Title: An Open-Label, Dose Escalation, Phase 1, First-in-Human Study of TAK-164, an Antibody-Drug Conjugate, in Patients with Advanced Gastrointestinal Cancers Expressing Guanylyl Cyclase C

NCT Number: NCT03449030

Protocol Approve Date: 04 September2019

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

PROTOCOL

An Open-Label, Dose Escalation, Phase 1, First-in-Human Study of TAK-164, an Antibody-Drug Conjugate, in Patients with Advanced Gastrointestinal Cancers Expressing Guanylyl Cyclase C

Sponsor: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited

Please note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium," "sponsor," or "Takeda".

Study Number: TAK-164-1001

Compound: TAK-164

Date: 04 September2019 **Amendment Number:** 05

Amendment History:

Date	Amendment Number	Amendment Type	Region
30 November 2017	Initial protocol	Not applicable	Global
26 January 2018	01	Substantial	Global
27 June 2018	02	Nonsubstantial	Global
13 September 2018	03	Substantial	Netherlands
29 March 2019	04	Substantial	Global
04 September2019	05	Substantial	Global

1.0 ADMINISTRATIVE

1.1 Contacts

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

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

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.

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 Conference on Harmonisation E6 Good Clinical Practice: 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.

PPD

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, 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 Conference on 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 B).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

1.3 Protocol Amendment 05 Summary of Changes

Rationale for Amendment 05

This document describes the changes in reference to the protocol incorporating Amendment 05. The primary reasons for this amendment are to limit the future maximal TAK-164 dose to 0.19 mg/kg once every 3 weeks (Q3W), to identify hepatotoxicity as a potential risk and implement an enhanced liver safety management plan, to integrate safety/tolerability data beyond Cycle 1 into the recommended phase 2 dose (RP2D) determination for the expansion phase, to limit the number of prior lines of therapy to 2 or 3 lines in the expansion phase (part B), and to enroll patients at the recommended imaging dose (RID) in the imaging substudy (part C).

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

Changes in Amendment 05

1. The future maximal TAK-164 dose was limited to 0.19 mg/kg Q3W.
2. Hepatotoxicity was added as a potential risk. An enhanced liver safety management plan was implemented.
3. Clarified that safety/tolerability data beyond Cycle 1 will be integrated into the RP2D determination for the expansion phase.
4. Limited prior lines of therapy to 2 or 3 lines in the expansion phase (part B).
5. Clarified that patients will be enrolled at the RID in the imaging substudy (part C).
6. Clarified that part C will be conducted in The Netherlands only.
7. Clarified that gastric carcinoma patients in part B and colorectal or gastric carcinoma patients in part C must express guanylyl cyclase C (GCC) with an H-score of ≥10.
8. Clinical laboratory directives were updated to reflect local capabilities.
9. Clarified protocol for biopsy.
10. Added definition and requirements for monitoring and reporting adverse events of special interest (AESIs).
11. Clarified procedure for collection of electrocardiograms (ECGs) at the end of infusion (EOI).
12. Updated Response Evaluation Criteria in Solid Tumors (RECIST) per RECIST version 1.1 guidelines.
13. Clarified that the specific mass dose of antibody-drug conjugate (ADC) will be determined during the dosimetry and imaging optimization (DIO) phase of the imaging substudy.
14. Clarified the timing of disease assessments.
15. Moved a section of text regarding part C from Section 13.1.6 to Section 13.1.3.

For specific descriptions of text changes and where the changes are located, see Appendix H.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

2.0 STUDY SUMMARY

Name of Sponsor(s): Millennium Pharmaceuticals, Inc	**Compound:** TAK-164	
Title of Protocol: An Open-Label, Dose Escalation, Phase 1, First-in-Human Study of TAK-164, an Antibody-Drug Conjugate, in Patients with Advanced Gastrointestinal Cancers Expressing Guanylyl Cyclase C	**IND No.:** Not Applicable	**EudraCT No.:** Not Applicable
Study Number: TAK-164-1001	**Phase:** 1	

Study Design:

This is a multicenter, nonrandomized, open-label, phase 1 study of TAK-164 in patients with advanced guanylyl cyclase C (GCC)-positive gastrointestinal (GI) cancer for whom standard treatment is no longer effective or for whom there is no available standard therapy. This study will be the first to administer TAK-164 to humans. For the dose escalation portion of the study (part A), the patient population will consist of adults, aged 18 years or older, with any various GI malignancies expressing GCC for whom standard treatment is no longer effective or for whom there is no available standard therapy. Maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) will be estimated in part A. In the expanded cohort (part B), patients with colorectal carcinoma (CRC) and gastric carcinoma will be enrolled at RP2D. In the expanded cohort (part C-imaging substudy), patients with CRC and gastric carcinoma will be enrolled at the recommended imaging dose (RID).

