [REDACTED]
[REDACTED]

8.9.1.1.4 Postinfusion Fluid Support on Cycle 1 Days 1, 8, 15, 22*:

- IV hydration: 250 to 1000 mL normal saline administered over 2 hours (can be modified based on patient weight, and clinical status).
- All patients should be monitored as specified in the Schedule of Events (see [Appendix A](#)).
- Overnight monitoring is required during dose escalation, as specified in the Schedule of Events (see [Appendix A](#)).

* Post infusion fluid support may be reduced or discontinued based on the patient's condition and clinical judgement after C1D22.

8.9.1.2 Management of CRS

Investigators will exercise independent medical judgment regarding the management of patients who experience CRS. The following general guidelines are recommended actions for investigators to consider based on the grade of reaction according to the ASTCT CRS consensus grading ([Appendix H](#)). When CRS is suspected, consider obtaining laboratory results for cytokine evaluation.

Table 8.a Management of CRS

CRS Grade	Management of Patient
Grade 1	Monitor patient for worsening of condition (eg, hypotension, hypoxia). Offer supportive care with antipyretics, IV hydration, and symptomatic management of organ toxicities and constitutional symptoms. Consider administering steroids (eg, dexamethasone [REDACTED] equivalent) and/or Tocilizumab 8 mg/kg for Grade 1 CRS that cannot be managed with the above-mentioned medications. For patients with extensive comorbidities or poor performance status, recommend to manage per Grade 2 guidance below.
Grade 2	Continue supportive care as per G1 and include oxygen supplement as needed. 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. • IV corticosteroids (eg, dexamethasone [REDACTED] equivalent). Follow premedication guidelines for the next scheduled dose administration.
Grade 3	Continue supportive care as per G2 and include vasopressors as needed. Closely monitor all organ functions including cardiac function. 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. • IV corticosteroids (eg, dexamethasone [REDACTED] equivalent). • Other medications/treatment as medically indicated. No further doses of TAK-186 if Grade 3 CRS unless agreed by medical monitor, on the case-by-case basis.
Grade 4	Continue supportive care as per G3 and include mechanical ventilation as needed. Closely monitor all organ functions including cardiac function. 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. • IV corticosteroids (eg, dexamethasone [REDACTED] equivalent). • Other medications/treatment as medically indicated. No further doses of TAK-186 should be given.

CRS: cytokine release syndrome; IV: intravenous; PO: by mouth.

Patients must be monitored for signs and symptoms of CRS as described in the Schedule of Events, 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.

8.9.1.3 Management of IRRs

Infusion-related reactions (IRRs) may be classified as a potential risk of TAK-186 therapy, and patients should be closely monitored for early signs and symptoms indicative of IRRs. If an IRR occurs, TAK-186 infusion should be slowed or stopped, and patients will be monitored until complete resolution of symptoms occurs and treated, as clinically indicated.

Table 8.b Management of IRRs

CTCAE Grade	Management
Grade 1 or 2 IRR	Hold infusion. Conduct symptomatic treatment, including IV saline, oxygen, H1/H2 antagonists, antipyretics, bronchodilators, corticosteroids, and vasopressors, depending on the symptoms. Restart at 50% infusion rate and titrate to tolerance.
≥ Grade 3 IRR	Discontinue infusion. Follow symptomatic treatment guidelines for Grades 1 and 2.
Anaphylaxis	Discontinue infusion. Follow institutional guidelines for appropriate management.

Guidelines derived from ([Rosello et al. 2017](#))

IV: intravenous.

8.9.2 Liver Function Test Abnormalities

While no evidence of hepatic immune toxicity was observed in nonclinical safety studies, elevation of circulating cytokines can cause transient increases in liver enzymes and bilirubin ([Baumgart et al. 2009](#)). Guidelines for management of transient increases in LFTs are presented as follows:

8.9.2.1 Transaminase Elevations

The following management guidelines are provided for investigators to use along with their clinical assessment and acumen of a patient developing increases in transaminases during TAK-186 administration.

Table 8.c Management of Transaminase Elevations

CTCAE Grade	Management
Grade 1 elevations	No specific therapy required.
Grade 2 elevations	Rule out viral and other etiologies. Consider imaging studies such as ultrasound or CT scan and liver biopsy to ascertain etiology of liver dysfunction. Hold administration of TAK-186 and consider starting oral prednisone 60 mg/day divided twice daily (BID) or an equivalent corticosteroid.* *If the elevation in transaminases is considered to be associated to CRS, for which steroids have already been administered and the CRS is recovering, additional steroid may not be needed. If improvement to Grade ≤ 1 does not occur in ≤ 48 hours, then consider IV steroids such as methylprednisolone 2 mg/kg/day divided BID or oral steroids such as prednisone 60 to 120 mg per day, divided BID. Monitor transaminases at least twice weekly (or more frequently as clinically appropriate in the judgment of the investigator) until not returned to Grade ≤ 1. • Taper oral steroids as clinically indicated with improvement in liver function. • If improvement to Grade ≤ 1 does not occur within 14 days, discontinue TAK-186. • Resume TAK-186 after improvement to Grade ≤ 1 or baseline.
Grade 3 or 4 elevations	Hold administration of TAK-186. Begin immediate IV steroids; suggest methylprednisolone at a dosage of 2 mg/kg/day divided BID or an equivalent corticosteroid*. *If the elevation in transaminases is considered to be associated to CRS, for which steroids have already been administered and the CRS is recovering, additional steroid may not be needed. Consider additional immune suppression with mycophenolate for patients who do not respond to corticosteroid therapy within 3 to 5 days. Monitor transaminases at least twice weekly (or more frequently as clinically appropriate in the judgment of the investigator) until not returned to Grade 1 or baseline. If the transaminases elevation does not improve to Grade 2 within 7 days and to Grade 1 within 14 days, discontinue TAK-186. Resume TAK-186 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 per day of prednisone or equivalent. • On resuming TAK-186, AST, ALT, and total and direct bilirubin laboratory test values will be evaluated at least once per week for 3 consecutive weeks. Permanently discontinue TAK-186 in the event of a second Grade ≥ 3 AST or ALT increase. Patients experiencing a second Grade ≥ 3 transaminases increase clearly associated with CRS but not experiencing a concurrent Grade ≥ 3 bilirubin elevation may continue on the study upon agreement between the investigator and the sponsor.

AST: aspartate aminotransferase; ALT: alanine aminotransferase; BID: twice daily; CRS: cytokine release syndrome; CT: computed tomography; IV: intravenous.

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8.9.2.2 Bilirubin Elevations

The following management guidelines are provided for investigators to use along with their clinical assessment and acumen of a patient developing increases in bilirubin during TAK-186 administration.

Table 8.d Management of Bilirubin Elevations

CTCAE Grade	Management
Grade 1 elevations	No specific therapy required.
Grade 2 elevations	Hold TAK-186 until improvement to Grade ≤ 1. Rule out viral and other etiologies. Consider imaging studies such as ultrasound or CT scan and liver biopsy to ascertain etiology of liver dysfunction. Consider oral steroids.* *If the elevation in bilirubin is considered to be associated to CRS, for which, steroids have already been administered and the CRS is recovering, additional steroid may not be needed. If improvement to Grade ≤ 1 does not occur within 14 days, discontinue TAK-186 and begin oral steroid.
Grade 3 or 4 elevations	Hold TAK-186. Initiate IV steroids; recommend methylprednisolone at a dosage of 2 mg/kg/day divided BID or an equivalent corticosteroid.* *If the elevation in bilirubin is considered to be associated to CRS, for which, steroids have already been administered and the CRS is recovering, additional steroid may not be needed. If no response to corticosteroid therapy is observed within 3 to 5 days, consider adding immune suppression therapy with mycophenolate. Monitor bilirubin at least twice weekly (or more frequently as clinically appropriate in the judgment of the investigator) until total bilirubin has returned to Grade ≤ 1. Resume TAK-186 administration if: - Laboratory elevations decrease 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 resuming TAK-186, measure AST, ALT, and total bilirubin at least once per week for 3 consecutive weeks. Permanently discontinue TAK-186 in the event of a Grade 4 total bilirubin or a second Grade ≥ 3 total bilirubin increase.

AST: aspartate aminotransferase; ALT: alanine aminotransferase; CRS: cytokine release syndrome; CT: computed tomography; IV: intravenous.

8.9.3 AEs Secondary to EGFR Blockade/Dermatologic Toxicity

The EGFR-binding sdAbs on TAK-186 block EGFR signaling. However, the TAK-186 doses evaluated in this study are far below any expected to demonstrate clinical toxicity observed through EGFR signal blockade observed with standard EGFR-blocking therapy. As well, in the 2-week non-GLP-compliant toxicology study a non-CD3 binding control version of TAK-186

with the same EGFR-binding domains was tested and showed no adverse skin results at a dose of 300 µg/kg given in 2 weekly doses. The mucocutaneous changes noted in the cynomolgus monkey 5-week GLP toxicity study are described in Section 4.1.3.2. The changes were manageable with steroids (used in animals with severe skin reactions) and reversible as observed at the time of the recovery animals' necropsy. The presence of ADA-related findings in monkeys does not predict for this reaction in humans (Bugelski and Treacy 2004; van Meer et al. 2013).

In the GLP-compliant toxicity study, no microscopic or macroscopic pathologic changes were associated with the lowest dose level (NOAEL 11/33 ug/kg), whereas the mid dose was tolerated with mild and largely reversible findings (HNSTD 33/100 ug/kg). The initial dose level used in this study is based on the HNSTD with an extended safety margin (Section 4.1.3.2) to account for the conditional activation of TAK-186. The following guidelines, based on European Society for Medical Oncology Guidance (Rosello et al. 2017) are to be implemented for early and aggressive management of skin toxicity.

8.9.3.1 Management Guidelines for Patients Experiencing Dermatologic Toxicity

Table 8.e Management of Dermatologic Toxicity

CTCAE Grade	Management
Grade 1 skin reaction: Skin lesions covering <10% of body surface area with or without symptoms	- Examine patient's entire skin surface. - Exclude other causes of skin lesions (viral, bacterial, fungal, or other drug-induced rashes). - Symptomatic treatment with low-dose topical corticosteroids (betamethasone 0.1% or hydrocortisone 1%) or antihistamines (diphenhydramine). - Persistent Grade 1 rash should be managed with higher dose topical corticosteroids and/or oral prednisone (1-2 mg/kg/day) if there is not improvement with topical therapies or the rash is associated with other dermal toxicities such as pruritus. - Recommend preventative measures: avoiding irritation, exposure to ultraviolet radiation, use of sunscreen and regular use of emollients.
Grade 2 skin reaction: Skin lesions cover 10% to 30% of body surface area with or without symptoms	- Examine patient's entire skin surface. - Exclude other causes of skin lesions (viral, bacterial, fungal, or other drug-induced rashes). - Apply moderate to high strength topical glucocorticoids BID. - Persistent Grade 2 rash should be managed with higher dose topical corticosteroids and/or oral prednisone (0.5-1 mg/kg/day) BID or an equivalent corticosteroid. - Recommend preventative measures as in Grade 1. - Consider oral or topical antihistamines. - Consider dermatologic consultation. - Consider biopsy of a skin lesion for histopathologic evaluation. - Hold TAK-186 if no improvement in ≤7 days.

Table 8.e Management of Dermatologic Toxicity

CTCAE Grade	Management
Grade 3 skin reaction: Skin lesions cover >30% of body surface or Grade 2 area with significant clinical symptoms, limited self-care	• Hold TAK-186. • Examine patient's entire skin surface. • Exclude other causes of skin lesions (viral, bacterial, fungal, or other drug-induced rashes). • Apply high strength topical glucocorticoids BID. • Administer oral glucocorticoids: - Mild to moderate lesions: prednisone (0.5-1 mg/kg/day) BID or an equivalent corticosteroid. - Severe lesions: IV methylprednisolone 0.5 to 1 mg/kg or an equivalent corticosteroid. Switch to oral steroids on therapeutic response with withdrawal over 2 to 4 weeks. • Recommend preventative measures as in Grade 1. • Administer oral or topical antihistamines. • Strongly recommend dermatologic consultation. • Consider biopsy of a skin lesion for histopathologic evaluation. • TAK-186 administration may be restarted at the next scheduled dose administration if symptoms resolve to Grade ≤2 within 7 days. • Discontinue TAK-186 with recurred Grade 3 skin reaction not manageable after sufficient care.
Grade 4 skin reaction: Epidermal detachment and necrosis, skin lesions cover >30% of body surface area, accompanying symptoms.	• Discontinue TAK-186. • Initiate IV methylprednisolone 1 to 2 mg/kg or an equivalent corticosteroid. Switch to oral steroids on therapeutic response with withdrawal over 2 to 4 weeks. • Biopsy a skin lesion for histopathologic evaluation. • Urgent dermatologic consultation. • Consider hospitalization, provide preventative antibiotics, fluid and supportive care as indicated.

BID: twice daily.

8.9.4 Management of Neurologic Adverse Events (ICANS)

Patients should be monitored for neurologic toxicities throughout the study including 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

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examination using an assessment tool such as the Immune Effector Cell-associated Encephalopathy (ICE) score 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.

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 ICANS are provided in Appendix J.

The following guidelines are provided for the management of ICANS during TAK-186 administration.

Table 8.f 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 with and 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 (or methylprednisolone equivalent) and reassess in or earlier if clinically indicated ○ If associated with concurrent CRS, add tocilizumab ^a

Table 8.f Management of ICANS

ICANS Grade	Sign or Symptom	Management		
		Diagnostic Work-Up	Supportive Care	Anti-IEC Therapies
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 [REDACTED] (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 $\geq$ Grade 3 encephalopathy - Consider diagnostic lumbar puncture if Grade 3 encephalopathy persists $\geq$ 2 days or earlier if other causes are suspected (eg, infections, autoimmune, leptomenigeal 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	- 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 [REDACTED] (or methylprednisolone equivalent) - If associated with concurrent CRS, add tocilizumab ^a - If Grade 3 encephalopathy is persistent for >24 hours, increase dexamethasone to [REDACTED] (or methylprednisolone equivalent) - Once ICANS improves to 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	- Transfer to ICU - Supportive care as in Grade 1 ICANS - For focal or generalized convulsive seizures, or	- Dexamethasone [REDACTED] (or methylprednisolone equivalent) - If associated with concurrent CRS, add

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Table 8.f Management of ICANS

ICANS Grade	Sign or Symptom	Management		
		Diagnostic Work-Up	Supportive Care	Anti-IEC Therapies
		of consciousness) Rule out other potential causes of seizure (beta-lactams, etc.)	nonconvulsive seizures, treat as summarized in Table 8.g	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

Table 8.f Management of ICANS

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 8.g or Table 8.h	- 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

Table 8.f Management of ICANS

ICANS Grade	Sign or Symptom	Management		
		Diagnostic Work-Up	Supportive Care	Anti-IEC Therapies
	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 8.i	- 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

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

CRS: cytokine release syndrome; CSF: cerebrospinal fluid; CT: computed tomography; EEG: electroencephalogram; ICANS: immune effector cell-associated neurotoxicity syndrome; ICE: immune effector cell-associated encephalopathy; ICU: intensive care unit; IV: intravenous; MRI: magnetic resonance imaging.

^a If tocilizumab is not available, other immune modulating agents can be considered, based on local guidance or the EBMT/EHA CAR-T cell handbook ([Rees 2022](#)) and drug availability.

^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 8.g 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

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; ICU: intensive care unit; IV: intravenous.

Table 8.h 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 8.g](#))
- 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

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; EEG: electroencephalogram; ICU: intensive care unit; IV: intravenous.

Table 8.i 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 [REDACTED] (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 8.g) - Metabolic profile every 6 hours and daily CT scans of head without contrast, with 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

CSF: cerebrospinal fluid; CT: computed tomography; EEG: electroencephalogram; IV: intravenous; MAP: mean arterial pressure; MRI: magnetic resonance imaging; OP: opening pressure.

8.9.5 Other Immune-Related AEs

The mechanism of action of TAK-186 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. However, the investigators should assess potential immune-related AEs (eg, hypophysitis, pneumonitis, hypo/hyperthyroidism) and report these AEs accordingly. Patients shall be followed for late-onset immune related AE after 90 days of last dose (see Section 9.11 and Appendix A for more details).

8.10 Blinding and Unblinding

This is an open-label study.

8.11 Description of Investigational Agents

TAK-186 is a sterile, preservative-free aqueous solution contained in single-use glass vials. TAK-186 is to be administered by IV infusion QW with a commercially available syringe pump over 60 (± 10) minutes for [REDACTED] the first cohort-assigned dose, with all subsequent infusions administered over 30 (± 10) minutes if the patient tolerates the first cohort-assigned dose well (unless modified as outlined in study procedures). Refer to the Pharmacy Manual for more details on preparation and administration of the study drug.

8.12 Preparation, Reconstitution, and Dispensation

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

TAK-186 is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling TAK-186.

Preparation of low TAK-186 doses requires addition of a Solution Stabilizer. The Solution Stabilizer is a sterile, aqueous solution contained in single-use glass vials and will be provided by the sponsor.

The doses of TAK-186 to be administered to patients in this study are described in units of micrograms/kilogram. The calculated dose is administered based on the patient's weight measured within 3 days of Cycle 1 Day 1 (baseline). On Day 1 of subsequent treatments, a change in body weight $\pm 10\%$ from baseline should prompt recalculation of total dose. Refer to the pharmacy manual for the formula for dose calculations, specific dilution volumes, and instructions for infusion preparation and administration.

The dose of TAK-186 for administration must be prepared by the study pharmacist or appropriately qualified staff using an aseptic technique. Note that **TAK-186 must 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. Administration through a central port is always preferred over a peripheral line.

8.13 Packaging and Labeling

TAK-186 is packaged and labeled according to current good manufacturing practice requirements. The labels for TAK-186 will fulfill requirements specified by local governing regulations. Additional details are provided in the Pharmacy Manual.

8.14 Storage, Handling, and Accountability

All study drug supplies will be supplied to the investigator by the sponsor. Study drug supplies must be kept in an appropriate, secure area (eg, locked). Any partially used TAK-186 vials or diluted dose administration solutions and any partially used Solution Stabilizer vials should be discarded using appropriate drug disposal procedures. Temperature logs will be maintained to ensure compliance with storage conditions. The sponsor will be notified promptly of any temperature excursions as described in the pharmacy manual. Vials should not be shaken after thawing. Standard practices should be used for avoidance of contact.

Accurate accounting of all study drug must be maintained. The investigator agrees to keep an inventory of study drugs using the institution's drug accountability logs or logs provided by the sponsor. Drug disposition records must be kept in compliance with applicable guidelines and country and local regulations.

A pharmacy manual will be provided to the investigator or designee. When the study is completed, copies of all study drug accountability records must be provided to the sponsor. Original drug accountability records must be maintained with the rest of the documentation for inspection by the study monitors. Additional details regarding storage, handling, and accountability can be found in the pharmacy manual.

Under no circumstances is the investigator allowed to release these clinical supplies for use by another physician not named on Form FDA 1572 (as required or other delegation of authority documentation as required), or to administer study drug to a patient who is not enrolled in this study. Study drug must be dispensed at an institution specified on Form FDA 1572 (as required or other delegation of authority documentation as required).

9.0 STUDY CONDUCT

This trial 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 for each member state/country, and other vendors participating in the study may be found in the study manual. A full list of investigators is available in the sponsor's investigator database.

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

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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 Informed (e)Consent

Each patient must provide written or electronic informed consent before any protocol-directed procedures are conducted, unless those procedures are performed as part of the patient's standard care.

Patients consenting electronically (eConsent), where available, will electronically sign consent forms. Paper consent forms will be used instead if required by local regulations.

eConsent provides the same information as written consent forms, but in an electronic format that may include multimedia components. eConsent does not replace the important discussion between the study patient and site staff or investigator. Regardless of the consent format, the investigational site is responsible for the consenting process.

The requirements of informed consent are described in Section 15.2.