This study is designed to determine safety, tolerability, and pharmacokinetics (PK) and to determine an MTD and/or RP2D of TAK-164 that may be safely administered to patients with advanced GCC-positive GI cancer. The study may also help define a therapeutic window of TAK-164 based on pharmacodynamics and systemic exposures achieved over the evaluated dose range. It is anticipated that approximately 100 patients could be enrolled, including the escalation phase (part A), the expansion phase (part B), and the imaging substudy (part C).

Once enrolled in the study, patients will receive TAK-164 treatment intravenously (IV) on Day 1 of each 21-day treatment cycle or every 3 weeks (Q3W).

Dose Escalation (Part A)

The starting TAK-164 dose will be 0.004 mg/kg Q3W and the maximal dose will not exceed 0.19 mg/kg Q3W. To determine the MTD and to guide the dose escalation portion of the study, a method based on a Bayesian model of modified toxicity probability interval (mTPI), will be used. Although dose escalation and MTD will be estimated based on observed dose-limiting toxicities (DLTs) in Cycle 1, safety/tolerability data beyond Cycle 1 will be integrated into the RP2D determination for the expansion phase. The DLT rate will be continuously monitored and safety analysis conducted during the dose expansion part of the study to allow regular assessments of the appropriateness of the dosing level.

Expansion Cohort (Part B)

Once the RP2D is established, the number of patients at that dose will be expanded to further characterize the safety, tolerability, and PK of TAK-164 (conjugated and unconjugated) and to evaluate disease response in patients based on the expression of GCC as measured by immunohistochemistry (IHC). Up to 25 patients with CRC of high GCC expression level (H-score ≥150) will be assessed. In addition, up to 25 patients with gastric carcinoma expressing GCC (H-score ≥10) will be included in the study. Patients with CRC GCC high expression level and patients with gastric cancer may experience a greater clinical benefit than patients with other GI malignancies, as supported by preclinical research. A minimum of approximately 20 patients will be enrolled in either cohort. The DLT rate will be continuously monitored and safety analysis conducted during dose expansion part of the study to allow regular assessments of the appropriateness of the dosing level.

The objectives are to evaluate the safety and tolerability of TAK-164 and to assess efficacy, as measured by overall response rate (ORR) and other efficacy variables, including disease control rate (DCR), duration of response (DOR), and progression-free survival (PFS). The evaluation of tumor status will be performed by computed tomography (CT) or magnetic resonance imaging (MRI) scans according to modified Response Evaluation Criteria in Solid

Tumors (RECIST) (version 1.1) [1] in all patients participating in this study at treatment intervals of 2 cycles. Pharmacodynamic evaluation will be performed by assessing CCI [redacted] on tumor tissue from pre- and postdose biopsies required to be obtained from a minimum of approximately 5 evaluable patients participating in the study.

All patients participating in this study who are judged by the investigator to be receiving clinical benefit may receive study drug until they experience progression of disease (PD) or unacceptable toxicity or they choose to withdraw from study due to other factors.

Imaging Substudy (Part C, To Be Conducted in The Netherlands Only)

Up to 25 patients with GCC-expressing metastatic colorectal carcinoma (mCRC) and/or gastric carcinoma at up to 2 investigational sites in The Netherlands will be enrolled to determine the in vivo biodistribution and tumor targeting of zirconium 89 (^{89}Zr)-TAK-164 by positron emission tomography (PET) imaging. In addition, the relationship of ^{89}Zr-TAK-164 tumor targeting with 18-fluorodeoxyglucose (^{18}F-FDG)-PET–determined response and RECIST version 1.1 response, and the relationship of ^{89}Zr uptake with GCC expression, in tumor tissues and other biomarkers will be investigated. Based on emerging data from the dose escalation phase (part A) and in agreement between the site investigator and sponsor, part C will be triggered at a dose that is considered safe and having treatment potential (RID).

Initially, approximately 6 patients (including 3 dosimetry patients) will be enrolled for dosimetry and imaging optimization (DIO). This DIO subgroup will receive only ^{89}Zr-TAK-164 (mass dose <50% of the RID) 14 days before the first regularly scheduled study dose at Cycle 1 Day 1 and a second ^{89}Zr-TAK-164 administration on Cycle 1 Day 1 in combination with unlabeled TAK-164 at a maximum mass dose of 100% of the RID. Imaging will be performed 1 hour after end of infusion (EOI) of the first ^{89}Zr-TAK-164 administration for dosimetry in the first 3 patients and for all patients at 2 time points between Day 2 and Day 7 after EOI. Imaging time points and mass dose of TAK-164 can be adjusted to optimize imaging conditions. Up to 19 additional patients will be enrolled into part C to receive a single dose of ^{89}Zr-TAK-164 at Cycle 1 Day 1 in addition to unlabeled TAK-164 as determined for optimal imaging. Once the RP2D of TAK-164 is determined, part C patients who have received TAK-164 at an RID lower than the RP2D of TAK-164 may dose-escalate to the RP2D in the absence of PD or unacceptable treatment-related toxicity at the investigator's discretion and with the sponsor's approval. If the full RID/RP2D is not administered at Cycle 1 Day 1, the differential will be provided after the second image acquisition. Part C patients will continue treatment with the RID/RP2D of TAK-164 at Cycle 2 Day 1 and beyond.

Primary Objective:

- To evaluate the safety of TAK-164 and to determine the MTD and/or RP2D.

Secondary Objectives:

Part A and part B secondary objectives are:

- To characterize the PK of TAK-164.
- To evaluate immunogenicity of TAK-164.
- To evaluate efficacy of TAK-164 as measured by overall response rate.
- To evaluate other efficacy measures such as DCR, which includes response (complete response [CR]+partial response [PR]) plus stable disease, DOR, and PFS.

Part C (imaging substudy) secondary objectives are:

- To determine the biodistribution of ^{89}Zr-TAK-164 in patients with mCRC and/or metastatic gastric carcinomas.
- To determine the tumor targeting of ^{89}Zr-TAK-164.
- To determine dosimetry of ^{89}Zr-TAK-164.

Patient Population: Patients with advanced GI cancer expressing GCC who are appropriate candidates for experimental therapy for whom standard treatment is no longer effective or for whom there is no available standard therapy.

Number of Patients: The maximum number of patients in this study is expected to be to approximately 100 evaluable patients (including up to 25 in the dose escalation phase and up to 25 patients in the imaging substudy [part C]).	**Number of Sites:** Up to 5 sites in the United States (US) in the dose escalation portion of the study. Additional sites will be added, globally, for the expansion portion of the study. Substudy part C will be conducted at up to 2 sites in The Netherlands including Amsterdam University Medical Centre (Amsterdam UMC), location Vrije Universiteit Medical Centre (VUMc).

Route of Administration: TAK-164 IV, ^{89}Zr-TAK-164 IV

Dose Level(s):

Part A

Q3W Schedule and Dose Levels:

- TAK-164 is administered on Day 1 of each 21-day cycle.
- Up to 3 initial patients per cohort will be enrolled at the starting dose of 0.004 mg/kg. Dose escalation is planned to proceed by evaluating patients at respective doses: 0.008 mg/kg, 0.016 mg/kg, 0.032 mg/kg, 0.064 mg/kg, 0.12 mg/kg, and 0.19 mg/kg.

The adjustments of percent increases between the dose levels is based on further review of the preclinical modeling that predicts human TAK-164 exposures for safety and efficacy. Also, currently available clinical experience supports the dose escalation scheme. Lower increments between dose levels may be proposed and discussed between sponsor and the investigators based on emerging clinical data.
MTD with a target toxicity of 25% is determined by mTPI (dose level of posterior mean toxicity closest to target toxicity). Although dose escalation and MTD will be estimated based on observed DLTs in Cycle 1, safety/tolerability data beyond Cycle 1 will be integrated into the RP2D determination for the expansion phase.

Approximately 25 patients will be enrolled during the dose escalation phase on the Q3W schedule. The escalation may be stopped upon a completion of enrollment of all patients planned to participate in the dose escalation part of the study or based on clinical judgment supported by medical observations.

Dose escalation will apply mTPI design. Up to 3 patients will be enrolled in dose cohort 1 and following completion of 1 treatment cycle interval reassessment will be performed to assess tolerability of TAK-164 to inform any dose adjustments that may be needed for subsequent patients. Decisions regarding dose escalation will be made on the basis of DLTs occurring during the first cycle of treatment.

A dose range of TAK-164 that may be safely administered as a single agent to patients will be assessed in the course of the dose escalation part of the study and this information will support the dose schedule recommendation for use in the expansion phase (part B and part C of the study). Safety/tolerability data beyond Cycle 1 will be integrated into the RP2D determination for the expansion phase.

Note that, depending on PK-defined exposure estimates, a dose level between the planned dose levels may be explored. In addition, based on safety/tolerability, alternative dosing schedules may be explored after discussion and concurrence with all lead investigators and the Takeda study clinician. However, no patients will receive a dose above 0.19 mg/kg Q3W.

Patients participating in the escalation stage, estimated to be approximately 25, will be followed until PD, unacceptable toxicity, or until they choose to withdraw consent from the trial.

More conservative dose escalation, evaluation of intermediate doses, and expansion of an existing dose level are all permissible following discussion between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-related toxicity, exposure, or pharmacodynamics of TAK-164.

Part B

Schedule: One treatment schedule (Q3W schedule) will be evaluated during part B, as informed by the data obtained from part A.

Patients participating in part B (expansion stage of the study) will be followed until PD, unacceptable toxicity, or until they choose to withdraw consent.