9.4 Treatment Group Assignments

Patients will be assigned sequentially to the dose escalation cohorts and cohort expansion cohorts.

9.5 Study Procedures

This section provides a general description of the procedures and assessments associated with this study. Refer to the schedule of events ([Appendix A](#)) for timing of assessments. On days when multiple procedures are required at the same time point, the PK sample should be collected first.

Additional details are provided as necessary in the sections that follow.

9.5.1 Patient Demographics

Each patient must be registered with the sponsor before enrollment (as defined in Section 9.5.11). The following information (but not limited to) will be provided by the investigator during registration:

- Age, year of birth.
- Date of signed informed (e)Consent.
- Disease type, stage, number of prior therapies.
- Assignment of cohort participation.
- Planned date of first TAK-186 administration.

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- Confirmation of eligibility.

Please refer to the study plans and manuals for a more detailed description of the procedures associated with enrollment.

9.5.2 Screening Period

The 28-day screening period will begin upon patient signing of the informed consent document. No screening activities outside of usual standard of care should be performed before obtaining informed consent from the patient. All screening activities, including standard of care, should be completed within 28 days before Cycle 1 Day 1 treatment visit. Only those patients who meet all inclusion criteria specified in Section 7.1 and are not precluded from enrollment by at least 1 exclusion criterion will be enrolled into this study. Results from assessments as part of regular medical care performed prior to signing the informed consent and within the allowed time window may be used as screening tests.

9.5.3 Medical History

A complete medical history is obtained during the screening period. The history will emphasize the background and progress of the patient's malignancy. 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.

Collect all concurrent medical conditions in the last 60 days and any significant prior medical conditions (eg, hospitalizations, surgeries, prior cancer history). During screening (within 28 days of the first dose of TAK-186), record any untoward event that occurs as medical history and not as an AE, unless it is due to a protocol-related procedure. Thereafter (ie, after the first dose of study drug), collect any untoward event as an AE. Refer to Section 9.5.9 for more information on recording concomitant medications.

9.5.4 Physical Examination

The investigator will perform physical examination of all patients. Physical examination will include height (baseline only), weight, and examination of skin, head, eyes, ears, nose, and throat, lymph nodes, heart, chest, lungs, abdomen, extremities, and neurologic systems. Directed physical exams will be performed within each cycle as specified in the Schedule of Events (Appendix A).

Weight will be measured during screening, <72 hours prior to Cycle 1 Day 1 (QW dose administration) and then before administration of each TAK-186 dose. Refer to Section 8.12 for dosing recalculation for patients with $\pm 10\%$ weight change.

9.5.5 ECOG Performance Status

ECOG performance status should be measured as specified in Appendix G.

9.5.6 Patient Height

Height will be measured only during screening (within 28 days before the first dose of TAK-186).

9.5.7 Vital Signs

Vital signs, including temperature, pulse rate, blood pressure, respiratory rate, and oxygen saturation, are to be obtained as specified in the Schedule of Events ([Appendix A](#)). It is recommended that vital signs measurements be obtained in a seated, semirecumbent or supine position after an appropriate rest (approximately 5 minutes in the position).

Patients will be given a diary to record their oral temperature (BID) in the morning and evening, and at any time the patient feels febrile during Cycle 1, as specified in the Schedule of Events ([Appendix A](#)). The diary should be brought to the site at each visit through Cycle 2 Day 1 and reviewed by study staff. If the patient experiences a temperature of $\geq 38^{\circ}\text{C}$ at any time during the study, they will be instructed to call the investigator. Sites will report clinically significant fever as AEs according to NCI CTCAE v5.0 guidelines, if clinically applicable.

9.5.8 Pregnancy Test

A serum pregnancy (choriogonadotropin beta) test will be completed for all reproductively female patients during screening; this test must be negative for the patient to be enrolled.

A serum pregnancy test will be performed for persons/WOCBP at screening and within 72 hours before the first dose of study drug. The results from these tests must be available and negative before the first dose of study drug is administered. If Cycle 1 Day 1 serum pregnancy results will not be available before dosing, a urine pregnancy test may be performed.

9.5.9 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF from enrollment through EOT. See Section [8.6](#) and Section [8.7](#) for a list of medications and therapies that are prohibited or allowed during the study.

9.5.10 Adverse Events

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

9.5.11 Enrollment

A patient is considered to be enrolled in the study at initiation of the first dose of study drug. Procedures for completing enrollment information are described in the study manual.

9.5.12 Electrocardiogram

Twelve-lead ECGs will be obtained according to the Schedule of Events ([Appendix A](#)) in order to evaluate the potential cardiac effects of TAK-186, including QT interval. It is recommended that, to the extent possible, ECGs be obtained premeal at approximately the same time of the day to minimize diurnal variations. However, this may not be possible because of infusion times and clinic logistics; nonetheless, within 4 hours before triplicate ECGs, food intake should be limited to bland snacks (eg, avoid food/beverage/condiment such as coffee, tea, or spice).

ECGs done at screening, Cycle 1 Day 1 (predose), and on Day 1 of each subsequent cycle should be obtained in triplicate (3 ECGs per time point at approximately 1-minute intervals). ECGs done at other time points are single evaluations unless triplicate ECGs are clinically indicated. Local interpretation will be used for data analysis purposes.

9.5.13 Clinical Laboratory Evaluations

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

In the event of an unexplained clinically significant abnormal laboratory test result, the test should be repeated immediately and followed up until it has returned to the normal range and/or an adequate explanation of the abnormality is found.

Other tests such as PK, ADA, cytokines, determination of leukocyte subsets, evaluation of T-cell activation status, expression of T-cell markers, determination of T-cell infiltration, and tumor EGFR expression will be carried out at sponsor-specified central laboratory or specialty laboratory (refer to the laboratory manual). Please consult the laboratory manual for specific directions on collection and processing samples.

9.5.13.1 Clinical Chemistry, Hematology, and Urinalysis

Blood samples for analysis of the clinical chemistry and hematology parameters and urine samples for analysis of the parameters shown in [Appendix I](#) will be obtained as specified in the Schedule of Events ([Appendix A](#)).

9.5.14 Disease Assessment

Patients will undergo CT with contrast as appropriate, MRI, radiographs, and/or bone scanning to monitor and assess disease progression, using RECIST version 1.1 ([Eisenhauer et al. 2009](#)) and modified RECIST v1.1 ([Wolchok et al. 2009](#)). Contrast CT scans of the chest, abdominal cavity, and pelvis will be obtained at screening. Specific disease sites that cannot be adequately imaged by CT may be documented by MRI. Contrast enhanced (unless contraindicated) MRI scans of the brain will be performed for all patients at baseline with a diagnosis of lung cancer

and for all other patients with signs and symptoms suggestive of CNS metastasis. Follow-up brain scans will be performed only if the screening brain scan was positive or in cases where it is clinically indicated (eg, suspicion of CNS metastases). Contrast CT scans of the brain (unless contraindicated) may be used if MRI cannot be performed. The same technique with appropriate contrast usage (MRI or CT) used at screening should be utilized throughout the study.

Anatomical measurements (summed across target lesions) will be collected at baseline and at each subsequent evaluation using an imaging modality consistent with that used at screening. Objective assessments will be performed at each time point as described in the schedule of events (see [Appendix A](#)). When possible, the same qualified physician will interpret results to reduce variability. Radiographic images will be maintained at the site, and test results and physicians' findings will be filed in patient source documents. Deidentified copies of any imaging scans, including those from screening and any unscheduled scans, may be collected and transferred to the sponsor or its designee (eg, central imaging vendor or imaging contract research organization [iCRO]) for storage and any future analysis.

9.5.15 Pharmacodynamic and Biomarker Samples

9.5.15.1 Pharmacodynamics/Biomarkers Sample Collection

A laboratory manual and supply kits will be provided for pharmacodynamic laboratory assessments. Serial blood samples will be collected for biomarker analyses including but not limited to the following assessments:

- Cancer-associated proteins.
- Cytokine analysis.
- Peripheral T-cell enumeration and activity; measured by flow cytometry.
- ctDNA.
- Pre- and posttreatment tissue samples for assessment of readouts, including but not limited to EGFR expression, PD-L1 expression, immunoregulatory markers, and genomic biomarkers.

Procedures for the acquisition, handling, and processing of pharmacodynamic biomarker specimens will be provided in the laboratory manual. Samples are to be obtained at the time points specified in the Schedule of Events and PK, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling Schedules ([Appendix A](#) and [Appendix B](#), respectively). Sample collection for certain tests may be stopped once emerging data warrants. If such a decision is made, the sponsor will document and communicate to all participating sites. All samples will be stored at the study sponsor's facility or at a contract laboratory facility until assessments are completed and checked.

Tests to be performed for pharmacodynamic/biomarker assessments are provided in Section [9.5.15.2](#).

9.5.15.2 Pharmacodynamic and Biomarker Assays

- Characterize the pharmacodynamic activity of TAK-186 by evaluating markers such as, not limited to, tumor protein markers (eg, carcinoembryonic antigen [CEA]), cytokines (eg, IL-2, IL-6, IL-10, IFN γ), and T-cell phenotypes (eg, activation, proliferation, exhaustion).
- Evaluate tumor biopsies for EGFR and PD-L1 expression, characteristics of the TME, and posttreatment changes (eg, T-cell infiltration, enumeration, and activation).
- Explore the relationships between PK, pharmacodynamics, patient safety, and TAK-186 antitumor activity.
- Longitudinal ctDNA monitoring will be done at baseline and on-treatment.

9.5.15.3 Tumor Biopsy

Fresh paired tumor biopsy samples are optional for patients in the dose-escalation phase and backfill cohorts. During the cohort-expansion phase, patients will be required to consent to fresh paired tumor biopsies. Samples will be preferably taken from the same lesion. Once the target number of biopsies has been collected, additional paired pretreatment and on-treatment biopsies will not be required; sample collection will be optional after this time point.

Patients are required to provide fresh paired tumor biopsy samples first during screening (pretreatment) and then within 7 days before Cycle 2 Day 1 (on treatment), as specified in the Schedule of Events ([Appendix A](#)).

For fresh tumor biopsies, the lesion must be accessible (those occurring outside the brain or those that are accessible by an interventional or endoscopic procedure) for a low-risk biopsy procedure that does not place the patient at an unjustifiable risk in the opinion of the investigator.

The investigator should inform the sponsor's medical monitor and document the reason for not attempting the biopsy in an enrolled patient for all patients for whom the procedure is required and feasible.

Patients who have an archived biopsy specimen available that was obtained up to 90 days prior to treatment initiation and have received no other treatment from the time of biopsy until the start of treatment with TAK-186, may submit that archived specimen in lieu of a pretreatment biopsy upon agreement from the sponsor.

The following are the guidelines for biopsy:

- The pretreatment biopsy should be obtained from patients before the study treatment starts, preferably within 28 days of C1D1. No washout period for prior therapies is required before the biopsy.
- Biopsy should not be obtained from lesions used as RECIST 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 should be obtained from the same lesion used for the 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.
- Up to 3 additional biopsy cores may be obtained if this can be performed 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.
- If the pretreatment biopsy is deemed inadequate for testing and evaluation by the sponsor, the planned paired on-treatment biopsy is not required.

Additional instructions for the processing and storage of tumor biopsy specimens are provided in the laboratory manual. If the sponsor makes the decision to terminate the study for any reason, the collection and analysis of all pharmacodynamic, PK, biomarker and ADA samples may be stopped.

9.5.16 Pharmacokinetic and ADA Assessments

Blood samples for PK and ADA evaluation will be collected at the time points shown in [Appendix B](#). Blood samples will be collected from the arm contralateral to the site of IV infusion. Plasma concentrations of study drug and ADA titers will be measured at the sponsor's designated central laboratory using appropriate validated assays. ADA-positive samples will be tested for neutralizing ADA.

9.5.17 Additional Exploratory Research

Patients may provide consent for the acquisition and use of the following tumor and tissues, blood, and biological samples for exploratory analysis:

- Leftover tissue and/or blood samples obtained from protocol-specific procedures in this study. Such leftover samples may be used for future exploratory research.
- If a patient undergoes a non-protocol-related, medically indicated procedure at any time during the study that has the likelihood of yielding tissue, blood, or other fluids, any

remaining or a portion of the samples not necessary for medical diagnosis may be obtained. Leftover samples may be used for future exploratory research.

9.5.18 Patient-Reported Outcomes Assessments

Patient-reported outcome (PRO) instruments will be administered electronically to patients in the cohort-expansion phase on the day of regularly scheduled visits, before administration of TAK-186 or any other study medications, as outlined in the Schedule of Events ([Appendix A](#)). The patient should be given enough space and time to complete the questionnaires. The patient should answer the questionnaires on their own without any assistance from site staff. If a patient does not complete any baseline PRO assessments, they are not required to complete further PRO assessments at later visits.

If the sponsor makes the decision to terminate the study for any reason, the patient-reported outcome collection and analysis may be stopped.

9.5.18.1 *Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)*

The PRO-CTCAE is a PRO measure developed to evaluate symptomatic toxicity in patients on cancer clinical trials ([Basch et al. 2016](#)). The PRO-CTCAE was designed to be used as a companion to the CTCAE measurement system. The PRO-CTCAE characterizes the frequency, severity, interference with usual/daily activities, and/or presence or absence of symptomatic toxicities that can be meaningfully reported from the patient perspective. The PRO-CTCAE includes an item library of 124 items representing 78 symptomatic toxicities drawn from the CTCAE (<https://healthcaresdelivery.cancer.gov/pro-ctcae/item-library.pdf>). All components of the PRO-CTCAE measurement system are developed and validated in accordance with well-established measurement principles, as well as guidelines for PRO instrument development and validation articulated by the International Society for Quality of Life Research, ISPOR – The Professional Society for Health Economics and Outcomes Research, the US FDA, and the European Medicines Agency (EMA).

In this study, specific items from the PRO-CTCAE library will be selected (up to 20 concepts, no more than 30 questions total) for inclusion based on clinical data, review of published AE data on other treatments, and identified symptomatic AEs likely to be associated with the treatment with TAK-186.

9.5.18.2 *Functional Assessment of Cancer Therapy (FACT) Item Bank*

The FACT item bank is designed to assess health-related quality of life (HRQoL) in cancer patients. Items from the FACT item bank will be utilized to assess overall side-effect burden (single item FACT-GP5) and up to 2 additional items to capture any other key side effects not captured by the PRO-CTCAE (eg, fever).

9.6 Completion of Study Treatment (for Individual Patients)

Patients will be considered to have completed study treatment if they complete 7 cycles of treatment with TAK-186 without disease progression or experience intolerable toxicity and the investigator deems the patient not suitable to continue the treatment.

After completion of study treatment, the patient will proceed to EOT visit. The EOT visit should be performed 30 (+10) days after the last dose of TAK-186. If the investigator's decision to discontinue study drug is beyond 30 days after the last dose, EOT visit should occur as soon as possible. All required procedures and tests should be performed at the EOT visit. A list of evaluations is provided in the Schedule of Events ([Appendix A](#)).

9.7 Completion of Study (for Individual Patients)

Patients will be considered to have completed the study if the patient has completed 7 cycles and completed the 48-week post-treatment follow-up or until death, whichever occurs first.

The end-of-study visit will occur at the time of completion of posttreatment follow-up period.

9.8 Discontinuation of Treatment With Study Drug and Patient Replacement

Study drug must be permanently discontinued for patients meeting any of the following criteria as described in Section [8.5.4](#):

If a patient is withdrawn from the study or from TAK-186 dose administration for any reason other than PD, the investigator should make every effort to notify the sponsor within 24 hours.

Once study drug has been discontinued, all study procedures outlined for the EOT visit will be completed as specified in the schedule of events (see [Appendix A](#)). The primary reason for study drug discontinuation will be recorded on the eCRF.

9.9 Withdrawal of Patients From Study After Study Drug Discontinuation

All patients who receive at least 1 dose of study drug will be followed for a total of 48 weeks after the last dose, unless the following criteria are met:

- Lost to follow-up:
A patient may be determined to be lost to follow-up after failure of 3 documented phone and/or other electronic contacts that include, but are not limited to, email, mail, or telephone communication retrieval from online or other databases (eg, Social Security indexes). If a patient does not have access to electronic means of communication, a letter should be mailed to the patient at the patient's last known address.
- The study is terminated.
- Withdrawal of consent.
- Death.
- Investigator discretion.

- Other.

If a patient withdraws consent, no new information will be collected from the patient after the time point of consent withdrawal, but information publicly available (eg, death record from local database) may still be collected by the site or sponsor for analysis purposes, where allowed by local regulation.

9.10 Study Compliance

TAK-186 will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of TAK-186 dose calculation, administration, and dose administration. This includes recording if the full assigned TAK-186 dose was infused and time interval, or if not the full assigned dose, the amount remaining in the syringe and duration of infusion. Any decrease below the calculated infusion rate should be recorded and whether the full dose was received. The site monitor will review dose calculation, administration, regimen, and medication accountability during investigational site visits and at the completion of the study.

9.11 Immune-Related AE Follow-up

Patients will have an onsite follow-up visit to assess immune-related AEs 90 (+7) days after the last dose of TAK-186, unless subsequent systemic anticancer therapy is started before this time. Relevant laboratory tests and examinations may be required if an immune-related AE is suspected. All immune-related AEs must be reported as specified in Section 10.2.

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

9.12 Posttreatment Follow-up Assessments

The posttreatment follow-up period includes:

- **Survival Follow-up:** All patients will be followed for survival status for up to 48 weeks, or until death, lost to follow-up, or noncompliance, whichever occurs first. In addition, the start of another anticancer therapy for the disease under study will be collected.

Patients who discontinue study treatment for reasons other than radiological disease progression (see Section 9.8) shall continue with posttreatment assessments as outlined in the schedule of events (Appendix A) until radiological disease progression occurs.

NOTE: Related SAEs 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 ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient who has provided informed (e)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 subject 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 AE will also be considered to be any untoward effect of a study-related procedure, which is conducted after signed informed consent.

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. If laboratory evaluations were done during screening and again before the first dose of TAK-186, the most recent laboratory values collected should be used as baseline.

10.1.3 TEAEs

All AEs, except immune-related AEs, with start date from first dose of study drug until 30 days after the last dose of study drug, and immune-related AEs with start date from first dose of study drug until 90 days after the last dose of study drug will be considered treatment-emergent adverse events (TEAEs). Events meeting this definition will be those occurring during or after administration of the first 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 Adverse Drug Reaction Definition

An adverse drug reaction is a noxious and unintended response related to the medicinal product at any dose. As used herein, the phrase “response to a medicinal product” means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility (ie, the relationship cannot be ruled out).

10.1.5 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 one 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.

For all doses in all cycles, patients can be monitored overnight if the patient develops symptoms suggestive of CRS during the in-clinic observation period and admitted to the hospital at any time if clinically indicated. All hospitalizations for the sole purpose of drug administration and observations are considered planned for the purpose of the study and should not be considered SAEs. Agents necessary for CRS management including, but not limited to, tocilizumab must be available for each of these hospital admissions. AEs that occur during such planned hospitalization that meet the usual indication of hospitalization by the investigator's medical judgement or AEs that prolong hospitalization should be reported as SAEs. Hospitalization following the onset of symptoms suggestive of CRS with the purpose of close monitoring and supportive treatment should also be considered an SAE.

Elective surgical procedures are to be excluded from reporting SAEs.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 5.0, effective 27 November 2017 (ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf) and ASTCT CRS consensus grading for CRS (see [Appendix H](#)).

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 above 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 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). If a patient experiences an AE after the informed consent document is signed and before treatment with study drug, it should be captured as medical history; however, if the investigator believes the AE may have been caused by a protocol-related procedure it will be recorded as an AE and entered on the eCRF. 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 study drug was given are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial; eg, surgery was performed earlier or later than planned.

Elective surgical procedures are to be excluded from reporting SAEs.

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 and ASTCT CRS consensus grading for CRS (see [Appendix H](#)).