Part C (To Be Conducted in The Netherlands Only)

Schedule: The DIO subgroup will receive ^{89}Zr-TAK-164 (mass dose <50% of the RID) 14 days before the first regularly scheduled study dose at Cycle 1 Day 1 and a second ^{89}Zr-TAK-164 administration on Cycle 1 Day 1 in combination with unlabeled TAK-164 at a maximum mass dose of 100% of the RID. Imaging will be performed 1 hour after EOI of the first ^{89}Zr-TAK-164 administration for dosimetry in the first 3 patients and for all patients at 2 time points between Day 2 and Day 7 after EOI. Imaging time points and mass dose of TAK-164 can be adjusted to optimize imaging conditions. Up to 19 additional patients will be enrolled into part C to receive a single dose of ^{89}Zr-TAK-164 at Cycle 1 Day 1 in addition to unlabeled TAK-164 as determined for optimal imaging. Once the RP2D of TAK-164 is determined, part C patients who have received TAK-164 at an RID lower than the RP2D of TAK-164 may dose-escalate to the RP2D in the absence of PD or unacceptable treatment-related toxicity at the investigator's discretion and with sponsor's approval. If the full RID/RP2D is not administered at Cycle 1 Day 1, the differential will be provided after the second image acquisition. Part C patients will continue treatment with the RID/RP2D of TAK-164 at Cycle 2 Day 1 and beyond.

Duration of Treatment:	**Period of Evaluation:**
Treatment with TAK-164 can be continued in the absence of unacceptable toxicity until the first documentation of PD by imaging (physician discretion) or consent withdrawal. The maximum duration of treatment is 12 cycles. All patients participating in this study who are judged by the investigator to be receiving clinical benefit will be permitted to remain on therapy until PD or they choose to withdraw from the study due to toxicity or other factors.	Assessments of disease will be performed at specified time points. Radiographic evaluation will be conducted at treatment intervals of 2 cycles. Follow-up visits for PFS, which will evaluate a response, will be conducted at the site every 3 months from last dose of study drug for patients who discontinue for reasons other than PD. Those follow-up visits will continue for up to 6 months or until PD, the start of alternative therapy, or conclusion of the study (whichever occurs first).

Main Criteria for Inclusion:

- Histologically or cytologically confirmed measurable advanced and/or metastatic solid GI tumor that expresses GCC protein (H-score ≥10), for which standard treatment is no longer effective or for whom there is no available standard therapy. For the escalation part of the study (part A), GI malignancies include, but are not limited to, mCRC, gastric carcinoma, esophageal carcinoma, small intestine cancer, and pancreatic cancer. The expansion part of the study (part B) is limited to patients with CRC expressing a high-level GCC (H-score ≥150) and gastric carcinoma expressing GCC (H-score ≥10). Part C includes patients with CRC and gastric carcinoma expressing GCC (H-score ≥10).
  - The expansion part of the study (part B) will be limited to patients with 2 or 3 prior lines of systemic standard of care therapy.
- Voluntary written consent must be obtained from the patient prior to enrollment in the study with the understanding that consent may be withdrawn by the patient at any time without consequences on receiving future medical care.
- Male or female patients 18 years or older.
- Adequate bone marrow function, defined as an absolute neutrophil count of ≥1.5 × 10^9/L, platelet count ≥100 × 10^9/L, and hemoglobin ≥9 g/dL. Receiving transfusions or hematopoietic growth factors to meet enrollment criteria are not allowed within 14 days preceding the first dose of study drug.
- Adequate hepatic function with:

- Total bilirubin ≤1.5 × upper limit of normal (ULN).
- Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) must be ≤2.5 × ULN (AST and ALT may be elevated up to 3 × ULN if the elevation can be reasonably ascribed to the presence of metastatic disease in liver).
- Serum albumin ≥3.0 g/dL.

- Adequate renal function as defined by creatinine clearance ≥60 mL/min.
- Eastern Cooperative Oncology Group performance score of 0 or 1.
- Life expectancy of at least 12 weeks.
- Completion of prior chemotherapy, biologic therapy, immunotherapy, or radiation therapy at least 4 weeks prior to enrollment.
- Resolution of all toxic effects of prior treatments (except alopecia) to Grade ≤1 by National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.
- A portion of patients should have tumors amendable for serial biopsy and a willingness to provide consent for pharmacodynamic assessment.

Additionally, for part C (imaging substudy), patients must fulfill the following criteria:

- At least 1 extrahepatic metastatic lesion ≥2 cm in the longest diameter.

Main Criteria for Exclusion:

- Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the screening period, or male or female patients of reproductive potential who are not employing an effective method of birth control.
- Serious preexisting medical or psychiatric conditions that, in the opinion of the investigator, would preclude participation in the study.
- Chronic or active infection requiring systemic therapy, as well as a history of symptomatic viral infection which has not been fully cured (eg, HIV or viral hepatitis B or C).
- Symptomatic central nervous system (CNS) malignancy or metastasis. Screening of asymptomatic patients without history of CNS metastases is not required.
- History of congestive heart failure with New York Heart Association class greater than 2 (Class 1 and 2 are eligible), unstable angina (within 3 months prior to study enrollment), recent myocardial infarction (within 6 months of study enrollment), transient ischemic attacks, stroke, arterial or venous vascular disease, or clinically significant symptomatic arrhythmia despite anti-arrhythmic therapy.
- Corrected QT by Fridericia method interval >470 msec.
- Treatment with anticancer chemotherapy or biologic therapy or with an experimental anticancer agent within 28 days of the initial dose of study drug.
- Patient has a history of severe allergic or anaphylactic reactions to recombinant proteins or excipients used in TAK-164 or ^{89}Zr-TAK-164 formulation.
- Patient has concurrent alcohol abuse or a history of drug-induced liver injury (DILI).

Main Criteria for Evaluation and Analyses:

Primary endpoints for this study are:

- Number of patients with a DLT.
- Percentage of patients with adverse events (AEs).
- Percentage of patients with Grade 3 or above AEs.
- Percentage of patients with drug-related AEs.
- Percentage of patients with drug-related Grade 3 or above AEs.
- Percentage of patients with serious adverse events.
- Percentage of patients with AEs leading to discontinuation.
- Percentage of participants who meet the markedly abnormal criteria for safety laboratory tests at least once postdose.
- Percentage of participants who meet the markedly abnormal criteria for vital sign measurements at least once postdose.
- MTD and/or an alternate RP2D of TAK-164.

Secondary endpoints for this study are:

- TAK-164 PK parameters: C_{max}, $t_{max,}$ and AUC_{last} during Cycle 1 Day 1 and Cycle 2 Day 1. In addition, observed concentration at the end of a dosing interval (C_{trough}) may be reported for other dosing days during which a single predose PK sample is collected.
- ORR as assessed per modified RECIST version 1.1 [1].
- DCR.
- DOR.
- PFS.
- Antidrug antibody in serum.

Imaging-specific secondary endpoints (part C only):

- Qualitative and quantitative (in terms of standardized uptake value [SUV]) determination of patient-level biodistribution of ^{89}Zr-TAK-164 at all ^{89}Zr-TAK-164 imaging time points.
- Qualitative and quantitative (SUV) determination of ^{89}Zr-TAK-164 uptake in tumor lesions identified with CT/^{18}F-FDG-PET at all ^{89}Zr imaging time points.

Statistical Considerations:

Part A: Dose Escalation

mTPI:

The mTPI study design by Ji [2] will be utilized to determine MTD.

The starting dose of 0.004 mg/kg will be used to treat the first cohort of patients and the dose escalation schema will be followed, as planned.

The dose and schedule recommended for the use in part B and part C (expansion) of the study will be based on safety, PK, and pharmacodynamics antitumor response data observed in part A.

Part B: Dose Expansion

Approximately 50 patients with CRC, GCC high expression level (H-score ≥150) and patients with gastric

carcinoma expressing GCC (H-score ≥10) will be assessed. A minimum of approximately 20 patients will be enrolled in either cohort. The DLT rate will be continuously monitored and safety analysis conducted during dose expansion part of the study to allow regular assessments of the appropriateness of the dosing level.

Part C: Imaging Substudy (To Be Conducted in The Netherlands Only)

All patients with at least one ^{89}Zr-TAK-164 PET scan will be included in the analyses. All patients who receive any amount of ^{89}Zr-TAK-164 will be included in the safety analyses. Imaging outcome data will be summarized and the correlation with pathology and clinical outcome data explored.

Sample Size Justification: A total of approximately100 patients will be enrolled in this study including dose escalation (part A), dose expansion (part B), and imaging substudy (part C). Part A and part C each will include up to 25 patients.

Part B: The sample size was estimated for CRC and gastric cancer separately. For CRC, assuming a targeted ORR of 16% with a 2-sided exact 80% confidence interval (CI) such that the lower limit is greater than 5%, approximately 25 response-evaluable patients will provide close to 60% power to observe at least 4 responses, ie, 4/25 = 16%; exact 80% CI (7.2%, 29.5%). For gastric cancer, assuming a targeted ORR of 20% with a 2-sided exact 80% CI such that the lower limit is greater than 10%, approximately 25 response-evaluable patients will provide close to 60% power to observe at least 5 responses, ie, 5/25 = 20%; exact 80% CI (10.1%, 34.0%).

Approximately 50 response-evaluable patients in total need to be enrolled.

Additional patients may be enrolled based on clinical judgment and the totality of clinical outcomes may be considered.