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 (e)consent through 30 days after administration of the last dose of study drug and recorded in the eCRFs.
- Immune-related 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 (e)consent through the EOT visit after administration of the last dose of study drug and recorded in the eCRF. After this period, only related SAEs 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).
- The investigator must follow all SAEs until resolution, stabilization, or return to baseline.

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a patient becomes pregnant or suspects pregnancy while participating in this study, the patient must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately 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 patient impregnates a partner during participation in this study, the sponsor must also be contacted immediately by sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. Every effort should be made to follow the pregnancy for the final pregnancy outcome and status of mother and child, even if the patient was discontinued from the study.

Pregnancy complications must be reported as SAE. Elective terminations for medical reasons will be considered a complication of pregnancy. The medical reason will be considered an SAE and termination will be considered as the outcome of the medical reason. Spontaneous miscarriages must be reported as an SAE.

10.5 Procedures for Reporting Product Complaints or Medication Errors (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 in the study manual.

A medication error is a preventable event that involves an identifiable patient and leads to inappropriate medication use, which may result in patient harm. Whereas overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error (including overdose) situation should immediately report this via the contact information provided in the study manual.

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or a medication error 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, including the EMA, investigators, and IRBs and IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. 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 sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the trial. 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

Full details of procedures for data handling will be documented in the Data Validation Manual and CDS Strategy and Operational Plan. AEs, medical history, prior and concomitant procedures, and CRS signs and Symptoms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each patient who signs an informed (e)consent.

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 informed (e)consent forms, 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) and telemedicine records. 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 Section 4.9.5 requires the investigator to retain essential documents specified in 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 (SAP) 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 statistical summaries will be primarily descriptive consisting of the frequencies of each category of discrete variables and of means, standard deviations, medians, minimum, and maximum values for continuous variables and number and percentages will be used for categorical variables.

Safety and efficacy summaries will be provided by dose level and schedule, and/or by tumor type (NSCLC, CRC, HNSCC, etc). Response rates may be calculated for specific disease subgroups, if appropriate.

Baseline will be considered the closest value obtained before administration of the first dose of TAK-186. In general, data that are reported as missing will be treated as missing in all data summaries. In descriptive summaries for safety, outlying data (ie, extreme relative to the majority of the data) will not be altered or removed from the summary.

13.1.1 Analysis Sets

The following populations will be used for analysis: the DLT-evaluable, safety (all-treated), PK, immunogenicity, and pharmacodynamics, and defined as follows:

- **DLT-evaluable population:** all patients who receive at least 3 target doses of TAK-186 in a dose cohort [REDACTED], or at least 2 target doses of TAK-186 with [REDACTED], or experience a DLT within the DLT-evaluation period.
- **Safety population (All-Treated):** all patients who receive at least 1 dose of TAK-186. This population will be used for safety and efficacy analyses. Patients who receive at least 1 dose of TAK-186 and have relevant blood sampling will be included in PK, immunogenicity, and pharmacodynamics analyses. Details are as follows:

PK population: all patients who receive at least 1 dose of TAK-186 and sufficient PK data to reliably estimate 1 or more PK parameters.

Immunogenicity population: all patients who receive at least 1 dose of TAK-186 and have a baseline immunogenicity sample and at least 1 postbaseline immunogenicity sample for assessment.

Pharmacodynamics population: all patients who receive at least 1 dose of TAK-186 and have sufficient dosing and pharmacodynamics data to reliably measure pharmacodynamics parameters.

PRO analysis population: all patients in the cohort-expansion phase with a baseline and at least one postbaseline measurement of any PRO. The analyses of PROs will be based on the PRO analysis population set.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Patient disposition, demographics, baseline characteristics, disease history, medical history, concomitant medications, and study drug exposure data will be summarized using descriptive statistics.

13.1.3 Efficacy Analysis

13.1.3.1 Objective Response and Response Duration

The primary measure of efficacy analysis for this study is ORR and is defined using RECIST v1.1 criteria ([Appendix C](#)). Two-sided exact 90% CIs will be constructed around the ORRs. In addition, a supplementary analysis using modified RECIST v1.1 criteria ([Appendix D](#)) to assess ORR and best overall response (BOR) will be carried out for comparison. Determination of the ORR will be calculated based on the proportion of patients achieving a CR or PR among those patients who received at least 1 dose of TAK-186. Confirmed objective responses (subsequently documented with a confirmatory CT or MRI scan ≥ 28 days after initial CR or PR) will be used to calculate overall ORRs. Objective responses that are not subsequently documented with a confirmatory CT or MRI scan (eg, unconfirmed responses) will be used in a supportive analysis for ORR of confirmed and unconfirmed response. DoR will be calculated for responders as the time from initial response (CR or PR) to the time of documented PD or death, whichever occurs first using both RECIST v1.1 ([Appendix C](#)) and modified RECIST v1.1 ([Appendix D](#)) criteria. Kaplan-Meier methodology will be used to estimate DoR, PFS, and OS. Responders who complete the study without documented PD will be censored at the date of their last tumor assessment. Any patient who dies after 2 or more missed assessments will also be censored at the date of their last tumor assessment.

13.1.3.2 Progression-Free Survival

PFS will be calculated as the time from the date of the first dose of study drug until the date of any documented confirmed PD using both RECIST v1.1 ([Appendix C](#)) and modified RECIST

v1.1 ([Appendix D](#)) or the date of death from any cause. A patient's PFS will be censored if at the time of last assessment for progression, the patient remains progression free or if the patient dies after 2 or more missed tumor assessments. PFS will be determined using both conventional RECIST v1.1 (one objective progression) and modified RECIST criteria (confirmed objective progression, ie, 2 scans demonstrating objective progression). For the modified criteria, if the subsequent scan confirms progression or an additional scan is not performed, the PFS date will be based on the first occurrence of progression. However, if the patient has later scans showing no PD following initial unconfirmed progression of disease, then it is not a confirmed disease progression and the PFS per modified RECIST for this patient is censored at the last tumor assessment date. Kaplan-Meier methods will be used to estimate PFS over time and the median duration of PFS. In addition, PFS rates will be calculated at 3 months, 6 months and 12 months from the first dose of study drug using Kaplan-Meier methods. The method of Brookmeyer and Crowley ([Brookmeyer and Crowley 1982](#)) will be used to construct 90% CIs around PFS estimates of the median for each expansion cohort.

13.1.3.3 OS

OS will be calculated as the time from the first dose of study drug until death due to any cause. OS will be censored for patients who were known to be alive at last contact. In addition, landmark 3 months, 6 months, 12 months, 18 months, and 24 months OS rates will be determined using Kaplan-Meier methods.

The primary analysis of this study will be carried out when all patients have discontinued therapy or, if continuing therapy, have data available through approximately 6 months of follow-up.

13.1.4 Pharmacokinetic Analysis

Noncompartmental PK analysis will be performed on individual plasma concentrations using industry standard software such as Phoenix WinNonlin. Single and multiple-dose PK parameters of maximum plasma concentration, time to maximum concentration (t_{max}), area under the concentration-time curve for a dose administration interval (AUC_{tau}), AUC_{last} , area under the concentration-time curve from time 0 to infinity (AUC_{inf}), CL, volume of distribution at steady state, and terminal half-life will be derived from plasma concentration versus time data. Other PK parameters may also be reported, as applicable.

Individual TAK-186 plasma concentrations will be listed by time point and summarized by dose level. Individual and mean TAK-186 plasma concentration-time profiles for each dose level will also be presented graphically. PK parameters will be listed and summarized using descriptive statistics, including arithmetic and geometric mean, median, standard deviation, coefficient of variation (CV), geometric CV, minimum, and maximum.

Population PK analyses may be conducted using data from this study alone or combined with data from other studies.

13.1.5 Pharmacodynamic Analysis

Summary statistics analyzing changes from baseline for pharmacodynamic parameters including those listed in Section 9.5.15.2 may be summarized and/or presented graphically as possible depending on the data. In addition, possible associations between changes in pharmacodynamic measures of interest and TAK-186 dose and exposure may be explored.

13.1.6 Immunogenicity Analyses

The proportion of patients who are negative for TAK-186 ADAs at baseline and become positive in this assay, the proportion of patients who are negative at baseline and remain negative, and the proportion who have positive ADAs at baseline that increase or decrease in titer over the course of treatment will be summarized. Neutralizing ADA status will be determined for ADA-positive samples, and the effect on PK, safety, and efficacy (antitumor activity) will be evaluated.

13.1.7 Biomarker Analysis

Multiple markers, including those listed in Section 9.5.15.2, will be assessed for correlation with patient response and further evaluation of TAK-186 mechanism of action. Multiple exploratory biomarkers will be evaluated to assess dose activity, mechanism of action, and the potential for use in patient selection and stratification at later clinical stages.

13.1.8 Safety Analysis

13.1.8.1 AEs

AEs will be summarized using the safety population. AEs will be graded using NCI CTCAE version 5.0 and coded using the MedDRA. Data will be summarized using Preferred Term (PT) and primary System Organ Class (SOC). Only TEAEs will be summarized in tables. Events before treatment (eg, due to study-related procedure) will be listed in an appendix. In addition, events that start before treatment but worsen in intensity while on treatment will be considered TEAEs.

The following tables of AE data will be created to summarize the number and percentage of patients who experience at least 1 event of each of the following types. Tables will include events irrespective of attribution unless otherwise indicated.

The tables will include the following:

- All TEAEs.
- Drug-related TEAEs of any grade.
- CTCAE Grades 3 or 4 TEAEs.
- CTCAE Grades 3 or 4 drug-related TEAEs.
- All SAEs (may be a listing if there are few events).

- Drug-related SAEs.
- Fatal AEs (may be a listing if there are few events).
- TEAEs that lead to dose interruption.
- TEAEs that lead to dose reduction.
- TEAEs that lead to dose delay.
- TEAEs that lead to discontinuation of study drug.

All these tables will display the number and percentage of patients who experience the given event and will display events by MedDRA SOC and PT. AEs will be displayed alphabetically for SOC and in descending order of overall PT incidence within each SOC.

In addition, an overall summary of AEs will display the number and percentage of patients who experience at least 1 event of each of the following types:

- All TEAEs.
- All DLTs
- Drug-related TEAEs of any grade.
- CTCAE Grades 3 or 4 TEAEs.
- CTCAE Grades 3 or 4 drug-related TEAEs.
- All SAEs (may be a listing if few events are reported).
- Drug-related SAEs.
- TEAEs that lead to dose interruption.
- TEAEs that lead to dose reduction.
- TEAEs that lead to dose delay.
- TEAE that lead to discontinuation of study drug.
- Fatal AEs (may be a listing if few events are reported).
- Deaths occurred within 30 days of treatment discontinuation.
- Deaths due to study drug-related AE (regardless of onset date).

13.1.8.2 Laboratory Assessments

Summaries will be grouped by laboratory panel (eg, hematology, blood chemistry, and urinalysis) and will be displayed for each laboratory parameter. Shift tables will be used to display the percentage of patients who have a shift in their lab grades at baseline to maximum postbaseline CTCAE severity grade.

13.1.8.3 Other Safety Assessments

ECGs will be collected and analyzed for evidence of cardiac toxicity, especially prolongation of QT interval. Vital signs will be summarized with descriptive statistics.

13.1.9 PRO Analysis

All PRO analyses will use the PRO analysis population set. Data on symptomatic AEs and overall side-effect burden will be summarized using descriptive statistics. The change from baseline of selected scores will also be summarized using descriptive statistics over time. Compliance will be summarized for each questionnaire by the number of expected and number and percentage of responses received over time and overall. Further details on the specific descriptive analyses to be performed are reported in the SAP.

13.2 Interim and Futility Analyses

An interim futility analysis is planned when the first 15 patients in each cohort become evaluable for efficacy either by having at least 3 postbaseline scans or have discontinued therapy, whichever occurs earlier.

Based on the Bayesian predictive probability design using ORR data, patient enrollment in each cohort may be stopped if the predictive probability of success given the observed interim analysis data is <20%. Table 13.a shows the futility stopping boundaries at each interim analysis for each cohort in the cohort-expansion phase.

Table 13.a Futility Boundary at the Interim Analysis for Each Cohort

Interim Analysis	Number of Patients Treated	Minimum Number of Responders to Proceed	
		HNSCC/NSCLC	CRC
IA	15	2	1

CRC: colorectal cancer; HNSCC: head and neck squamous cell carcinoma; IA: interim analysis; NSCLC: non-small cell lung cancer.

Assuming the true ORR is 10% for patients with HNSCC/NSCLC (ie, uninteresting response rate), the probability of early termination at the interim analyses is 82%. For patients with CRC, the probability of early termination at the interim analyses is 83% if the true ORR is 5% (ie, uninteresting response rate). Table 13.b shows the probability of early termination under different assumptions of true ORR for each cohort in the cohort-expansion phase.

Table 13.b Probability of Early Termination for Futility Under Different Assumptions of True ORR for Each Cohort

True ORR	HNSCC/NSCLC	CRC
5%	96%	83%
10%	82%	55%
15%	60%	32%
20%	40%	17%
25%	24%	8%
35%	6%	1%
40%	3%	0.5%

CRC: colorectal cancer; HNSCC: head and neck squamous cell carcinoma; NSCLC: non-small cell lung cancer; ORR: objective response rate.

13.3 Determination of Sample Size

The number of patients to be enrolled into the dose-escalation phase of the study cannot be determined in advance and could be up to approximately 48 patients. More than 48 patients may be enrolled depending on results during the study, adding patients into backfill, and number of TAK-186 doses evaluated. This number does not account for replacement of non-evaluable patients or the backfill patients.

Approximately 30 patients with NSCLC will be enrolled during the cohort-expansion phase. Additional patients with EGFR expressing solid tumors, such as CRC and HNSCC, may be enrolled with approximately 30 patients per tumor type. Further, patients may be enrolled to allow comparison between 2 different doses or regimens of TAK-186 for selected tumor type(s) by 1:1 randomization to each dose/regimen (eg, 40 patients randomized 1:1 for NSCLC). Therefore, the total sample size of the cohort-expansion phase of the study is estimated to be up to approximately 210 patients. A Bayesian predictive probability design will be used to allow interim analyses to stop early for futility within each tumor histology (Lee and Liu 2008). See Section 13.2 for details of the interim futility analyses. It is not planned to stop early for efficacy at any of the interim analyses.

For patients with NSCLC/HNSCC, efficacy of TAK-186 will be considered clinically relevant if at least 8 of 30 treated patients have a confirmed PR or better response at the end of the cohort-expansion phase. With a noninformative beta prior with shape parameters 1 and 1 for ORR, 8 of 30 patients with a response provide at least 80% posterior probability of true ORR being higher than 20%. The design has reasonable operating characteristics. With a true ORR of 10% (ie, uninteresting response rate), the probability of declaring success (ie, at least 8 responders out of 30 patients) is less than 1%. On the other hand, with a true ORR of 35% and 40%, the probability of declaring success is 85% and 94%, respectively.

For patients with CRC, efficacy of TAK-186 will be considered clinically relevant if at least 5 of 30 treated patients have a confirmed PR or better response at the end of the cohort-expansion

phase. With a noninformative beta prior with shape parameters 1 and 1 for ORR, 5 responders out of 30 patients provides at least 80% posterior probability of true ORR being greater than 12%. The design has reasonable operating characteristics. With a true ORR of 5%, the probability of declaring success (ie, at least 5 responders out of 30 patients) is 1%. On the other hand, with a true ORR of 25% and 30%, the probability of declaring success is 86%, and 95%, respectively.

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

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Where permitted by local and country regulations, alternative approaches such as remote source data review via phone or video may be used to ensure data quality and integrity and patient safety. Additional details are in the monitoring plan. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee 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 sufficient 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 UK Medicines and Healthcare products Regulatory Agency [MHRA], the Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). 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.

14.4 Investigational Product Disposal at End of Study

Upon study completion or termination, unopened vials of study drug or solution stabilizer will be returned to the sponsor or its representative, unless the study site has received written authorization from the sponsor to destroy study drug at the site, as applicable and allowed by local and country regulations. All drug returns must have appropriate documentation and be clearly identified by protocol number and study site number on the outermost shipping container. If study drug destruction of drug at the site is approved, the investigator must ensure arrangements are made for proper disposal and that records of disposal are documented and maintained, and copies provided to the sponsor.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual patients (herein “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 B](#). 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 IB, 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 notify the 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 trial. Until the site receives notification of activation, 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 (e)Consent, and Patient Authorization

Written and electronic 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, including the use of electronic devices and associated technologies (if applicable). 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 patient 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 or electronic 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 (e)signed and dated by the patient, or the patient's legally acceptable representative, at the time of (e)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 in the case of written informed consent. The investigator must also (e)sign and date the ICF and patient authorization (if applicable) at the time of (e)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 (e)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 provided 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 (e)consent. The date the revised (e)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), 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 (e)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 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 patient access to trials via registries. In certain situations/registries, Takeda may assist patients or potential patients 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 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.

Data collected in this clinical study belong to the study sponsor who will formulate a policy on the use of study data. This policy will be codified in the Clinical Trial Agreement. This includes authorship issues, including scheduling and prioritizing analyses for reports, publications, and presentations; and developing a review and approval process.