Part C: (Imaging Substudy): Up to 25 patients in total will be enrolled. Other Immuno-PET studies using ^{89}Zr that explored only biodistribution and tumor targeting collected meaningful data with 6 to 12 patients [3]. CCI [redacted]

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 Study Supplier List. The identified vendors for specific study-related activities will perform these activities in full or in partnership with the sponsor.

The study is being funded by Takeda. Payments for the conduct of the study that will be made to study sites (and, if applicable, investigators and/or other study staff) will be specified in the Clinical Study Site Agreement(s). All investigators and subinvestigators must declare potential conflicts of interests to the sponsor. The sponsor will provide a financial disclosure form that must be signed by each investigator and subinvestigator before the study starts at their study site; in addition, any potential conflicts of interests that are not covered by this financial disclosure form should be disclosed separately to the sponsor prior to the start of the study at their site.

All institutional affiliations of the investigator and subinvestigator should be declared on their curriculum vitae, which must be provided to the sponsor prior to the start of the study.

3.2 Coordinating Investigator

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

3.3 List of Abbreviations

Abbreviation	Term
^{18}F-FDG	18-fluorodeoxyglucose
5-FU	5-fluorouracil
5-HT3	5-hydroxytryptamine 3 serotonin receptor
^{89}Zr	zirconium-89
ADA	antidrug antibody
ADC	antibody-drug conjugate
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
CI	confidence interval
CL	clearance
C_{max}	single-dose maximum (peak) concentration
CNS	central nervous system
CR	complete response
CRC	colorectal cancer/carcinoma
CRO	contract research organization
CT	computed tomography
CCI	[redacted]
CYP	cytochrome P450 enzyme
DCR	disease control rate
DDI	drug-drug interaction
DILI	drug-induced liver injury
DIO	dosimetry and imaging optimization
DLT	dose-limiting toxicity
DOR	duration of response
EANM	European Association of Nuclear Medicine
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOI	end of infusion

Abbreviation	Term
EOT	end-of-treatment
FDA	Food and Drug Administration
FGN849	free payload for TAK-164
GCC	guanylyl cyclase C
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GI	gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
^{3}H	tritium
HEK	human embryonic kidney
HER2	human epidermal growth factor receptor 2
hERG	human ether-à-go-go-related gene
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICRP	International Commission on Radiological Protection
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IRB	Institutional Review Board
IV	intravenous; intravenously
ldCT	low-dose computed tomography
LFT	liver function test
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
mCRC	metastatic colorectal cancer/carcinoma
MRI	magnetic resonance imaging
MSI	microsatellite instability
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
MTV	metabolic tumor volume
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCS	Netherlands Commission on Radiation Dosimetry
ORR	overall response rate
OS	overall survival
PD	progression of disease
PERCIST	Positron Emission Tomography Response Criteria in Solid Tumors
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein

Abbreviation	Term
pH2A.X	phospho-histone H2A.X
PK	pharmacokinetic(s)
PR	partial response
p_T	toxicity probabilities
PTE	pretreatment event
Q2W	once every 2 weeks
Q3W	once every 3 weeks
QTcF	corrected QT by Fridericia method
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RID	recommended imaging dose
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SCID	severe combined immunodeficiency
SD	stable disease
s-FGN849	sulfonated FGN849
SUL	standardized uptake value corrected for lean body mass
SUSAR	suspected unexpected serious adverse reactions
SUV	standardized uptake value
$t_{½}$	terminal disposition half-life
TAb	total antibody
TEAE	treatment-emergent adverse event
TLG	total lesion glycolysis
t_{max}	single-dose first time of occurrence of maximum (peak) concentration
TBL	total bilirubin
ULN	upper limit of normal
UPM	unit probability mass
US	United States
Vd	volume of distribution
VOI	volume of interest
WBC	white blood cell

3.4 Corporate Identification

Millennium	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd
TDC Americas	Takeda Development Center Americas, Inc
TDC	TDC Japan, TDC Asia, TDC Europe, and/or TDC Americas, as applicable
Takeda	Millennium Pharmaceuticals, Inc, TDC Japan, TDC Asia, TDC Europe, and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

4.2 Scientific Background

Antibody-directed cancer chemotherapy in the form of antibody-drug conjugates (ADCs) can improve therapeutic indices, with the potential to enhance efficacy and decrease systemic toxicity. After the ADC is internalized by the target tumor cell and shuttled to the lysosomal compartment, enzymatic cleavage of the chemical linker releases the cytotoxic drug [4]. In an effort to further exploit ADC technology to improve treatment of gastrointestinal (GI) malignancies, Takeda Pharmaceuticals Inc (Takeda) has developed TAK-164, a new ADC which targets guanylyl cyclase C (GCC) and consists of a human monoclonal antibody (mAb) specifically targeting GCC, a potent cytotoxic agent, and a linker. Prior and ongoing clinical studies evaluating an ADC-based therapy with another cytotoxic agent, monomethylauristatin E have shown promising results [5]. The mechanism of action of TAK-164 should result in potent target-dependent eradication of GCC-expressing tumor cells.