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 [REDACTED]														Cycle 2					Cycle 3 and Beyond					EOT/ 30 Days After Last Dose ^b	Immune- related AE Follow- up/90 Days After Last Dose ^c	Survival Follow- up / EOS ^d
	Day	1	2	8	9	15	16	17	22	29	36	43	49 ^e	50 ^f	56 ^g	1	2	3	8	15/ 22/ 29/36/ 43/50	56	1	8	15/22/ 29/36/ 43/50	56			Q12W
Visit window (±) days		0	0	3	0	3	0	0	3	3	3	3	3	3	3	3	0	0	3	3	3	3	3	3	3	+10	+7	7
Administer TAK-186 ^g		X		X		X			X	X	X	X		X		X			X	X		X	X	X				
Post-infusion observation ^h		X		X		X			X	X	X	X		X		X			X	X		X	X	X				
ICF ⁱ	X																											
Medical history	X																											
Physical examination/ directed physical examination ^j	X	X ^k		X		X			X	X	X	X		X		X			X	X		X	X	X		X		
ECOG performance status	X	X														X						X				X		
ECG ^l	X	X	X	X	X	X	X	X		X						X	X	X	X	X ^m		X						
Vital signs ⁿ	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		

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Table A1 Schedule of Events, [REDACTED]

Evaluation/ Procedure	Screening (Within 28 Days of First Dose)	Cycle 1 ^a 														Cycle 2						Cycle 3 and Beyond				EOT/ 30 Days After Last Dose ^b	Immune- related AE Follow- up/90 Days After Last Dose ^c	Survival Follow- up / EOS ^d	
	Day	1	2	8	9	15	16	17	22	29	36	43	49 ^e	50 ^f	56 ^g	1	2	3	8	15/ 22/ 29/36/ 43/50	56	1	8	15/22/ 29/36/ 43/50	56			Q12W	
	Eligibility checklist and patient registration ^o	X																											
Patient diary review ^p				X		X			X	X	X	X		X		X													
LABORATORY ASSESSMENTS																													
Comprehensive chemistry panel ^q	X	X ^k	X	X	X	X	X		X							X	X			X ^m			X	X			X		
Special chemistry ^q	X	X ^k							X							X							X				X		
Hematology ^q	X	X ^k							X							X							X				X		
Coagulation ^q	X	X ^k														X							X				X		
Endocrine test ^q	X																												
Urinalysis ^q	X	X ^k														X							X				X		
Pregnancy test ^r	X	X														X							X				X ^r		
PK ^s		X	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X	X ^m			X				X		
Cytokines ^s		X	X	X	X	X	X	X	X	X						X	X	X	X										
Flow cytometry (subset) ^s		X	X	X	X	X	X	X	X			X		X		X	X	X					X ^t						

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Table A1 Schedule of Events, [REDACTED]

Evaluation/ Procedure	Screening (Within 28 Days of First Dose)	Cycle 1 ^a 														Cycle 2					Cycle 3 and Beyond				EOT/ 30 Days After Last Dose ^b	Immune- related AE Follow- up/90 Days After Last Dose ^c	Survival Follow- up / EOS ^d		
	Day	1	2	8	9	15	16	17	22	29	36	43	49 ^e	50 ^f	56 ^f	1	2	3	8	15/ 22/ 29/36/ 43/50	56	1	8	15/22/ 29/36/ 43/50	56			Q12W	
Antidrug antibody ^s		X		X		X			X	X	X	X		X		X				X ^u		X				X			
EFFICACY ASSESSMENTS																													
Tumor marker ^v	X															X						X				X ^w			
ctDNA ^s		X														X						X				X			
Tumor assessment (CT/MRI) ^x	X												X		X						X				X	X ^w		X ^y	
Brain MRI ^z	X												X		X						X				X	X ^w			
Archival tissue ^{aa}	X																												
Biopsy ^{bb}	X											X _{cc}		X ^{cc}															
Survival follow-up contact																												X	

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Table A1 **Schedule of Events,** [REDACTED]

Evaluation/ Procedure	Screening (Within 28 Days of First Dose)	Cycle 1 ^a														Cycle 2						Cycle 3 and Beyond				EOT/ 30 Days After Last Dose ^b	Immune- related AE Follow- up/90 Days After Last Dose ^c	Survival Follow- up / EOS ^d	
	Day	1	2	8	9	15	16	17	22	29	36	43	49 ^e	50 ^f	56 ^f	1	2	3	8	15/ 22/ 29/36/ 43/50	56	1	8	15/22/ 29/36/ 43/50	56			Q12W	
Patient-Reported Outcomes																													
PRO assessments ^{dd}		X ^{ee}		X		X			X	X	X	X		X		X			X	X			X	X ^{ff}		X			
SAFETY ASSESSMENTS																													
Safety check ^{gg}		X		X		X			X	X	X	X		X		X			X	X									
Concomitant medications	Recorded from the signing of ICF through 30 days after the last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.																												
Assessment of AEs	Recorded from the signing of ICF through 30 days after the last dose of study drug.																												
Immune-related AEs	Recorded from the signing of the ICF through 90 days after the last dose of study drug.																								X				
AE: adverse event; CD: Cycle Day; CEA: carcinoembryonic antigen; CNS: central nervous system; CT: computed tomography; CRS: cytokine release syndrome; ctDNA: circulating tumor DNA; DLT: dose-limiting toxicity; ECG: electrocardiogram/electrocardiography; 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; iCRO: imaging contract research organization; IRR: infusion-related reaction; MRI: magnetic resonance imaging; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC: non-small cell lung cancer; PK: pharmacokinetic(s); PRO: patient-reported outcome; 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-186 dose and Cycle 1 Day 28 in the dose-escalation phase.																													
^b EOT visits will be conducted 30 (+10) days after the last dose of TAK-186. If the investigator decision to discontinue study drug is beyond 30 days after last dose, EOT visit should occur as soon as possible.																													
^c Patients will attend a follow-up visit to assess immune-related AEs 90 (+7) days after last TAK-186 dose, unless subsequent systemic anticancer therapy is started before this																													

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Table A1 Schedule of Events, [REDACTED]

Evaluation/ Procedure	Screening (Within 28 Days of First Dose)	Cycle 1 ^a												Cycle 2					Cycle 3 and Beyond				EOT/ 30 Days After Last Dose ^b	Immune- related AE Follow- up/90 Days After Last Dose ^c	Survival Follow- up / EOS ^d	
	Day	1	2	8	9	15	16	17	22	29	36	43	49 ^e	50 ^f	56 ^f	1	2	3	8	15/ 22/ 29/36/ 43/50	56	1	8	15/22/ 29/36/ 43/50	56	

Evaluation/ Procedure

time. Relevant laboratory tests and examinations may be required if immune-related AE is suspected.

^d The EOS visit should be performed when the patient completes the 48-week 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 **For dose escalation only:** Cycle 1 will complete on Day 49. Cycle 1 Day 49 visit applicable only for patients in dose escalation.

^f **For cohort expansion only:** Cycle 1 assessments listed for Day 50 and Day 56 are applicable.

^g TAK-186 will be administered over 60 (± 10) minutes. Based on emerging data (eg, severity of the IRRs), the infusion time may be adjusted to shorter than 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-186 infusion must be documented. After the DLT-evaluation period, a minimum of a 4-day interval should occur between doses of TAK-186.

^h Post-infusion observations: The following observations are required for Cycle 1:

Overnight observation: C1D1, C1D8, C1D15.

4-hour observation: C1D22, C1D29.

Starting with Cycle 2, 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 of CRS during the in-clinic observation period or otherwise, if clinically indicated.

ⁱ Informed consent is to be obtained before enrollment (no time constraint). Study-specific procedures must be conducted only after informed consent is obtained.

^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 and on Cycle 1 Day 1. If physical examination during screening was completed within 7 days of C1D1, a complete physical examination does not need to be repeated. On Day 1 of all subsequent cycles and on other days, a directed physical examination may be performed instead of the full physical examination focused on areas based on the patient's recent medical history and the investigator's clinical discretion. A basic neurologic examination using an assessment tool such as the ICE score will be conducted to evaluate neurologic status at baseline and repeated as clinically indicated after the first symptoms of ICANS are suspected until resolution.

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Table A1 **Schedule of Events,** [REDACTED]

	Screening (Within 28 Days of First Dose)	Cycle 1 ^a														Cycle 2					Cycle 3 and Beyond				EOT/ 30 Days After Last Dose ^b	Immune- related AE Follow- up/90 Days After Last Dose ^c	Survival Follow- up / EOS ^d		
		Day	1	2	8	9	15	16	17	22	29	36	43	49 ^e	50 ^f	56 ^g	1	2	3	8	15/ 22/ 29/36/ 43/50	56	1	8				15/22/ 29/36/ 43/50	56
Evaluation/ Procedure																													

^k Predose test need not be repeated if performed during screening within 72 hours of C1D1.

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

Screening: Performed in triplicate at one time point within 28 days of the first dose of TAK-186.

Cycle 1:

Days 1, 8, and 15: Pre-infusion within -30 min to 0 min of SOI, EOI within 0 to + 30 min of EOI, 1 hour after EOI (within ±30 min).

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

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

Day 29: Pre-infusion (within -30 min to 0 min) and EOI (within 0 to +30 min).

Cycle 2:

Day 1: Pre-infusion (within -30 min to 0 min) and EOI (within 0 to + 30 min).

Days 2, 3 (24 and 48 hours after EOI), and 8: One ECG within ±3 hours after SOI.

All Other ECGs: Pre-infusion (within -30 min to 0 min) on TAK-186 infusion days.

^m For ECG, comprehensive chemistry panel and PK: Only done in Cycle 2, on Days 15 and 22 (when PK lab samples are drawn).

ⁿ 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: Pre-infusion (within -30 min to 0 min); at 15 minutes after SOI (within ±5 minutes); at EOI (within +10 minutes); and at 1, 2, 3, 4, 5 and 6 hours after EOI (within ±10 minutes for each time point).

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Table A1 Schedule of Events, [REDACTED]

Evaluation/ Procedure	Screening (Within 28 Days of First Dose)	Cycle 1 ^a														Cycle 2					Cycle 3 and Beyond				EOT/ 30 Days After Last Dose ^b	Immune- related AE Follow- up/90 Days After Last Dose ^c	Survival Follow- up / EOS ^d
	Day	1	2	8	9	15	16	17	22	29	36	43	49 ^e	50 ^f	56 ^g	1	2	3	8	15/ 22/ 29/36/ 43/50	56	1	8	15/22/ 29/36/ 43/50	56		
Days 2, 9, and 16: 24 hours after EOI (within ±3 hours). Day 17: 48 hours after EOI (within ±3 hours). Days 29, 36, and 43; Day 50 for cohort expansion only, as applicable: Pre-infusion (within -30 min to 0 min), at EOI (within +10 minutes), and at 1 and 4 hours after EOI (within ±15 minutes for each time point). Starting with Cycle 2: Pre-infusion (within -30 min to 0 min) and at EOI (within +10 minutes). Post-EOI vital signs monitoring can be deferred if patient has been clinically stable and per the investigator's discretion. ^o Register patient: Administration of the initial TAK-186 dose to the first 3 patients treated in each dose escalation cohort will be staggered by a minimum of 48 hours. ^p Through the end of Cycle 1, on non-dose administration days or when the patient is not hospitalized, patients will be asked to record their temperature twice daily in a patient diary (first in the morning and then in the evening) and any time the patient feels febrile. The diary should be brought to the site at each visit through C2D1. If a patient experiences a temperature ≥38°C at any time during the study, they will be instructed to call the investigator. Clinically significant fever will be reported as an AE according to NCI CTCAE v5.0 guidelines. ^q Laboratory assessments: See Appendix I for the list of laboratory tests. Samples to be obtained before infusion (on-treatment days) and analyzed by the local laboratory. Assessment to be done within 72 hours before dose administration. ^r Pregnancy test: A serum hCG 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 last test was not done within 7 days of EOT. ^s See Appendix B for specific time points and details. ^t Flow Cytometry: For Cycle 3 and beyond, only done on Day 1 of Cycle 3. ^u Antidrug antibody: Only done on Days 1 and 15 of Cycle 2. ^v Tumor marker, as indicated, for tumor type including but not limited to: CA-125 for ovarian cancer, CA19-9 for pancreatic cancer, and CEA for NSCLC and colon cancer (within -7 to 0 days before dose administration/study visit).																											

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Table A1 **Schedule of Events,** [REDACTED]

	Screening (Within 28 Days of First Dose)	Cycle 1 ^a														Cycle 2					Cycle 3 and Beyond				EOT/ 30 Days After Last Dose ^b	Immune- related AE Follow- up/90 Days After Last Dose ^c	Survival Follow- up / EOS ^d		
		Day	1	2	8	9	15	16	17	22	29	36	43	49 ^e	50 ^f	56 ^g	1	2	3	8	15/ 22/ 29/36/ 43/50	56	1	8				15/22/ 29/36/ 43/50	56
Evaluation/ Procedure																													

^w Tests performed only if previous evaluation was >6 weeks before the EOT visit.

^x Tumor assessments: Imaging with contrast-enhanced (unless contraindicated) CT or MRI scans will include all known or suspected disease sites. Tumor assessment time points will remain fixed by the calendar regardless of delayed doses of TAK-186 (within -3 to 0 days before dose administration). For patients who require additional imaging for an on treatment biopsy, the timing of this imaging can be associated with the biopsy. The same technique with appropriate contrast usage (CT or MRI) used at screening should be utilized throughout the study. Imaging should include chest, abdomen, and pelvis, and any other anatomical region appropriate for the patient’s disease. Deidentified copies of any imaging scans, including those from screening and any unscheduled scans, may be collected and transferred to the sponsor or its designee (eg, central imaging vendor or iCRO) for storage and any future analysis.

^y Survival follow-up tumor assessment: Data collected only for standard of care assessments. See Section 9.11 for additional details on assessments during follow-up period.

^z Contrast-enhanced (unless contraindicated) MRI scans of the brain will be performed for all patients with lung cancer at baseline and if indicated based on signs and symptoms for all other patients. Follow-up brain scans will be performed (within -3 to 0 days before the planned dose administration) only if the screening brain scan was positive for metastasis or in cases where it is clinically indicated (eg, suspicion of CNS metastases). Contrast CT scans (unless contraindicated) may be used if MRI cannot be performed. The same technique with appropriate contrast usage (MRI or CT) used at screening should be utilized throughout the study.

^{aa} Patients must allow acquisition of an existing FFPE archival tumor tissue sample, either a block or unstained slides. Tissue sample(s) may be submitted to the central laboratory by C1D15. Patients who provide fresh pre-treatment biopsy samples will not be required to submit archival tumor samples. Refer to the laboratory manual for specific instructions.

^{bb} Paired pre- and on-treatment biopsies will be performed on patients in cohort expansion. Paired tumor biopsies are optional for patients in dose escalation and backfill cohorts. The pretreatment biopsy should be obtained within 28 days of the C1D1 visit. The on-treatment tumor biopsy should be performed within 7 days before C2D1. If the pretreatment biopsy is deemed inadequate for testing and evaluation, the planned paired on-treatment biopsy will not be required. The requirement for these biopsy specimens may be waived once endpoint criteria are met (see Section 5.3). See Section 9.5.15.3 for additional guidance on tumor biopsies.

^{cc} The on-treatment tumor biopsy should be performed within 7 days before C2D1. For dose escalation, on-treatment biopsy can be performed between C1D43-C1D49. For cohort expansion, on-treatment biopsy can be performed between C1D50-C1D56.

^{dd} PRO assessments should be collected for patients in the cohort-expansion phase. All PRO assessments should be conducted before the administration of TAK-186 or any other

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Table A1 **Schedule of Events,** [REDACTED]

	Screening (Within 28 Days of First Dose)	Cycle 1 ^a														Cycle 2					Cycle 3 and Beyond				EOT/ 30 Days After Last Dose ^b	Immune- related AE Follow- up/90 Days After Last Dose ^c	Survival Follow- up / EOS ^d	
	Day	1	2	8	9	15	16	17	22	29	36	43	49 ^e	50 ^f	56 ^f	1	2	3	8	15/ 22/ 29/36/ 43/50	56	1	8	15/22/ 29/36/ 43/50	56			Q12W
Evaluation/ Procedure																												
study medications.																												
^{ee} If the PRO assessment is not performed on C1D1, the patient does not need to complete subsequent PRO assessments.																												
^{ff} PRO will be assessed on Day 8 and Day 36 from Cycle 3 onwards.																												
^{gg} A safety check of patients will be performed by the site staff approximately 48 hours after EOI for each TAK-186 dose administered in Cycles 1 and 2. In-person or remote safety check (eg, via telephone) is permissible.																												

Appendix B PK, Immunogenicity, and Pharmacodynamic Biomarkers

Table B1 PK, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling With [REDACTED]

Cycle	TAK-186 Dose administration	Cycle Day	PK Sampling Time (hours) ^a	ADA Sampling Time (hours)	Cytokine Sampling Time (hours)	Flow Cytometry Subset (hours)	ctDNA
1	X	1	Predose ^b	Predose ^b	Predose ^b	Predose ^b	Predose ^b
			EOI				
			6		6 ^c		
		2	24		24 ^c	24 ^c	
	X	8	Predose ^b	Predose ^b	Predose ^b	Predose ^b	
			EOI				
			6		6 ^c		
		9	24		24 ^c	24 ^c	
	X	15	Predose ^b	Predose ^b	Predose ^b	Predose ^b	
			EOI				
			2		2 ^c		
			4			4 ^c	
			6		6 ^c		
		16	24		24 ^c	24 ^c	
		17	48		48 ^c	48 ^c	
	X	22	Predose ^b	Predose ^b	Predose ^b	Predose ^b	
			EOI				
	X	29	Predose ^b	Predose ^b	Predose ^b		
			EOI				
	X	36	Predose ^b	Predose ^b			
			EOI				
	X	43	Predose ^b	Predose ^b		Predose ^b	
			EOI				

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Table B1 PK, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling With

Cycle	TAK-186 Dose administration	Cycle Day	PK Sampling Time (hours) ^a	ADA Sampling Time (hours)	Cytokine Sampling Time (hours)	Flow Cytometry Subset (hours)	ctDNA
	X	50 ^d	Predose ^b	Predose ^b		Predose ^b	
			EOI				
2	X	1	Predose ^b	Predose ^b	Predose ^b	Predose ^b	Predose ^b
			EOI				
			2				
			4			4 ^c	
			6		6 ^c		
		2	24		24 ^c	24 ^c	
		3	48		48 ^c	48 ^c	
	X	8	Predose ^b		Predose ^b		
			EOI				
	X	15	Predose ^b	Predose ^b			
			EOI				
	X	22	Predose ^b				
			EOI				
3 and beyond ^e	X	1	Predose ^b	Predose ^b		Predose ^{b, f}	Predose ^b
			EOI				
CRS/ICANS ^g			As required		As required		
EOT			No specific time	No specific time			No specific time

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Table B1 PK, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling With

Cycle	TAK-186 Dose administration	Cycle Day	PK Sampling Time (hours) ^a	ADA Sampling Time (hours)	Cytokine Sampling Time (hours)	Flow Cytometry Subset (hours)	ctDNA
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ADA: antidrug antibody; Cycle x Day x; CRS: cytokine release syndrome; ctDNA: circulating tumor DNA; eCRF: electronic case report form; EOI: end of infusion; EOT: end of treatment; ICANS: immune effector cell-associated neurotoxicity syndrome; PK: pharmacokinetic; SOI: start of infusion.

Actual SOI and EOI times and PK, ADA, cytokine, and flow cytometry sample collection times will be recorded on the eCRFs. All sampling times are hours after EOI unless otherwise specified.

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

^b Predose blood samples are to be collected on the day of the administration of TAK-186 prior to premedication.

^c All post-dose cytokine and flow cytometry samples should be collected ± 30 minutes for time points indicated for samples collected on the same day as infusion and ± 3 hours for samples collected on non-infusion days.

^d For cohort expansion only.

^e Samples should only be collected up to Cycle 7 Day 22, which is considered to be treatment completion

^f C3D1 only.

^g In patients who experience signs and symptoms of CRS/ICANS, additional PK and cytokine samples should be obtained, if medically feasible, at the time of onset of CRS/ICANS, 4 hours (± 30 minutes) and 24 hours (± 3 hours) after. If the onset of CRS/ICANS coincides with a post infusion scheduled blood sample collection for PK and/or cytokine, samples for both the scheduled collection and onset of CRS/ICANS should be collected. If either the 4-hour or 24-hour time points are within ± 30 minutes of a scheduled blood sample for PK and/or cytokine, there is no need to repeat this blood sample collection for CRS/ICANS.

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Appendix C Conventional RECIST v1.1 Guidelines

Adapted from *New Response Evaluation in Solid Tumors: revised RECIST guideline (version 1.1)* (Eisenhauer et al. 2009).

All patients will be required to have at least 1 measurable lesion to be considered as having measurable disease at baseline for the determination of eligibility for this study. Measurable lesions are defined below.

Measurability of tumor at baseline.

DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

Measurable

Tumor lesions: Must be accurately measured in at least one dimension (*longest* diameter in the plane of measurement is to be recorded) with a *minimum* size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in *short* axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the *short* axis will be measured and followed. See also notes below on 'Baseline documentation of target and nontarget lesions' for information on lymph node measurement.

Nonmeasurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment.

Bone lesions:

- Bone scan, positron emission tomography scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are nonmeasurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion before study enrollment.

SPECIFICATIONS BY METHODS OF MEASUREMENTS

Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation should always be done rather than clinical examination unless the lesions(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised.

Tumor markers: Tumor markers *alone* cannot be used to assess *objective* tumor response.

TUMOR RESPONSE EVALUATION

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above).

BASELINE DOCUMENTATION OF 'TARGET' AND 'NONTARGET' LESIONS

Where more than one measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. For example, in instances where patients have only one or 2 organ sites involved, a maximum of 2 and 4 lesions respectively will be recorded. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion(s) which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes which are defined as measurable and may be identified as target lesions must meet criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered nontarget lesions. Nodes that have a short axis < 10 mm are considered nonpathological and should not be recorded or followed.

A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters*. If lymph nodes are to be included in the sum, then, as noted above, only the *short axis* is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as *nontarget lesions* and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. In addition, it is possible to record multiple nontarget lesions involving the same

organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

RESPONSE CRITERIA

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

Evaluation of target lesions

Complete Response: Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm.

Partial Response: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (*Note:* the appearance of one or more new lesions is also considered progression).

Stable Disease: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. In order to qualify for CR, each node must achieve a short axis <10 mm. For PR, stable disease (SD) and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the eCRFs. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (*Note:* It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but

should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore, providing this default value will prevent false responses or progressions based upon measurement error. However, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on-treatment. When non-nodal lesions ‘fragment’, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesions. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the ‘coalesced lesion’.

Evaluation of nontarget lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of nontarget lesions. While some nontarget lesions may actually be measurable, they need not be measured and instead should be assessed only *qualitatively* at the time points specified in the protocol.

Complete Response: Disappearance of all nontarget lesions. All lymph nodes must be nonpathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more nontarget lesions(s).

Progressive Disease: Unequivocal progression (see comments below) of existing nontarget lesions. (*Note:* the appearance of one or more new lesions is also considered progression).

Special notes on assessment of progression of nontarget disease

The concept of progression of nontarget disease requires additional explanation as follows:

When a patient also has measurable disease. In this setting, to achieve ‘unequivocal progression’ on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest ‘increase’ in the size of one or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression *solely* on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only nonmeasurable disease. The same general concepts apply here as noted above; *however*, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in nontarget disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: eg, an increase in tumor burden representing an additional 73% increase in ‘volume’ (which is equivalent to a 20% increase diameter in a measurable lesion).

Examples include an increase in a pleural effusion from ‘trace’ to ‘large’, an increase in lymphangitic disease from localized to widespread, or may be described in protocols as ‘sufficient to require a change in therapy’. If ‘unequivocal progression’ is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New lesions

The appearance of new malignant lesions denotes disease progression. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: eg, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some ‘new’ bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient’s baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a ‘new’ cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered that reveals metastases. The patient’s brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

EVALUATION OF BOR

The BOR is the best response recorded from the start of the study treatment until the EOT taking into account any requirement for confirmation. The patient’s BOR assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions.

The parameters assessed based on the objective responses includes the following:

- **ORR** consisting of CR or PR. Both confirmed (confirmation of response with second scan ≥ 4 weeks later) and unconfirmed responses will be assessed.
- **Duration of Response** measured from the date of first objective response to first occurrence of objective PD or death, whichever occurs first.
- **Disease Control Rate** defined as percentage of patients who achieve PR or CR or SD, with a duration of ≥ 2 consecutive scans.
- **Progression-Free Survival and OS** measured from the date of first dose to, respectively, first occurrence of objective PD or death, whichever occurs first (PFS), or date of death (OS). Both conventionally defined RECIST v1.1 objective progression (objective

progression defined as one event of objective PD) and modified RECIST v1.1
progression (objective progression defined as 2 events of objective PD) will be evaluated.

Time point response

It is assumed that at each protocol-specified time point, a response assessment occurs. provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Missing assessments and nonevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements is made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with 3 measured lesions and at follow-up only 2 lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

BOR: all time points

The BOR is determined once all the data for the patient are known.

Table C1 Single Time Point Response: Patients with Target (±Nontarget) Disease

Target lesions	Nontarget lesions	New lesions	Overall response ^a
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR: complete response; NE: not evaluable; PD: progressive disease; PR: partial response; SD: stable disease.

^a Single time-point CR or PRs are considered unconfirmed until a confirmatory scan done ≥28 days after the initial scan.

Best response determination in trials where confirmation of CR or PR IS required: Complete or partial responses may be claimed only if the objective response is confirmed on a followup scan obtained no less than 4 weeks after the initial scan demonstrating an objective response. In this circumstance, the BOR can be interpreted as in [Table C2](#).

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Table C2 BOR When Confirmation of CR and PR Required

Overall response First time point	Overall response Subsequent time point	BOR
CR	CR	CR
CR	PR	SD, PD, or PR ^a
CR	SD	SD
CR	PD	SD
CR	NE	SD
PR	CR	PR ^b
PR	PR	PR
PR	SD	SD ^c
PR	PD	SD
PR	NE	SD
NE	NE	NE

BOR: best overall response; CR: complete response; NE: not evaluable; PD: progressive disease; PR: partial response; SD: stable disease.

Minimum duration of 6 weeks required for SD.

^a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

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

^c If a patient has assessments that are PR or SD, then PR without an intervening visit of PD, it is defined as a PR.

Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the eCRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is *not* a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and nontarget disease as shown in [Table C1](#) and [Table C2](#).

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If, at

the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

CONFIRMATION/DURATION OF RESPONSE

Confirmation

Objective responses should be confirmed by CT and/or MRI scans obtained no less than 4 weeks after the original scan.

Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease

Stable disease is measured from the start of treatment until the criteria for progression are met, taking as reference the *smallest sum on study* (if the baseline sum is the smallest, this is the reference for calculation of PD). The minimum duration of 6 weeks between scans demonstrating SD must occur for a patient to be considered to have SD.

Appendix D Modified RECIST Guidelines

Partially Adapted from *Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria* (Wolchok et al. 2009).

The Modified and Conventional RECIST v1.1 guidelines are identical except in the way the single time point response and BOR are defined for PD by adding a condition for the confirmation of PD as described below.

EVALUATION OF BOR

The BOR is the best response recorded from the start of the study treatment until the EOT taking into account any requirement for confirmation. The patient's BOR assignment will depend on the findings of both target and nontarget disease.

Unlike conventional RECIST criteria, the initial appearance of new lesions, initial time point nontarget lesions deemed to have progressed or first instance of target lesion growth $\geq 20\%$ shall not automatically denote disease progression. In the modified criteria, patients who are otherwise clinically stable, but have met conventional RECIST v1.1 PD criteria allows for one further treatment cycle beyond the first instance of objective PD at the discretion of the investigator. If the patient has 2 consecutive scans demonstrating PD, then the patient has a Confirmed Objective Progression with the date of first progression based on the first scan showing PD.

Time point response

It is assumed that at each protocol-specified time point, a response assessment occurs (see Table D1) provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

BOR: all time points

The BOR is determined once all the data for the patient are known.

Table D1 Single Time Point Response: Patients with Target (±Nontarget) Disease

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR	No	uCR ^a
CR	Non-CR/non-PD	No	uPR ^a
CR	Not evaluated	No	uPR
PR	Non-PD or not all evaluated	No	uPR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	uPD ^b
Any	PD	Yes or No	uPD ^b
Any	Any	Yes	uPD ^b

Red text represents change from conventional RECIST v1.1.

CR: complete response; NE: not evaluable; PD: progressive disease; PR: partial response; SD: stable disease; uCR: unconfirmed complete response; uPD: unconfirmed progressive disease; uPR: unconfirmed partial response.

^a Unconfirmed CR or PR until confirmative scan ≥28 days from first scan demonstrating initial response.

^b Unconfirmed progression in clinically stable patients pending next scan confirming PD.

Best response determination in trials where confirmation of CR or PR is required: Complete or partial responses may be claimed only if the objective response is confirmed on a followup scan obtained no less than 4 weeks after the initial scan demonstrating an objective response. In this circumstance, the BOR can be interpreted as in [Table D2](#).

Table D2 BOR when Confirmation of CR, PR and PD Required

Overall response First time point	Overall response Subsequent time point	BOR
CR	CR	CR
CR	PR	SD, PD, or PR ^a
CR	SD	SD
CR	PD	SD
CR	NE	SD
PR	CR	PR ^b
PR	PR	PR
PR	SD	SD ^c
PR	PD	SD
PR	NE	SD
PD	CR	SD ^d
PD	PR	SD ^e
PD	SD	SD
PD	PD	Confirmed PD
PD	NE	Unconfirmed PD
NE	NE	NE

Red text represents change from conventional RECIST v1.1.

BOR: best overall response; CR: complete response; NE: not evaluable; PD: progressive disease; PR: partial response; SD: stable disease.

^a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

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

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

^d Will become a CR if a later visit >4 weeks has an assessment of CR with no intervening PD visit responses.

^e Will become a PR, as per Wolchok criteria, if a later visit >4 weeks has an assessment of PR with no intervening PD visit responses.

Appendix E 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 responsibilities imposed on investigators by the FDA are summarized in the Statement of Investigator (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

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 trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-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 21 Code of Federal Regulations (CFR) Part 56, 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 3 months of study completion.
8. Ensure that requirements for informed (e)consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed (e)consent from each patient who participates in the study, and document the date of (e)consent in the patient's medical chart. Valid informed (e)consent 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 following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should

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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 an SAE, notify the sponsor within 24 hours.

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Appendix F 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.
- IRBs and IECs.

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 above.

Appendix G 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 MM, 1982 ([Oken et al. 1982](#)).

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Appendix H Grading of CRS

CRS will be graded as described in [Table H1](#) ([Lee et al. 2019](#)).

Table H1 ASTCT CRS consensus Grading for CRS

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 one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or ^b				
Hypoxia	None	Requiring low-flow nasal cannula ^c or blow-by oxygen	Requiring high-flow nasal cannula ^c , facemask, nonrebreather mask, or Venturi mask (not attributable to any other cause).	Requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation) (not attributable to any other cause)

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

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

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 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 driven by 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, a patient with temperature of 39.5°C , hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.

^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.

Appendix I Clinical Chemistry, Hematology and Urinalysis

Table I1 Clinical Chemistry and Hematology Tests	
Pregnancy test: Serum human chorionic gonadotropin (hCG) Hematology: Hematocrit (Hct) Hemoglobin (Hgb) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Platelet count Red blood cell (RBC) count White blood cell (WBC) count with differential counts Special Chemistry: Amylase Lipase Lactate dehydrogenase (LDH) C-reactive protein (CRP) Coagulation: Prothrombin time Activated partial thromboplastin time (APTT) Endocrine tests: Free thyroxine (T4) Thyroid-stimulating hormone (TSH)	Comprehensive Chemistry Panel: Albumin (ALB) Alkaline phosphatase (ALP) Alanine aminotransferase (ALT; SGPT) Aspartate aminotransferase (AST; SGOT) Bicarbonate (HCO ₃) or carbon dioxide (CO ₂)* Blood urea nitrogen (BUN) or Urea* Calcium (Ca) Chloride (Cl) Creatinine Glucose Magnesium Phosphorus Potassium (K) Sodium (Na) Total protein Uric acid Bilirubin (total and direct) Tumor Markers: CA-125 CA19-9 CEA Others as indicated

* As applicable by local standards

Table I2 Clinical Urinalysis Tests

Urinalysis	
Appearance*	Nitrite
Bilirubin	Occult blood
Color*	pH
Glucose	Protein or albumin
Ketones	Specific gravity
Microscopic examination of sediment	

* To be completed where applicable by local standards

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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).

ASTCT: American Society for Transplantation and Cellular Therapy; CTCAE: Common Terminology Criteria for Adverse Events; EEG: electroencephalography; ICANS: immune effector cell-associated neurotoxicity syndrome; ICE: immune effector cell-associated encephalopathy; ICP: intracranial pressure; N/A: 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 Protocol History

Amendment History:

Date	Amendment Number	Amendment Type	Region
01 July 2024	7 GB v1	Substantial	United Kingdom
01 December 2023	7	Substantial	Global
02 November 2023	6 UK v1	Non substantial	United Kingdom
08 February 2023	6	Substantial	Global
12 August 2022	5	Substantial	Global
07 March 2022	4	Substantial	Global
01 August 2021	3	Substantial	Global
25 May 2021	2	Substantial	Global
23 March 2021	1	Substantial	Global
04 November 2020	Original protocol	Not applicable	Global

Protocol Amendment 7 GB v1: Summary of Changes and Rationale

This section describes the changes in reference to the protocol incorporating Amendment 7 GB v1. The primary purpose of this amendment is to add immune effector cell-associated neurotoxicity syndrome (ICANS) to the list of potential and identified risks of TAK-186; add a new section on the management of neurologic adverse events (ICANS); and add stopping rules criteria for ICANS.

Changes and revised text in the body of the protocol are also applied to the synopsis, where applicable.

Minor grammatical, editorial, formatting, and administrative changes that do not affect study conduct are applied throughout the document for clarification and administrative purposes.

Protocol Amendment 7 GB v1		
Summary of Changes Since the Last Version of the Approved Protocol		
New Section Number and Title	Summary of Changes	Rationale
4.3 Potential Risks and Benefits	Immune effector cell-associated neurotoxicity syndrome added to list of potential risks.	Revised in the interest of enhanced patient safety.
6.1.2 Cohort Expansion Phase	Added stopping rules criteria for ICANS.	Revised in the interest of enhanced patient safety.
Management of Neurologic Adverse Events Appendix J ASTCT ICANS Consensus Grading for Adults Appendix K Management of ICANS	New sections added for immune effector cell-associated neurotoxicity syndrome management guidelines.	Revised in the interest of enhanced patient safety.
Appendix A Schedule of Events, Table A1 and Table A2:	Added neurologic examination to physical examination assessments at	Revised in the interest of enhanced patient safety.

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Protocol Amendment 7 GB v1		
Summary of Changes Since the Last Version of the Approved Protocol		
New Section Number and Title	Summary of Changes	Rationale
footnote k and abbreviations.	baseline and after first symptoms of immune effector cell-associated neurotoxicity syndrome are suspected.	
Appendix B PK, Immunogenicity, and Pharmacodynamic Biomarkers, Table B1 and B2: footnote e and abbreviations.	Added pharmacokinetic and cytokine sampling times for events of immune effector cell-associated neurotoxicity syndrome.	Revised in the interest of enhanced patient safety.
Appendix B PK, Immunogenicity, and Pharmacodynamic Biomarkers, Table B1.	Inserted abbreviations and footnotes.	Corrected omission in table.

Protocol Amendment 7: Summary of Changes and Rationale

This section describes the changes in reference to the protocol incorporating Amendment 7. The primary purpose of this amendment is to include a revised cohort expansion design for determination of efficacy and safety of single-agent TAK-186 in patients with unresectable, locally advanced, or metastatic solid tumors expressing EGFR, including non-small cell lung cancer (NSCLC), colorectal cancer (CRC), and head and neck squamous cell carcinoma (HNSCC).

Other protocol changes include update to estimated sample size for cohort expansion phase; addition of patient-reported outcomes (PROs) to study objectives; clarifying the description of other objectives and associated endpoints; revising the guidance for obtaining tumor biopsy specimens from study patients; clarifying language on description of study drug characteristics, study procedures, and diagnostic tests; and an adaptation to Takeda's protocol template.

The adaptation of the protocol to the Takeda template results in reformatted sections and administrative changes related to the template update and do not affect study conduct.

Changes and revised text in the body of the protocol are also applied to the synopsis, where applicable.

Minor grammatical, editorial, formatting, and administrative changes that do not affect study conduct are applied throughout the document for clarification and administrative purposes.

Protocol Amendment 7			
Summary of Changes Since the Last Version of the Approved Protocol			
New Section Number and Title	Old Section Number and Title	Summary of Changes	Rationale
2.0 Study Summary	Protocol Synopsis	Revised phase 2 cohort expansion design. Clarification of monitoring requirements for cytokine release syndrome (CRS) and infusion-related reactions. Clarification of eligibility criteria regarding tumor biopsy.	To demonstrate early signs of clinical efficacy in an initial indication. To align the text in the study summary and body of the protocol.
4.0 Introduction	1.0 Introduction	Epidemiology was made relevant to current study design. Disease background information has been updated to align nomenclature with nonclinical reports and investigator's brochure (IB). The rationale for the proposed study has been revised to reflect the new study design. Potential risks and benefits have been inserted.	Adapt to template and align information with other relevant documents to help effectively conduct the study.
5.0 Study Objectives and Endpoints	2.0 Study Objectives and Endpoints	Patient-reported outcomes have been added as an exploratory objective and corresponding endpoint. Exploratory endpoints were clarified. Cleaved collagen collection and evaluation was removed.	To communicate new exploratory objectives. Emerging clinical data did not support a need for continued collection of circulating collagen levels.
6.0 Study Design	3.1 Study Design	Study design and treatment schema have been updated to reflect new cohort expansion designs. Mandatory paired biopsy language for cohort expansion has been added. Clarification for CRS monitoring has been provided. Clarification for infusion-related reaction monitoring has been provided. Dose escalation and dose cohort rules are described. The number of patients planned to be enrolled in the study has been updated. Duration of study and individual patient's study participation has been added.	Update design and demonstrate early signs of clinical efficacy in an initial indication.

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Protocol Amendment 7			
Summary of Changes Since the Last Version of the Approved Protocol			
New Section Number and Title	Old Section Number and Title	Summary of Changes	Rationale
		Study completion and end of study definitions have been clarified.	
7.0 Study Population	4.0 Patient Selection and Withdrawal Criteria	Tumor histology has been modified for cohort expansion to align with new study design. CRC K-Ras has been revised for clarification. Language on mandatory consent to paired tumor biopsies for dose escalation and clarification of tumor biopsies during cohort expansion have been added. Urine pregnancy tests have been removed.	Clarifications made with respect to updated design.
8.0 Study Drug	5.0 Study Treatment 7.0 Concomitant Therapy and Restrictions	Section now includes subsections for Definitions of DLT, Drug-Related Grade 2 AEs That Will Not Trigger Expansion, Dose Escalation Rules, Dose Modification Guidelines, Criteria for Starting Subsequent Treatment Cycle, Additional Criteria to Start a Delayed Subsequent Dose, Infusion Interruption and Resumption Criteria, Criteria for Discontinuation of TAK-186, Prohibited Concomitant Medications and Procedures, Permitted Concomitant Medications and Procedures, Precautions and Restrictions, Management of Clinical Events, Blinding and Unblinding, and Description of Investigational Agents. Infusion guidelines have been updated to include a TAK-186 administration window. Guidelines regarding dose recalculation for patients with weight change have been added. Preparation, packaging, storage, and handling language has been revised for clarity. References for additional details provided in the Pharmacy Manual have been added.	For consistency with the new template and inclusion of language to provide further clarification.

Protocol Amendment 7			
Summary of Changes Since the Last Version of the Approved Protocol			
New Section Number and Title	Old Section Number and Title	Summary of Changes	Rationale
8.9 Management of Clinical Events	6.1 CRS/Infusion Reaction 6.2 Premedication and Postinfusion Support 6.3 Management of CRS/Infusion Reactions	CRS and IRRs grading and management have been separated. Guidelines for the management of clinical events have been updated for clarity and consistency. Language regarding assessment of potential immune-related AEs (irAEs) has been added.	To clarify safety management section.
9.0 Study Conduct	8.0 Study Assessments and Procedures	Study personnel and organization information has been added. The subsection Study Procedures has been updated to reflect all assessment and procedure guidelines during the conduct of the study.	Adapt to template and help the effective conduct of the study.
9.5.15 Pharmacodynamic and Biomarker Samples	8.12 Pharmacodynamics, Biomarkers, and PK	Added language to clarify and stop sample collection based on emerging data. The requirement to collect samples for circulating collagen levels and archival tissue for whole exome sequencing have been removed. Language for mandatory paired biopsy for patients in backfill cohorts during dose escalation and cohort expansion has been added. Guidelines for determining accessible lesion(s) have been clarified. Guidance for use of archived tumor biopsy specimens in lieu of a pretreatment biopsy sample has been provided.	To align with the new study design. Emerging clinical data did not support a need for collection of circulating collagen levels. Clarifications made to help effectively conduct the study.
9.5.17 Additional Exploratory Research	8.12.3 Optional Tumor Tissue, Blood, and Biological Sample Collection	Leftover samples may be used for future exploratory research.	Adapt to template and help effectively conduct the study.
9.5.18 Patient-Reported Outcomes Assessments	NA	PROs have been added for patients enrolled in cohort expansion.	To assess PROs during cohort expansion.