4.2.1 Disease Under Treatment

TAK-164 is being developed to be a standard of care in the metastatic and adjuvant setting for patients with GI cancers that express GCC.

The expression of GCC is maintained throughout the spectrum of adenoma and carcinoma in the colorectum [6,7]. Also, GCC expression has been observed in lymph nodes harboring metastatic cells and is being studied as a potential marker for more accurate staging of this disease [8]. In addition to colorectal carcinoma (CRC), other GI malignancies have been found expressing GCC, such as gastric, esophageal, small intestine, and pancreatic carcinomas.

4.2.1.1 CRC

CRC is the fourth most common visceral malignancy (after prostate, breast, and lung cancer) and the second leading cause of cancer death in the United States (US). In 2017, there will be an estimated 95,520 new cases of colon cancer and 39,910 cases of rectal cancer diagnosed in the US. While the numbers for colon cancer are fairly equal in men (47,700) and women (47,820), a larger number of men (23,720) than women (16,190) will be diagnosed with rectal cancer. An estimated 27,150 men and 23,110 women will die from CRC in 2017 (Globocan.iarc.fr/Pages/fact_sheets_. Colorectal Cancer: Estimated Incidence, Mortality and Prevalence Worldwide in 2012. Accessed 07 August 2017). The estimated incidence of CRC worldwide in 2012 for both sexes is 1,361,000, 746,000 men and 614,000 women, with 374,000 and 320,000 deaths, respectively. The estimated prevalence of people with CRC worldwide is 3,544,000 (1,953,000 men 1,590,000 women). CRC incidence has been increasing in the US among adults younger than 55 years [9,10]. The prognosis of CRC is primarily related to stage, histologic and molecular differentiation, lymphovascular invasion, and extent of tumor-free surgical resection margins [11].

Several therapeutic agents have been introduced that have been effective in the treatment of CRC as demonstrated by improved response and 5-year survival. Introduced for clinical use over 40 years ago, 5-fluorouracil (5-FU) remains the cornerstone for management of metastatic disease, achieving a response rate of about 20% when given in standard doses [12]. Administration of 5-FU as a continuous infusion for protracted periods has been shown to improve the therapeutic index in patients with advanced colon cancer with respect to response rate and reduced toxicity [13]. Among various pharmacologic strategies undertaken to enhance the activity of 5-FU, a combination with leucovorin has been proven most effective. Since 1996, 3 new cytotoxic drugs (capecitabine, irinotecan, and oxaliplatin) and 3 new mAbs (bevacizumab, cetuximab, and panitumumab) have been introduced for the treatment of CRC [14]. Various chemotherapeutic agents such as oxaliplatin and irinotecan, when given in combination with 5-FU (ie, FOLFOX and FOLFIRI regimen), seem to be equivalent in efficacy when administrated as first-line therapy [15]. Targeted therapies, primarily inhibitors of vascular endothelial growth factor and epidermal growth factor receptors, have shown promise for improving treatment outcome in patients with advanced disease [16]. Similarly, treatment with the checkpoint inhibitor pembrolizumab has shown remarkable responses in patients with deficient mismatch repair gene expression, as evidenced by high microsatellite instability (MSI) [17]. Although the introduction of newer drugs has extended survival for patients with metastatic CRC (mCRC) by a range of 12 to approximately 27 months [18], the disease remains incurable and a need for new and better therapeutic agents persists.

4.2.1.2 Gastric Carcinoma

Gastric carcinoma is the fourth most common cancer worldwide, with an estimated prevalence of 153,8000 cases in 2012 and incidence of 952,000 (Globocan.iarc.fr/Pages/fact_sheets_ Gastric Cancer: Estimated Incidence, Mortality and Prevalence Worldwide in 2012; accessed 7 August 2017). Gastric carcinoma is the second leading cause of cancer-related death worldwide [19]. The incidence is highest in Japan, China, South America, and Eastern Europe. In the US, an estimated 21,000 new cases (12,730 men and 8270 women), and about 12,000 deaths (7000 men and 5000 women) were expected in 2012 (Globocan.iarc.fr/Pages/fact_sheets_ Gastric Cancer: Estimated Incidence, Mortality and Prevalence Worldwide in 2012; accessed 7 August 2017). Gastric cancer affects mostly older people (the average age at the time of diagnosis is 71) and the risk is approximately 2 times higher in men than in women. Environmental risk factors include smoking, high salt intake, and consumption of poorly preserved food, while precursor conditions (largely linked to distal gastric carcinoma) include chronic atrophic gastritis, gastric polyps, and *Helicobacter pylori* infection. Pathologic stage remains the most important determinant of prognosis in gastric carcinoma.