Protocol Amendment 7			
Summary of Changes Since the Last Version of the Approved Protocol			
New Section Number and Title	Old Section Number and Title	Summary of Changes	Rationale
9.6 Completion of Study Treatment (for Individual Patients) 9.7 Completion of Study (for Individual Patients) 9.8 Discontinuation of Treatment With Study Drug and Patient Replacement 9.9 Withdrawal of Patients From Study After Study Drug Discontinuation	5.5 Discontinuation of Study Treatment and/or Withdrawal from the Study	Definitions for these sections have been updated for clarity and consistency.	To provide clarity and consistency.
9.11 Immune-related AE follow-up	6.6 Immune-Related AEs	Immune-related AEs should be assessed through 90 days after the last dose of TAK-186.	To communicate irAE follow-up guidelines for patient safety.
9.12 Posttreatment Follow-up Assessments	8.6 Posttreatment Follow-up Period	Posttreatment follow-up assessments have been added to clarify survival follow-up guidelines: All patients will be followed for survival status for up to 48 weeks, or until death, lost to follow-up, or noncompliance, whichever occurs first.	To provide clarity and consistency.
10.0 Adverse Events	8.9.2 AEs	This section contains definitions and procedures for recording and reporting AEs, drug exposures, and complaints.	Adaptation of protocol template.
12.0 Data Handling and Recordkeeping	11.8 Records Retention	Revised template language.	Adaptation of protocol template.
13.0 Statistical and Analytical Plans	9.4 Statistical Analysis Methodology 9.5 Sample Size Calculations	Sample size estimates have been revised to align with new study design. Planned data output tables have been updated for consistency.	Sample size has been increased to up to 210 patients for the cohort expansion phase to align with the new protocol

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Protocol Amendment 7			
Summary of Changes Since the Last Version of the Approved Protocol			
New Section Number and Title	Old Section Number and Title	Summary of Changes	Rationale
			design.
14.0 Quality Control and Quality Assurance	10.0 Quality Control and Quality Assurance	Revised template language.	Adaptation of protocol template.
15.0 Ethical Aspects of the Study	11.1 Ethics	Revised template language.	Adaptation of protocol template.
Appendix A Schedule of Events	13.1 Appendix: Schedule of Assessments	Schedule of Events table has been updated to reflect all protocol changes including, but not limited to, events for patients enrolled in cohort expansion. Footnotes have been revised for clarity and consistency.	To align with the body of the protocol to help effectively conduct the study.
Appendix B PK, Immunogenicity, and Pharmacodynamic Biomarkers	13.2 Appendix: PK, Immunogenicity, and Pharmacodynamic Biomarkers	PK, Immunogenicity, and Pharmacodynamic Biomarkers tables have been revised to reflect sample collection time point changes. Footnotes have been added to clarify collection windows.	To align with the body of the protocol to help effectively conduct the study.
Appendix E Responsibilities of the Investigator		Added template language.	Adaptation of protocol template.
Appendix F Investigator Consent to Use of Personal Information		Added template language.	Adaptation of protocol template.
Appendix H Grading of CRS	6.1.1 Grading of CRS/Infusion Reaction	Grading of CRS table has been moved to appendices.	To help effectively conduct the study.
Appendix I Clinical Chemistry, Hematology, and Urinalysis	13.3 Appendix: Clinical Laboratory Tests	LDH and CRP have been added to the Clinical Chemistry and Hematology Tests table. Footnotes have been added to clarify that assessments will be completed as applicable by local standards.	To help effectively conduct the study per local standards.

Protocol Amendment 6 UK v1: Summary of Changes and Rationale

This section describes the changes in reference to the protocol incorporating Amendment 6 UK v1. The primary purpose of this amendment is to include definitions of WOCBP and postmenopausal state, clarify contraception requirements for female patients in the study, clarify period for avoidance of live vaccines after stopping study treatment, and include the requirement to substantially amend the protocol and be approved by authorities if study recruitment should be restarted when enrollment is on halt due to a trigger of stopping rules.

Changes and revised text in the body of the protocol are also applied to the synopsis, where applicable.

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

Protocol Amendment 6 UK v1		
Summary of Changes Since the Last Version of the Approved Protocol		
Section Number and Title	Summary of Changes	Rationale
Synopsis, 4.1.1 Inclusion Criteria	Included definitions of woman of childbearing potential and postmenopausal state, clarified contraception requirements for female patients in the study based on Clinical Trials Facilitation and Coordination Group guidance.	Clarified in response to Medicines & Healthcare products Regulatory Agency (MHRA) feedback.
3.1.2 Cohort-Expansion Phase	Added the following statement: If enrollment is halted due to triggering of the stopping rule, recruitment can only be restarted following approval of a substantial protocol amendment by the regulatory authorities.	Included in response to MHRA feedback.
7.1 Prohibited therapies	Clarified that live vaccines should be avoided for 3 months after last dose of TAK-186.	Included in response to MHRA feedback.

Protocol Amendment 6: Summary of Changes and Rationale

This section describes the changes in reference to the protocol incorporating Amendment 6. The primary purpose of this amendment is to modify study conduct by applying a dose optimization approach to the determination of the RP2D (recommended phase 2 dose) of single-agent TAK-186 to be administered to patients with locally advanced or metastatic HNSCC, NSCLC, or CRC.

The dose optimization approach is designed to obtain sufficient data to inform dose selection early in clinical development and select an optimal dose for administration to patients in later phase (phase 2 or phase 3) registrational studies. This dose optimization approach aligns with the US FDA Oncology Center of Excellence Project Optimus initiative to update the dose optimization and selection paradigm in oncology drug development with the intent of selecting doses of investigational agents that maximize efficacy with minimal toxicity.

The study design has been modified to identify 2 RDEs (recommended doses for expansion), a low and high dose of TAK-186, during the dose-escalation phase of the study based on the safety, PK, and pharmacodynamic data, including empirical exposure safety analysis, and biomarker response data. Patients with either HNSCC, NSCLC, or CRC are then to be randomized 1:1 to the 2 RDEs, the low and high dose of TAK-186, during the cohort expansion phase of the study to select an RP2D of TAK-186 for patients in the 3 indications in parallel at the end of the cohort expansion phase.

TAK-186 (also known as MVC-101) is used as the name of the drug product throughout this amended protocol to reflect the updated compound name upon Takeda's acquisition of the compound. MVC-101 is presented in parenthesis to retain the genealogy of the drug candidate.

Other protocol changes include clarifying the description of study objectives and associated endpoints, revising the dose escalation guidelines, revising the guidance for obtaining paired, fresh tumor biopsy specimens from study patients, revision and update of the study drug characteristics, study procedures and diagnostic tests, and the statistical analyses to be applied to the study data. The discussion of concomitant therapy and restrictions was expanded to include a caution that study patients receiving sensitive CYP enzyme substrates concomitantly with TAK-186 should be carefully monitored for side effects.

Some of the modifications in study conduct were instituted in response to regulatory (US FDA) feedback. Changes and revised text in the body of the protocol are also applied to the Synopsis, where applicable.

Minor grammatical, editorial, formatting, and administrative changes that do not affect study conduct are applied throughout the document for clarification and administrative purposes.

Protocol Amendment 6		
Summary of Changes Since the Last Version of the Approved Protocol		
Section Number and Title	Summary of Changes	Rationale
Throughout	The compound name has been updated to TAK-186; MVC-101 is retained to reflect the genealogy of the drug candidate.	The compound name has been updated to TAK-186 upon Takeda's acquisition of the compound.
Synopsis, Secondary Objectives	Determination of recommended phase 2 dose (RP2D) defined as a secondary (rather than primary) study objective.	The primary objectives focus on the safety and tolerability of TAK-186 in alignment with the goals of a phase 1/2 study.
Synopsis, Exploratory Objectives	Revised description of exploratory objectives, including determination of the correlation of epidermal growth factor receptor (EGFR) and other biomarker expression with TAK-186 antitumor response.	Clarification of biomarker studies designed to characterize the biology of the study drug.

Protocol Amendment 6		
Summary of Changes Since the Last Version of the Approved Protocol		
Section Number and Title	Summary of Changes	Rationale
Synopsis, Study Design	Starting at the dose cohort receiving [REDACTED] patients will be encouraged to provide paired biopsy specimens at screening and within 7 days of Cycle 2. During the cohort-expansion phase, paired biopsy specimens, preferably from the same lesion, will be required from patients at selected study sites until it is determined that enough samples are available for analysis.	Revised guidance for obtaining paired biopsy specimens from patients during dose escalation and cohort expansion.
Synopsis, Dose-Escalation Phase	The following dose escalation rules will be applied: 1. Dose increments will be limited to 100% for [REDACTED] full treatment doses up to the first [REDACTED] dose levels [REDACTED] 2. Maximum dose increments for the next dose cohort will be limited to 50% after the [REDACTED] dose for [REDACTED] full treatment doses if patients in a given dose cohort experience 2 or more Grade ≥ 2 CRS during the DLT-evaluation period. 3. Maximum dose increments will be limited to 30% for the next dose cohort for [REDACTED] full treatment doses if patients in a given dose cohort experience 2 DLTs during the DLT-evaluation period. The highest dose administered in the study will not exceed [REDACTED]	Revised in response to regulatory (US FDA) feedback and in the interest of enhanced patient safety.
Synopsis, Patient Population	Removed the text pertaining to tumor histologies of interest during dose escalation and cohort expansion.	Takeda confidential information; the comprehensive list of tumor histologies is provided in the body of the protocol.
Synopsis, PK, Immunogenicity Analysis, PD Assessments	Revised description of the antidrug antibody (ADA) assessments to include measurement of ADA titer and detection of neutralizing ADA for ADA-positive samples. Revised description of pharmacodynamic assessments to include changes in peripheral immune cells and measurement of cytokines. Cytokines will be measured by a sponsored-designated assay.	The additional assessment will allow a more comprehensive description of the TAK-186 immunogenicity. Pharmacodynamic assessments are to determine the pharmacodynamic profile of TAK-186 and its relationship with antitumor activity.
Synopsis, Study Drug Dosage and Route of Administration	Revised statement pertaining to the temperature at which the single-use vials containing TAK-186 are stored.	Correction.

Protocol Amendment 6		
Summary of Changes Since the Last Version of the Approved Protocol		
Section Number and Title	Summary of Changes	Rationale
Synopsis, Rationale for Study Design, Cohort-Expansion Phase, Sample Size Calculations	The sample size in each of the 3 indications during cohort expansion has been increased from 25 patients to 60 patients.	The larger sample size allows for a more accurate and clinically meaningful assessment of overall response rate and other efficacy endpoints.
Synopsis, Analysis Populations	Added descriptions of pharmacokinetic (PK), immunogenicity, and pharmacodynamics analysis populations.	Results will be presented in the clinical study report for patients in these analysis populations.
1.1, Background Information	Introductory text to describe the updated compound name, TAK-186.	Updated text in the protocol to reflect the current compound name.
1.1.1.1, Head and Neck Squamous Cell Cancer	Description of incidence of head and neck squamous cell carcinoma in Canada and US.	Introductory text in anticipation of investigative sites in Canada and the United States (US).
1.1.1.2, Non-Small Cell Lung Cancer	Description of incidence of non-small cell lung cancer NSCLC in Canada and the United States (US).	Introductory text in anticipation of investigative sites in Canada and the US.
1.1.1.3, CRC	Description of incidence of colorectal cancer (CRC) in Canada and the US.	Introductory text in anticipation of investigative sites in Canada and the US.
1.1.3.1, TAK-186 Pharmacology	Revised and updated description of TAK-186 pharmacology.	Updated information from ongoing nonclinical research findings.
1.1.3.2, TAK-186 Pharmacokinetics and Toxicology	Revised and updated description of the TAK-186 PK and toxicology findings.	Updated information consistent with ongoing nonclinical research findings.
1.1.5, Rationale for Study Design	Revised to reflect the dose optimization strategy for determination of the RP2D of TAK-186 and desired dose(s) for administration in subsequent studies.	Alignment with the US Food and Drug Administration (FDA) Oncology Center of Excellence Project Optimus and associated FDA guidance pertaining to determination of RP2D.
1.1.6, Potential Risks of TAK-186	Listing of the potential risks or adverse effects of TAK-186 on the basis of available nonclinical and clinical data.	Section added to provide an overview of the potential risks for patients who receive TAK-186.
2.1.2, Secondary Objectives	Determination of RP2D as a secondary (rather than primary) study objective. Rewording of objectives pertaining to biomarker expression and relationship with TAK-186 antitumor activity.	Scientific enquiry to support determination of TAK-186 efficacy for patients with selected solid tumors characterized by EGFR overexpression.
2.2, Endpoints	Description of study endpoints to match the study's objectives.	Added section aligns with the sponsor's Oncology template and facilitates clinical trial disclosure, according to the sponsor's and other regulatory guidelines.

Protocol Amendment 6		
Summary of Changes Since the Last Version of the Approved Protocol		
Section Number and Title	Summary of Changes	Rationale
3.1, Study Design	Revised description to reflect the dose optimization strategy, characterized by determination of 2 RDEs during the dose-escalation phase and determination of the RP2D during the cohort-expansion phase of the study.	Alignment with the US FDA Project Optimus guidelines for determination of RP2D.
3.1.1.1, [REDACTED]	Revised to state that the next planned dose during the dose-escalation phase of the study will be [REDACTED]	Revised in response to regulatory (US FDA) feedback and in the interest of enhanced patient safety.
3.1.1.2, Dose Escalation Rules	The following dose escalation rules will be applied: 1. Dose increments will be limited to 100% for [REDACTED] full treatment doses up to the first [REDACTED] dose levels [REDACTED] 2. Maximum dose increments for the next dose cohort will be limited to 50% after the [REDACTED] dose for [REDACTED] full treatment doses if patients in a given dose cohort experience 2 or more Grade ≥ 2 CRS during the DLT-evaluation period. 3. Maximum dose increments will be limited to 30% for the next dose cohort for [REDACTED] full treatment doses if patients in a given dose cohort experience 2 DLTs during the DLT-evaluation period. The highest dose administered in the study will not exceed [REDACTED]	Revised in response to regulatory (US FDA) feedback and in the interest of enhanced patient safety.
3.1.1.2, Dose Escalation Rules Table 3a, Dose Escalation Plan with Example for Initiating [REDACTED] Table 3b, Dose Escalation Plan with Example for Initiating [REDACTED]	Revised to reflect the revised guidelines for dose escalation and the doses at which paired tumor biopsy specimens are required from study participants.	Revised in response to regulatory (US FDA) feedback and in the interest of enhanced patient safety.
3.1.2, Cohort-Expansion Phase	Revised description of study conduct during the cohort-expansion phase of the study, including the increased number of patients to be evaluated in each of the 3 indications being explored in the study.	Modified study conduct to align with Project Optimus; US FDA Dose Optimization and Selection Paradigm.

Protocol Amendment 6		
Summary of Changes Since the Last Version of the Approved Protocol		
Section Number and Title	Summary of Changes	Rationale
3.1.2, Cohort-Expansion Phase	Starting with the first 10 patients and every 5 patients to a maximum of 30 patients in cohort expansion, patient accrual will be suspended in the event of Grade 3 or higher CRS that does not resolve within 24 hours to Grade 1 or lower, according to Bayesian rules.	Description of the stopping rules for the study.
3.2.1, Hematologic DLTs	Grade 3 or higher anemia without associated clinical signs was added to the list of adverse events (AEs) to be excluded from the AEs considered dose-limiting toxicities (DLTs).	Revised assessment of clinical important AEs that should be considered DLTs.
3.2.2, Nonhematologic DLTs	Grade 3 CRS / infusion reaction resolving to $\leq$ Grade 1 in less than 24 hours with medical intervention was removed from the list of exceptions for nonhematologic DLTs.	Revised in response to regulatory (US FDA) feedback and to enhance patient safety.
3.5.3, Timeframes for Primary and Secondary Endpoints to Support Disclosure	Tabular summary of the primary and secondary endpoints for clinical trial disclosure.	Compliance with the sponsor's clinical trial disclosure guidelines and other regulatory requirements.
3.6, Posttrial Access	Description of Takeda's policy regarding patient access to TAK-186 outside the clinical study.	Section added to describe Takeda's policy regarding access to this experimental treatment outside the context of the clinical study.
3.6.1, Duration of Posttrial Access	Description of the circumstances that underly termination of TAK-186 treatment, including no clinical benefit, negative benefit-risk ratio, and other considerations.	Ethical considerations and patient protection.
4.1.1, Inclusion Criteria: Tumor Biopsy	Statement added: The requirement for biopsy specimens may be waived once endpoint criteria are met.	Clarifying the circumstances under which paired biopsy specimens are required to reduce burden on study participants
4.1.1, Inclusion Criteria: Laboratory Features	Creatinine clearance of ≥ 30 mL/minute using Cockcroft Gault equation	Revised in response to regulatory (US FDA) feedback.
4.1.1, Inclusion Criteria: Reproductive Features	Male patients with partners of childbearing potential must use barrier contraception during the entire study treatment period through 120 days after the last dose of study drug.	Revised guidance in accordance with the sponsor's current requirements for protection of male study participants and their partners with childbearing potential.
5.1.1, TAK-186	Revised description of the study drug, including the statement that the preparation of low doses of TAK-186 requires addition of Solution Stabilizer.	Updated information from the sponsor.
5.1.1, Solution Stabilizer	Revised description of Solution Stabilizer.	Updated information from the sponsor.

Protocol Amendment 6		
Summary of Changes Since the Last Version of the Approved Protocol		
Section Number and Title	Summary of Changes	Rationale
5.1.2, Drug Preparation and Administration	Revised description of drug preparation and dose administration.	Updated information from the sponsor.
5.4.1, Study Drug Packaging and Labeling	Deleted description pertaining to the manner in which TAK-186 is supplied.	Updated information from the sponsor.
7.0, Concomitant Therapy and Restrictions	The following text was added: Elevated cytokines may modulate cytochrome P450 (CYP) enzyme activity. Therefore, patients who are administered sensitive CYP enzyme substrates (reference added to examples on the US FDA website) should be closely monitored for side effects. The website link is provided in the body of the protocol.	Added in response to regulatory (US FDA) feedback.
8.1, Informed (e)Consent	Added text to provide a more comprehensive description of the informed consent process to include (e)Consent.	The sponsor plans to include (e)Consent as an option for prospective study participants.
8.3, Registration and Enrollment	Defined enrollment as the time of initiation of the first dose of study drug.	Added clarification.
8.11, Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)	Takeda's current description of product complaints and medication errors and the associated guidance, reporting requirements.	The updated text provides the sponsor's current standard pertaining to product complaints and medication errors.
8.12.1.1, Pharmacodynamics / Biomarkers Sample Collection	T-cell activity in peripheral blood samples will be measured by flow cytometry.	The assessment method for determination of T-cell activity has been added.
8.12.1.3, Tumor Biopsy	Statement added that the requirement for paired fresh biopsy specimens may be waived for study participants at dose levels [REDACTED] during dose escalation and/or during cohort expansion if endpoint criteria are met.	This stipulation provides flexibility regarding the need for biopsy specimens for biomarker assessment and decreases the potential burden on study participants.
8.12.3, Optional Tumor Tissue, Blood, and Biological Sample Collection	Added statement that leftover samples may be used for exploratory research related to TAK-186 and other COnditional Bispecific Redirected Activation (COBRA) molecules in development.	The statement was amplified to include molecules other than TAK-186 on the COBRA platform.
8.12.4, Biologic Sample Retention and Destruction	Section (and associated text) has been deleted.	The sponsor's current standard is to describe the guidance for sample retention in the informed consent form.

Protocol Amendment 6		
Summary of Changes Since the Last Version of the Approved Protocol		
Section Number and Title	Summary of Changes	Rationale
9.2, Sample Size Considerations	The revised estimated sample size for the cohort-expansion phase is 180 patients. The statement pertaining to timing of the study's primary analysis has been revised; analysis is planned when all study participants have discontinued study treatment and 6 months of follow-data are available for analysis.	Sample size has been increased from 75 to 180 patients during cohort expansion. Statistical considerations; the revised timing facilitates analysis of more mature, clinically meaningful study data.
9.3, Analysis Populations	Updated description of analysis populations.	Statistical considerations; reporting study results.
9.5.4, Immunogenicity Analysis	Measurement of neutralizing ADA has been added to the planned immunogenicity analyses, and the relationship between TAK-186 immunogenicity and PK, safety, and antitumor efficacy will be explored.	More comprehensive description of the TAK-186 immunogenicity profile.
9.5.6, Biomarker Analysis	Multiple exploratory biomarkers will be evaluated to assess dose activity, mechanism of action, and the potential for use in patient selection and stratification at later clinical stages.	Revised text more clearly explains the reasons for the planned analyses.
9.5.7, Interim Analysis	Revised description of the planned interim analyses and the futility boundary for each of the 2 doses (low and high) and each cohort in the cohort-expansion phase of the study.	Revised assessment from the sponsor's statisticians.
11.9, Publication, Disclosure, and Clinical Trial Registration Policy	Verbatim text from the sponsor's current Oncology protocol template.	The text describes Takeda's current guidance on publication of study results and disclosure requirements.
Table 13.1a, Schedule of Assessments, [REDACTED] [REDACTED] Table 13.1b, Schedule of Assessments With [REDACTED] [REDACTED] Table 13.1c, Schedule of Assessments With [REDACTED] [REDACTED]	Added time points for measurement of cytokines and ADA; conduct of flow cytometry. Footnote f was revised to clarify that the initial physical examination could be performed within 7 days before administration of the first dose of study drug. A directed physical examinations <u>may</u> be performed on Day 1 and other days in each subsequent cycle instead of a full physical examination based on the patient's medical history and at the investigator's discretion.	Addition of diagnostic procedures to be performed on collected blood samples. The schedule for physical examinations was revised in response to feedback from investigative sites.
Table 13.2a through 13.2c, PK, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling, [REDACTED] With [REDACTED] [REDACTED] With [REDACTED] [REDACTED]	Added time points at which blood samples will be obtained for PK, ADA, and biomarker assessments.	Changes in these tables match the changes in the Schedule of Assessments.

Protocol Amendment 5: Summary of Changes and Rationale

Summary of Changes from Previous Version

This section describes the changes in reference to the protocol incorporating Amendment 5. The primary purpose of this amendment is to provide more detailed guidance on the management of patients with CRS, including administration of tocilizumab at the increased dose of 8 mg/kg upon onset of Grade 2 CRS, per ASTCT CRS consensus grading. Along the other previously described supportive measures, the administration of tocilizumab is intended to ameliorate the effect and decrease the risk of more severe CRS in patients.

This amendment also removes the requirement for mandatory biopsy specimens for backfill patients. Rather, the study conduct is modified to require paired biopsy specimens first during screening and then during treatment for patients in dose escalation beginning at the dose cohort receiving [REDACTED] and patients in the cohort-expansion phase.

Updates are provided in this amendment to the sponsor's contact (responsible medical officer) and medical monitor (project clinician).

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

Protocol Amendment 5			
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	Protocol Synopsis, Study Design; Section 3.1, Study Design; Section 3.1.1, Dose Escalation Phase; Section 6.1, CRS / Infusion Reaction; Section 6.3, Management of CRS / Infusion Reactions.	Provides more detailed guidance on the management of patients with CRS, including administration of tocilizumab at the dose of 8 mg/kg upon onset of Grade 2 CRS, per ASTCT CRS consensus grading.	The modifications in study conduct described in these sections are intended to emphasize the importance of early administration of tocilizumab to ameliorate the effects of CRS and mitigate against the development of more severe CRS in the interest of enhanced patient safety.

Protocol Amendment 5			
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	Protocol Synopsis, Study Design, Dose Escalation Backfill Patients; Section 3.1.1.3, Dose Escalation Backfill Patients; Section 8.12.1.3, Tumor Biopsy; Section 13.1 Appendices, Schedules of Assessments, Table 13.1a, footnote y, and Table 13.1b and Table 13.1c, footnote aa.	Deleted text stating that backfill patients are required to provide paired pre- and on-treatment biopsy samples as a condition for study enrollment. Added text to describe the patient populations for whom the paired pre- and on-treatment biopsy specimens will be required. A separate informed consent form will be provided for these patients.	This modification in study conduct is intended to remove a potential barrier to study enrollment for otherwise-eligible study participants, to enhance patient safety, and to facilitate the acquisition of more safety data at the various dose levels during the Dose Escalation Phase of the study. Paired biopsy specimens will also be required for patients to be enrolled in the Cohort Expansion Phase.
3	Section 8.9.3 Vital Signs; Schedules of Assessments, Tables 13.a through 13.c.	Added a patient diary with instructions for its use and time points for review by investigative site staff. Added a safety check to be performed by site staff at time points described in the Schedules of Assessments.	The additional procedures are designed to introduce additional measures to safeguard patients against severe CRS in the interest of enhanced patient safety.
4	Section 8.9.5 Clinical Laboratory Tests and Parameters	Deleted reference to the previous appendix, Table of Lab Testing Blood Volumes.	The appendix was removed in Amendment 2. Appendices were renumbered accordingly.
5	Title page, Protocol Approval – Sponsor Signatory, Emergency Contact	Updated the names and titles of the sponsor's contact (responsible medical monitor) and medical monitor (project clinician).	The name of the sponsor's contact and medical monitor were updated to reflect current roles as of the time of the approved protocol.

Protocol Amendment 4 (07 Mar 2022) – Summary of Changes

Content changes in the new version of the TAK-186 protocol amendment 4 include information updates from the previous version (TAK-186 protocol amendment 3, 01 August 2021). Further description of the changes between TAK-186 protocol amendment 4 and TAK-186 protocol amendment 3, 01 August 2021) is presented in the following tabulated summary of changes.

Section Number and Title	Summary of Changes	Rationale
Protocol Synopsis	Captured revisions to: Section 1.1.5 Rationale for Study Design, Sections 3.1, Section 3.1 Study Design, Section 3.1.1.1 [REDACTED] Section 3.1.1.2 Dose Escalation Rules, Section 3.1.2 Cohort Expansion Phase, Section 3.1.3 Survival Follow-up Period; Section 3.2.2 Nonhematologic DLT, Section 4.1 Selection of Study Patients, Section 4.1.1 Laboratory Features, Section 8.6 Posttreatment Follow-up Period, Section 8.12.1.3 Tumor Biopsy, Section 9.2 Sample Size Calculations, Section 9.5.7 Interim Analysis, Table 13a	The changes being made in the synopsis to match the rest of the protocol.
Section 3.1, Study Design	Figure 1, Figure 3.a Study Schema and corresponding text revised.	The schema updated for consistency with updated schedule of assessments.
Section 3.1 Study Design, Section 3.1.1.2 Dose Escalation Rules, Section 3.1.3 Survival Follow-up Period; Section 8.6 Posttreatment Follow-up Period; Appendix 13.1, Schedules of Assessments	Monitoring will take place overnight for at least 24 hours for first dose and at least 6 hours for the next 2 doses after their MVC-101 dose during Dose Escalation. For the no [REDACTED] scenario, starting with the 4th dose, patients must remain at the infusion center to monitor for signs or symptoms of an CRS/infusion reaction for at least 4 hours. If a [REDACTED] is implemented, overnight monitoring will be required after each [REDACTED] and after the initial cohort-assigned dose. For the [REDACTED] scenarios, starting with the 5th dose, patients must remain at the infusion center to monitor for signs or symptoms of an CRS/infusion reaction for at least 6 hours through the C1D22 dose. Survival follow-up text revised to: All patients will be followed for survival at 30 days following last treatment, then	Monitoring parameters were refined and carried throughout the protocol.

Section Number and Title	Summary of Changes	Rationale
	every 12 weeks for survival for 52 weeks by methods that include, but are not limited to, email, mail, telephone communication, or retrieval from online or other databases (eg, Social Security indexes) during a Survival Follow-up Period until the patient has died or is lost to follow-up, or the follow-up has continued for a total of 52 weeks after the last dose.	
Section 3.1.1 Dose Escalation Phase, Section 3.1.1.2 Dose Escalation Rules	DLT-evaluation period revised from 4 th dose administration to up through Cycle 1 Day 28. CRS/IRR monitoring changed to 2 doses. The rule to transition to specific tumor types beginning at the 5 th dose escalation cohort was deleted. Clarification that if a second Grade 2 CRS occurs at a higher dose a second [REDACTED] will be implemented.	CRS/IRR monitoring revised to capture all possible events and carried through protocol.
Section 3.1.1.1 [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED]
Section 3.1.1.3 Dose Escalation Backfill Patients; Section 4.1.1 Inclusion Criteria; Section 6.2.4 Subsequent Doses of MVC-101	HNSCC, NSCLC, or CRC patients only included in Backfill patients. Revised language from 4 th Dose Escalation Cohort to 4 th dose of each cohort.	Backfill language revised and clarity added to 4 th dose description.
Section 3.2.2 Nonhematologic DLT	An exception was revised for Grade 3 CRS resolving to Grade 1 in less than 24 hours. Topical corticosteroids were included.	Practical implications of CRS events were included in protocol.

Section Number and Title	Summary of Changes	Rationale
Section 4.1 Selection of Study Patients, Section 8.12.1.3 Tumor Biopsy	5 th planned Dose Escalation Cohort with HNSCC or CRC revised to [REDACTED] dose level cohort. Reference to Section 3.1.1.3 deleted. Table 1 and 3.a revised for dose escalation. Table 2 and 3.b for [REDACTED] administration added. Table 13.a	Language revised for clarity.
Section 4.1.1 Inclusion Criteria, Laboratory Features	Creatinine clearance revised to ≥ 30 mL/min.	Revised to capture all possible events.
Protocol Synopsis Sample Size, Section 1.1.5 Rationale for Study Design, Section 3.1.2 Cohort Expansion Phase, Section 9.2 Sample Size Calculations	Sample size revised to up to 25 response evaluable patients will be enrolled in each of the 3 patient cohorts, HNSCC, NSCLC, or CRC. The total sample size of the dose expansion part of the study is up to 75 patients.	Sample size increased for power.
Section 4.1.2 Exclusion Criteria	Excluded patients who had any vaccine 2 weeks prior.	Vaccine restriction added for patient safety.
Section 4.2.1 Withdrawal of Patients from the Study	Patient contact updated to include email, mail, or telephone communication retrieval from online or other databases (eg, Social Security indexes).	Follow-up text revised to match cite practices.
Section 7.1 Prohibited Therapies	Alcohol, herbal supplements, and medications prohibited.	Alcohol, herbal supplements, and medications restrictions added for patient safety.
Section 8.5 EOT Visit	EOT changed to 30 days.	EOT revised to match practice.
Section 8.9.1 AEs	AE section revised to: - up to 30 days after last dose. - collected until initiation of a new antitumor cancer therapy - revision of disease progression to: • 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, including death, during the study should be reported as AEs in the appropriate section of the eCRF.	AE language revised for patient safety.
Section 8.9.1.1.3 Treatment-Emergent AE, Section 8.9.1.4 Reporting of AEs to the Sponsor	Clarification of AE definition as AEs with start date from first dose of study drug until 30 days after the last dose of study drug.	AE clarifications added for patient safety.

Section Number and Title	Summary of Changes	Rationale
Section 8.9.1.5 Notification to Sponsor of Events Requiring Immediate Reporting	Takeda contact information updated.	Administrative update.
Section 8.9.3 Vital Signs	Oxygen saturation added.	Oxygen saturation added for robust data.
Section 8.9.4 ECG	Restrictions revised to recommend bland foods.	Bland foods added as an ECG precaution.
Section 9.2 Sample Size Calculations; Section 9.3 Analysis Sets; Section 9.5.7 Interim Analysis	DLT-evaluable Analysis Set detail added. Primary analysis revised to end of Cycle 2. Response rates tables and text deleted. Two interim analyses added.	Changes to capture DLT events and earlier analyses.
Section 9.5.1.2 Progression Free Survival	PFS revised to: However, if the patient has later scans showing no PD following initial unconfirmed progression of disease, then it is not a confirmed progression of disease and the PFS per modified RECIST for this patient is censored at the last tumor assessment date.	PFS revised to best practice.
Section 12 Reference List	Lee et al reference added.	References updated to reflect new literature added.
Section 13.1 Appendix Schedule of Assessments	Table 13a. Dose administration days changed, PK assessments, cytokines, flow cytometry, and ADA assessments added. Table 13.b Schedule of Assessments, With [REDACTED] and Table 13.c Schedule of Assessments, [REDACTED] added with corresponding footnotes. Footnotes revised to match changes in tables and body text.	Schedules of Assessments updated to reflect additional assessments and refinements.
Section 13.2 Appendix: Pharmacokinetics, Immunogenicity, and Pharmacodynamic Biomarkers	Table 13.2a PK, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling cycle days revised. Table 13.2b PK, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling With [REDACTED] and Table 13.2c PK, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling With [REDACTED] added with corresponding footnotes.	Schedules of Assessments updated to reflect additional assessments and refinements.

Protocol Amendment 3 (01 Aug 2021) – Summary of Changes

Protocol Amendment 3 includes changes to the name and address of the study sponsor legal entity name and address. Sponsorship of the clinical study was transferred on 01 August 2021 from Maverick Therapeutics, Inc. to Takeda Development Center Americas, Inc. with a place of business at 95 Hayden Avenue, Lexington, Massachusetts 02421, USA. Takeda Development Center Americas, Inc. will assume all rights, responsibilities, obligations, and contracts as sponsor of this clinical study, for all countries.

Substantial changes from Protocol Amendment 2, AU (25 May 2021) to Protocol Amendment 3 (01 Aug 2021) are summarized in the following table:

Section Number and Name	Description of Change	Brief Rationale
Throughout	The legal name and address of the study sponsor has been changed from Maverick Therapeutics, Inc., 3260 Bayshore Blvd., Brisbane, CA 94005 to Takeda Development Center Americas, Inc., 95 Hayden Ave., Lexington, MA 02421 USA	Maverick Therapeutics, Inc. was acquired by Takeda Development Center Americas, Inc. and will assume all rights, responsibilities, obligations, and contracts as sponsor of this study.
Synopsis – Study Population 4.1.1 Inclusion Criteria	Revised the duration of contraception use post last dose of study drug from 60 to 90 days for study patients of childbearing potential and for partners of male patients who are of childbearing potential.	Updated in line with CTFG recommended guidelines.

Protocol Amendment 2 (25 May 2021) – Summary of Changes

Protocol Amendment 2 includes modifications and additional time points for the safety labs, PK and PD sampling, additional safety visit assessments (ECGs, Vitals) for Days 9 and 10, and adding a Day 43 treatment visit, and adjusting the Tumor Assessment time point to Day 49. Appendix 13.1 Schedule of Assessments, 13.2 Pharmacokinetics Immunogenicity, and Pharmacodynamics Biomarkers Blood Sampling, and 13.4 Table of Laboratory Testing Blood Volumes were updated accordingly. Other administrative changes made and summarized in table below.

With the implementation of the [REDACTED] the Protocol Amendment 2 aims to update the initial planned schedule of assessments. Under the [REDACTED], week one dose will remain at a set dose [REDACTED] for future Cohort dose levels. Given this, the intensive PK and PD sampling currently scheduled during Week 1, Cycle 1 Days 1, 2, and 3, will not reflect the subsequent escalation Cohorts increasing dose levels. Therefore, the same schedule for of PK and PD sampling done during the prior protocol version Week 1 is now moved to Week 2, Cycle 1 Days 8, 9, and 10. This requires two additional visit days during Cycle 1 Week 2 (Day 9, and Day 10). Further, a treatment week is added to Cycle 1, shifting the response evaluations, and PK/ PD evaluations by one week to maintain a consistent number of weeks between the Cohort dose level and these samples/assessments. Additional safety

assessments (ECGs, vital signs measurements, and clinical laboratory data), have also been included to follow the new treatment schedule.

All affected protocol sections are detailed in the following table. Sequence of the sections follows the structure of the original protocol. Additions to the study protocol are shown in bold and deletions are shown in strikethrough text. Corrections of obvious typing errors or omissions are not highlighted. Substantial changes from Protocol Amendment 1, AU (23 Mar 2021) to Protocol Amendment 2 (25 May 2021) are summarized in the following table:

Section Number and Name	Description of Change	Brief Rationale
Throughout	Revised protocol version from Protocol Amendment 1, AU (23 Mar 2021) to Protocol Amendment 2 (25 May 2021) Typographical, administrative, and/or formatting changes were also made to improve the clarity of the document.	The version updated to align with the protocol amendment changes.
Section 3.1 Study Design	Figure 3-1, MVC-101 Treatment Schema Figure 3-1 was updated to remove C1D42 visit details and C1D49 visit details were added. These details were updated throughout the protocol, as applicable. During Dose Escalation, the initial infusion of MVC-101 will be administered over 60 minutes, with all subsequent infusions over 30 minutes. Based on the safety review of 30-minute infusion, the Sponsor may increase the infusion duration to 60-90 minutes if the shorter infusion is found to be less tolerable for the patient. The duration of the initial MVC-101 dose used in Cohort Expansion (the RP2D) will be based on the safety and PK evaluation in Dose Escalation but must be ≥30 minutes. Early administration of IV fluids and tocilizumab are mandatory for management of cytokine release syndrome (CRS)/infusion reactions (both in Escalation and Expansion Phases). For both the Dose Escalation and Cohort Expansion Phases, patients' first tumor assessment will be obtained at the end of Cycle 1 (on Cycle 1 Study Day ~~42~~ 49). Patients who remain clinically stable and do not experience a DLT or unacceptable toxicity that necessitates permanent discontinuation of the study drug at the completion of Cycle 1, will be eligible to receive additional treatment with MVC-101. Patients may receive up to 6 additional 8-week treatment cycles with MVC-101 (ie, total of 7 cycles for a maximum total of ~~54~~ 55 doses of MVC-101).	The treatment schema updated for consistency with updated schedule for Cycle 1 and updated the number of doses from 54 to 55.

Section Number and Name	Description of Change	Brief Rationale
Section 4.1.1 Inclusion Criteria	Pancreatic adenocarcinoma that is unresectable locally advanced or metastatic with ~~either no prior or~~ at least 1 prior chemotherapy regimen (eg, gemcitabine or fluoropyrimidine based therapy)	Pancreatic cancer inclusion criteria for no prior treatment is removed to follow standard of care guidelines for inclusion of patients after at least 1 prior cytotoxic chemotherapeutic regimen.
Section 4.1.2 Exclusion Criteria	13. Patients who are known to be human immunodeficiency virus positive or who are known to be hepatitis B or C positive. Patients treated for hepatitis C must have viral titers of 0 for ≥ 2 years to be eligible. Patients with hepatitis B having undetectable or ≤ 500 IU hepatitis B viral titers are eligible. HCC patients with known history of hepatitis B are excluded, regardless of hepatitis B viral titers.	Exclusion criteria updated to provide more clarity.
Section 6.1 Cytokine Release Syndrome/Infusion Reaction	The predicted mechanism of action of MVC-101 is the formation of an immunological synapse between the tumor target cells bearing EGFR and immune effectors bearing the T-cell-specific CD3 complex, leading to T-cell activation and killing of the tumor cell. Activation of T-cells is associated with the production of various cytokines. Patients who develop CRS/infusion reaction should be managed according to the standard of care practice of medicine. General guidelines to manage CRS are provided in this section. Some are required for the first 3 Dose Escalation Cohorts. Early administration of IV fluids and tocilizumab are highly recommended for management of cytokine release syndrome (CRS)/infusion reactions (both in Escalation and Expansion Phases). Tocilizumab (4 mg/kg) will be used for patients with Grade 2 CRS or higher CRS/infusion reactions including but not limited to, fever $\geq 38^{\circ}\text{C}$, hypotension (not requiring vasopressors), or hypoxia not requiring oxygen, as assessed by the American Society for Transplantation and Cellular Therapy (ASTCT) criteria (Lee et al. 2019). Severe reactions may require more intensive interventions including IV steroids, anti-TNFα antibodies, or IL1 inhibitors. ~~Early administration of IV fluids and tocilizumab will be used to manage CRS. Tocilizumab (4 mg/kg) is administered for Grade ≥ 2 infusion-related reactions/CRS including but not limited to,~~	Clarification of recommendations. Deleted repetitive language. Moved use of Tocilizumab to the first bullet, emphasizing recommendation for use.

Section Number and Name	Description of Change	Brief Rationale
	~~fever $\geq 38^{\circ}\text{C}$, hypotension (not requiring vasopressors), or hypoxia not requiring oxygen per ASTCT criteria.~~ Medications and supportive measures for the treatment of severe CRS/infusion reactions should be available for immediate use for CRS/infusion reactions during study drug administration. These include, but are not limited to: Tocilizumab 4 mg/kg Epinephrine SC (0.3 to 0.5 mL of a 1:1000 solution) Antihistamines (eg, diphenhydramine 25 to 50 mg IV) Corticosteroids (eg, hydrocortisone 40 to 80 mg IV push or equivalent, dexamethasone [REDACTED]) IV fluids (normal saline) Vasopressors Oxygen Bronchodilators Antipyretics	
Section 9.3 Analysis Sets	Landmark Response Evaluable Population: Patients with measurable disease on the baseline tumor assessment will be evaluated in separate groups based on MVC-101 dose administration: Have had >3 MVC-101 doses (successfully completed DLT period in Dose Escalation, or the first 3 doses for patients starting in Cohort Expansion). Received a minimum of ~~14~~ 15 weeks (2 cycles), ~~30~~ 31 weeks (4 cycles) or ~~54~~ 55 weeks (7 cycles) from the first dose of MVC-101.	Updated assessment time points for consistency with Cycle 1 duration.
Section 9.5.1.2 Progression-Free Survival	Progression free- survival (PFS) will be calculated as the time from the date of the first dose of study drug until the date of any documented confirmed PD using both RECIST v1.1 (Appendix 13.5) and modified RECIST v 1.1 (Appendix 13.6) or the date of death from any cause. A patient's PFS will be censored if at the time of last assessment for progression, the patient remains progression-free or if the patient dies after 2 or more missed tumor assessments. PFS will be determined using both conventional RECIST v1.1 (one objective progression) and modified RECIST criteria (confirmed objective progression, ie, 2 scans demonstrating objective progressions). For the modified criteria, if the subsequent scan confirms	Updated assessment time points for consistency with Cycle 1 duration.

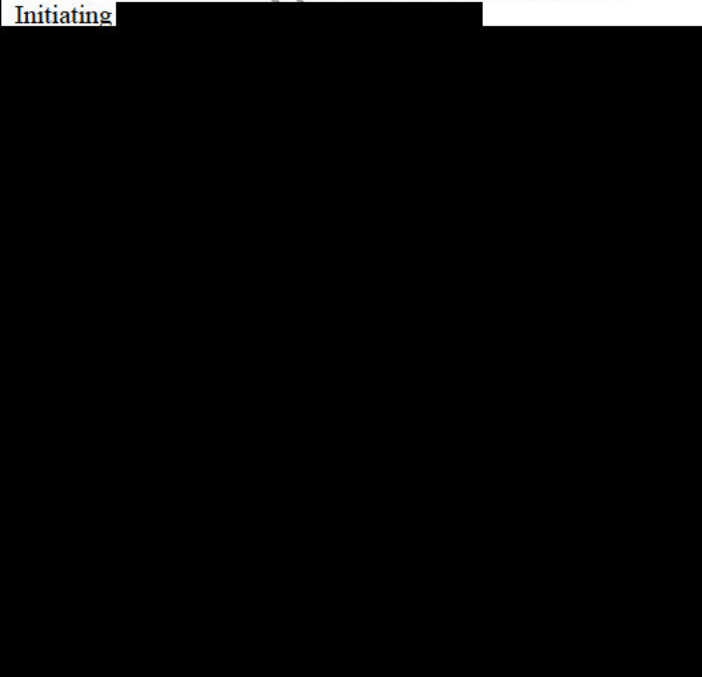
Section Number and Name	Description of Change	Brief Rationale
	progression or an additional scan is not performed, the PFS date will be based on the first occurrence of progression. In addition, to avoid inducing informative censoring for the modified criteria, any patient who has scans performed subsequent to a single assessment of PD, but never has a later PD recorded, will be assigned a PFS event date 8 weeks after their final scan. Kaplan-Meier methods will be used to estimate PFS over time and the median duration of PFS. In addition, PFS rates will be calculated at ~~14~~ 15 weeks (2 cycles), ~~30~~ 31 weeks (4 cycles) and ~~54~~ 55 weeks (7 cycles) from the first dose of study drug using Kaplan-Meier methods. The method of Brookmeyer and Crowley (Brookmeyer and Crowley 1982) will be used to construct 90% CIs around PFS estimates of the median for each expansion cohort.	
Section 9.5.1.3 Overall Survival	OS will be calculated as the time from the first dose of study drug until death due to any cause. A patient's OS will be censored if at the time of last contact, the patient was alive. In addition, landmark ~~14-15~~ weeks (2 cycles), ~~30-31~~ weeks (4 cycles) and ~~54~~ 55 weeks (7 cycles) OS rates will be determined using Kaplan-Meier methods.	Updated assessment time points for consistency with Cycle 1 duration.
Section 13.1 Appendix: Schedule of Assessments	Table 13–1 Schedule of Assessments Removed PK, Flow Cytometry, and Cytokine from C1D2 and C1D3 Added Flow Cytometry to C1D8 Added C1D9 and C1D10 visit with visit window, ECG, Vital Signs, Comprehensive Chemistry (C1D9 only), PK, Cytokine, and Flow Cytometry Removed Flow Cytometry from C1D15 Added Special Chemistry, Hematology, and Flow Cytometry to C1D22 Added PK and Flow Cytometry to C1D29 Removed PK, Flow Cytometry, Cleaved Collagen, and Biopsy from C1D36 Removed C1D42 visit Added C1D43 with Visit window, MVC-101 administration, Post infusion observation, Physical examination, vital signs, weight, PK, Flow Cytometry, Cleaved Collagen, and Biopsy Added C1D49 visit with visit window, tumor assessment, and brain MRI/CT Updated footnote a to define DLT-evaluation period	Schedule of Assessments updated to add additional assessments.

Section Number and Name	Description of Change	Brief Rationale
	Updated footnote d to add C1D43 Updated footnote f to include C1D43 Clarified physical exam assessment windows in footnote f Updated footnote h and j to include C1D9 and C1D10	
Section 13.2 Appendix: Pharmacokinetics, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling	Removed PK, Cytokine at C1D1 2Hr Removed PK, Flow Cytometry at C1D1 4Hr Removed C1D2 and C1D3 Added Flow Cytometry to C1D8 Predose Removed Cytometry from C1D8 EOI Added PK and Cytokine to C1D8 2Hr Added PK and Flow Cytometry to C1D8 4Hr Added C1D9 (24Hr) with PK and Cytokine Added C1D10(48Hr) with PK and Cytokine Removed Flow Cytometry from C1D15 Predose Added C1D15 6Hr with PK and Cytokine Added Flow Cytometry to C1D22 Predose Added C1D29 Predose with PK, Cytokine, and Flow cytometry Added C1D29 EOI with PK, Cytokine, and Flow cytometry Removed PK, Flow Cytometry, and Cleaved Collagen from C1D36 Predose Added C1D43 Predose with PK, Flow Cytometry, and Cleaved Collaged Replaced "0 (Predose)" with "Predose" Updated footnote c to remove reference to SOI as 0 hour Replaced reference in footnote notes of Day 2 and 3 with Day 9 and 10	Table has been updated to add additional assessments.
Section 13.4 Appendix: Table of Laboratory Testing Blood Volumes	Updated blood volume table to reflect changes in 13.1 and 13.2	Text has been updated to reflect changes in blood volume due to addition of new time points.
Synopsis	The above changes have also been made to the Synopsis consistently, as applicable.	Text in the synopsis has been updated to maintain consistency and to align the text with the protocol body.

Protocol Amendment 1 (23 Mar 2021) - Summary of Changes

Protocol Amendment 1 includes minor changes to the inclusion and exclusion criteria (albumin lower range adjusted, tumor type added, ovarian cancer prior therapies updated, and guidance for hepatitis B positive HCC added), clarification of single patient dose escalation procedures, COVID-19 vaccine guidance, updates from Protocol Change Memo #1 dated 16 December 2020, and other administrative and formatting changes.

All affected protocol sections are detailed in the following table. Sequence of the sections follows the structure of the original protocol. Additions to the study protocol are shown in bold and deletions are shown in strikethrough text. Corrections of obvious typing errors or omissions are not highlighted. Substantial changes from Original, v1.0 (04 Nov 2020) to Protocol Amendment 1, AU (23 Mar 2021) are summarized in the following table:

Section Number and Name	Description of Change	Brief Rationale
Throughout	Revised protocol version from Original, v1.0 (04 Nov 2020) to Protocol Amendment 1, AU (23 Mar 2021). Typographical, administrative, and/or formatting changes were also made to improve the clarity of the document. Wording for Ethics Committee changed to Independent Ethics Committee.	The version updated to align with the protocol amendment changes.
Section 3.1.1.2 Dose Escalation Rules	Change in description of the single-patient cohort escalation step from "1+3" to "1+2" for clarification. Change does not impact the actual dose escalation rules. Table 3-6 Dose Escalation Plan with Example for Initiating 	Description clarified to more precisely reflect single patient cohort escalation plan.

Section Number and Name	Description of Change	Brief Rationale
Section 3.2 Dose Limiting Toxicity	MVC-101 dose administration should be withheld for AEs potentially meeting criteria for a DLT pending resolution of the event and MVC-101 attribution assessment. During the Dose Escalation Phase, the decision to dose escalate is based on DLTs defined as any of the following events, regardless of relationship except those events that are clearly due to extraneous causes occurring during the DLT-evaluation period of Cycle 1. The severity of non-CRS AEs will be graded according to the NCI CTCAE v5.0 and CRS/infusion reaction toxicity graded using the ASTCT criteria (Lee et al. 2019) (Section 6.1.1). Safety data from dose escalation and expansion cohorts will be reviewed, and all dose escalation decisions made by: Study Site Investigators Sponsor Safety Physician Independent (from Sponsor) Pharmacovigilance Safety Expert(s) Any other independent expert (eg, PK or toxicologist) on an as needed basis	Text updated to clarify the members of the group who will review safety data and be responsible for making decisions about dose escalation.
Section 4.1.1 Inclusion Criteria	6. The ~~sixteen~~ eighteen different tumors types will be included for the initial Dose Escalation Cohorts. Dose Escalation Tumor Histologies: (note: beginning in the 5th planned Dose Escalation Cohort [REDACTED] include only HNSCC, NSCLC, or CRC) Adrenocortical carcinoma that is unresectable, locally advanced or metastatic Epithelial ovarian cancer progressing during or following at least ~~3-1~~ prior cytotoxic chemotherapeutic regimens, and subsequent PARP inhibitor therapy in BRCA mutation positive patients (unless ineligible) 9. Acceptable laboratory parameters as follows: Albumin ≥ 3.20 g/dL	Inclusion criteria 6 updated to include patients with adrenocortical carcinoma tumor in dose escalation, epithelial ovarian cancer criteria updated to current standard of care guidelines that support entrance into a clinical trial after 1 prior cytotoxic chemotherapeutic regimen, and subsequent PARP inhibitor therapy in BRCA mutation positive patients (unless ineligible). Inclusion criteria 9 is updated to evaluate patients with lower albumin ranges.

Section Number and Name	Description of Change	Brief Rationale
Section 4.1.2 Exclusion Criteria	13. Patients who are known to be human immunodeficiency virus positive or who are known to be hepatitis B or C positive. Patients treated for hepatitis C must have viral titers of 0 for ≥ 2 years to be eligible. Patients with hepatitis B having undetectable or ≤ 500 IU hepatitis B viral titers are eligible. HCC patients with known history of hepatitis B are excluded.	Patients with concomitant HCC and hepatitis may be at higher risk for significant liver dysfunction.
Section 5.1.3.1 General Guidelines and Precautions	The calculated dose is administered based on the patient's weight measured within 3 days of Cycle 1, Day 1 (baseline). On Day 1 of subsequent treatments, a change in body weight $\pm 10\%$ from baseline should prompt recalculation of total dose. Refer to the Pharmacy Manual for the formula for dose calculations and example dose preparation calculations. ~~The calculated dose will be administered based on the patient's actual weight at Day 1 (Cycle 1, Day 1). Significant ($\geq 10\%$) change in body weight from baseline should prompt recalculation of dose.~~ Infusion or allergic reactions may occur with the infusion of protein-based therapeutics. Precautions for anaphylaxis should be observed during MVC-101 administration. Supportive measures may include, but are not limited to epinephrine, antihistamines, corticosteroids, IV fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen (paracetamol), or ibuprofen . Please refer to Section 6.2 for specific guidelines regarding the management of CRS.	Text updated to provide administrative clarification.
Section 6.2.2 30 Minutes Prior to Dose on Day 1 (Required for the Initial 3 Dose Escalation Cohorts)	Acetaminophen 650 mg or paracetamol 500 mg , or ibuprofen 400 mg by mouth (PO) Diphenhydramine 25-50 mg PO or IV or equivalent H1 antagonist H2 antagonist (eg famotidine, cimetidine) or proton pump inhibitor (eg esomeprazole, omeprazole) will be given PO or IV at the institutional standard dose ~~Ranitidine 300 mg PO or 50 mg IV or equivalent H2 antagonist~~ Dexamethasone [REDACTED]	Text updated to add paracetamol as an alternative to acetaminophen, and to clarify options for H2 antagonist and/or protocol pump inhibitor medications to be used as premedications. Dexamethasone route of administration added for clarification.
Section: 6.2.4.1 No Reactions of Grade >1 Severity to the Dose on Day 1	<u>30 minutes prior to the infusion (required for the initial 3 Dose Escalation Cohorts):</u> Acetaminophen 650 mg or paracetamol 500 mg , or ibuprofen 400 mg PO Diphenhydramine 25-50 mg PO or IV or equivalent H1 antagonist ~~Ranitidine 300 mg PO or 50 mg IV or equivalent H2 antagonist~~ (eg famotidine, cimetidine) or proton pump inhibitor (eg	Text updated to add paracetamol as an alternative to acetaminophen, and to clarify options for H2 antagonist and/or protocol pump inhibitor medications to be used as premedications or added

Section Number and Name	Description of Change	Brief Rationale
	esomeprazole, omeprazole) will be given PO or IV at the institutional standard dose (may be discontinued when corticosteroids are discontinued) Ondansetron 8 mg IV or PO (if nausea and/or vomiting occurred with prior dose administration) Reduce dexamethasone premedication by 50% and discontinue with next dose if only Grade ≤1 infusion reaction observed at the 50% dexamethasone level and if no MVC-101 dose delays of >7 days	to therapy for CRS/infusion reactions.
Section 6.2.4.2 Grade 2 or Higher Reaction to the Day 1 Dose of MVC-101	<u>30 minutes prior to the infusion (required):</u> Acetaminophen 650 mg or paracetamol 500 mg, or ibuprofen 400 mg PO Diphenhydramine 25-50 mg PO or IV or appropriate dose of equivalent H1 antagonist ~~Ranitidine 300 mg PO or 50 mg IV or equivalent~~ H2 antagonist (eg famotidine, cimetidine) or proton pump inhibitor (eg esomeprazole, omeprazole) will be given PO or IV at the institutional standard dose (may be discontinued when corticosteroids are discontinued) Ondansetron 8 mg IV or PO (if nausea and or vomiting occurred on prior dose administration) Dexamethasone [REDACTED] Dexamethasone dose may be reduced by 25-50% for each subsequent dose and may be discontinued in 2-4 subsequent doses, if no dose delays of >7 days nor infusion reactions occur If the reaction occurred while the infusion was ongoing, then begin MVC-101 infusion at a 50% reduced rate and 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	Text updated to add paracetamol as an alternative to acetaminophen, ibuprofen (omitted in error), and to clarify options for H2 antagonist and/or protocol pump inhibitor medications to be used as premedications or added to therapy for CRS/infusion reactions.
Section 7 Concomitant Therapy and Restrictions	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. COVID-19 vaccination is not required but encouraged as oncology patients receiving treatment are a vulnerable group. The following guidance is provided to coordinate the timing of vaccination and study treatment: Patients in Screening should schedule their 2nd dose at least 2 weeks prior to Day 1 (assuming vaccine is a 2-dose vaccine). If a single-dose vaccine is approved, the single-dose should be at least 2 weeks before Day 1 Vaccination during Cycle 1 is discouraged	Text updated to provide guidance for COVID-19 vaccination usage.

Section Number and Name	Description of Change	Brief Rationale
	Starting with Cycle 2, at least 7 days must elapse from last treatment to COVID vaccination and patients must have 7 days elapse from vaccination to next treatment on study Deviation from the above guidelines should be discussed and agreed with the medical monitor	
Section 8.4 Medical History	A complete medical history ~~should be~~ is obtained during the Screening Period . Collect all concurrent medical conditions in the last 60 days and any significant prior medical conditions (eg, hospitalizations, surgeries, prior cancer history) ~~should be collected~~ . During Screening (within 28 days prior to first dose of MVC-101), record any untoward event that occurs ~~should be recorded~~ as medical history and not as an AE, unless it is due to a protocol-related procedure. Thereafter (ie, after the time of study drug administration), collect any untoward event ~~should be collected~~ as an AE.	Text updated for clarity.
Section 8.9.4 ECG	ECGs done on Screening, ~~Baseline Cycle 1 Day 1 (predose)*~~ , and on Day 1 of each subsequent cycle should be obtained in triplicate (3 ECGs per time point at approximately 1-minute intervals). ECGs done at other time points are single evaluations unless triplicate ECG is clinically indicated. Local interpretation will be used for data analysis purposes. * ~~Baseline Cycle 1 Day 1 (predose)~~ ECG does not need to be repeated if Screening ECG done within 72 hours of the initial MVC-101 dose.	Text updated for clarity.
Section 11.7.1 Modification of the Protocol	Any changes in the required procedures defined in this protocol, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the Sponsor or designee. Amendments to the protocol (including emergency changes) must be submitted to the appropriate regulatory authorities (eg, FDA) and in writing to the investigator's IRB/IEC , along with any applicable changes to the ICF, for approval. Such changes must be approved by the IRB/IEC before their implementation before patients can be enrolled into an amended protocol. Documentation of IRB/IEC approval must be sent to the Sponsor immediately upon receipt. See Appendix 13.8 for summary of changes for each amendment.	Text updated to provide additional clarity on protocol amendment procedures.

Section Number and Name	Description of Change	Brief Rationale
Section 13.1 Appendix: Schedule of Assessments	Table 13–1 Schedule of Assessments ^g ~~Can be omitted~~ Need not be repeated if performed during Screening within 72 hours of Cycle 1 Day 1. ^h ECG: ECGs done at Screening, ~~Baseline~~ C1D1 (predose) can be omitted if Screening ECG <72 hours of infusion start), and on Day 1 of each cycle should be obtained in triplicate (approximately 1 min apart). ECGs done at other time points are single evaluations unless triplicate ECG is clinically indicated. If infusion is interrupted, ECGs will be done based on the time when infusion resumes.	Footnote text updated to provide clarity
Section 13.4 Appendix: Table of Laboratory Testing Blood Volumes	^c Cycle 3 and beyond. ~~A total of 3 cycles are calculated~~ ^f ~~Only done~~ Will be collected on Day 22 of Cycles 2-7 ^g Will be collected on Day 15 and Day 22 of Cycle 2	Footnote text updated to provide clarity on blood volumes and other administrative corrections were made for clarification.
Section 13.6 Appendix: Modified RECIST Guidelines	Table 13–4 Single Time Point Response: Patients with Target ($\pm$ Nontarget) Disease ^a Unconfirmed CR or PR until confirmative scan $\geq$ 28 days from 1 st scan demonstrating initial response	Footnote text updated to provide clarity.
Synopsis	The above changes have also been made to the Synopsis consistently, as applicable. Updated the inclusion and exclusion criteria presented in the Synopsis for consistency with the protocol inclusion criteria section 4.1.1 and exclusion criteria section 4.1.2	Text in the synopsis has been updated to maintain consistency and to align the text with the protocol body.

Signature Page for CP-MVC-101-01 Protocol Amend 8

Title:

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