Several chemotherapeutic drugs, when used as single agents, have been associated with an objective response in over 15% of patients (5-FU producing 20%). Combination therapy in advanced gastric carcinoma may produce response rates in the range of 50% with a median survival barely exceeding 11 months. Recent studies are addressing the role of biologics such as trastuzumab and bevacizumab in advanced gastric carcinoma. Herceptin® (trastuzumab), the anti-human epidermal growth factor receptor 2 (HER2) mAb, provides the first targeted

biological therapy to show a survival benefit in HER2+ patients with advanced gastric cancer [20]. Approximately 15% to 18% of gastric tumors show high levels of HER2 [21,22].

Despite recent advancements in the treatment of gastric carcinoma and the addition of ramucirumab [22] to therapeutic modalities which can be offered to patients with gastric carcinoma, more effective therapies are required to provide better options for this unmet clinical need.

4.2.1.3 Esophageal Carcinoma

Esophageal carcinoma is relatively uncommon, with 456,000 new cases worldwide and 40,000 deaths. In the US, 16,940 new cases (13,360 in men and 3580 in women) and approximately 15,690 deaths (12,720 men and 2970 women) were expected by the American Cancer Society in 2016 (cancer.net/cancer-types/esophageal-cancer/statistics, accessed 17 October 2017). Treatment options for patients with both locoregional and advanced disease are limited. Several drugs, when used as single agents, have been associated with a reduction of more than 50% of measurable tumor mass in over 15% of patients. Such agents include 5-FU, cisplatin, doxorubicin, paclitaxel, docetaxel, and irinotecan [23-27].

4.2.1.4 Small Intestine Cancer

Malignant neoplasms of the small intestine are among the rarest types of cancer, accounting for approximately 2% of all GI cancers. In the US, there were 10,190 new cases and approximately 1390 deaths expected in 2017 (Cancer.org/cancer/small-intestine-cancer/about/what-is-key-statistics.html. Accessed 7 August 2017). The most common type of small intestine cancer is adenocarcinoma. Other types of small intestine cancer include sarcoma, carcinoid tumor, GI stromal tumor, and lymphoma [28-31]. As in other GI malignancies, the predominant modality of treatment is surgery when resection is possible, and cure relates to the ability to resect the cancer completely. Malignant lesions are often discovered when they have metastasized to distant sites. The overall 5-year survival rate for resectable adenocarcinoma is only 20%. The 5-year survival rate for resectable leiomyosarcoma, the most common primary sarcoma of the small intestine, is approximately 50%. For unresectable metastatic disease, treatment options consist of palliative treatments.

4.2.1.5 Pancreatic Cancer

Pancreatic cancer accounts for about 3% of all cancers in the US and about 7% of all cancer deaths. Carcinoma of the pancreas is the fourth leading cause of cancer death in the US. In the US, there are 53,670 new cases (27,970 men and 25,700 women) and approximately 43,090 (22,300 men and 20,790 women) deaths expected in 2017 (Cancer.org/cancer/pancreatic-cancer/about/key-statistics.html; accessed 7 August 2017). Cancer of the exocrine pancreas is rarely curable and has an overall survival (OS) rate of less than 4% [32]. The highest cure rate occurs if the tumor is truly localized to the pancreas; however, this stage of the disease accounts for fewer than 20% of cases. For patients with localized disease and small cancers (<2 cm) with no lymph node metastases and no extension beyond the capsule of the pancreas, complete surgical resection can yield actuarial 5-year survival rates of 18% to 24% [33]. For patients with

advanced cancers, the OS rate of all stages is less than 1% at 5 years, with most patients dying within 1 year [34]. In patients with advanced pancreatic cancer gemcitabine has demonstrated activity and is a useful palliative agent [35-37]. As a first-line therapy for patients with metastatic adenocarcinoma of the pancreas, gemcitabine shows a significant improvement in survival compared to 5-FU (1-year survival observed in 18% patients treated with gemcitabine versus 2% with 5-FU) [35]. Erlotinib has been shown to prolong survival modestly when combined with gemcitabine [38]. Many phase 2 studies have evaluated a combination regimen with either a platinum analogue (cisplatin or oxaliplatin) or fluoropyrimidine versus single-agent gemcitabine, but not one of these studies has demonstrated a statistically significant advantage of combination chemotherapy [39,40]. However, Nab-paclitaxel in combination with gemcitabine produces a significant improvement in OS, when compared to the treatment with gemcitabine alone [41]. Similarly, treatment with FOLFIRINOX provides a superior clinical benefit, when compared to gemcitabine (median OS 11.1 months vs 6.8 months) [42]. Therefore, FOLFIRINOX is now considered a standard treatment option for patients with advanced pancreatic cancer.

Symptoms caused by pancreatic cancer may depend on the site of the tumor within the pancreas and the degree of involvement. Palliative surgical or radiologic biliary decompression, relief of gastric outlet obstruction, and pain control may improve the quality of life while not affecting OS [43,44].

4.2.2 Study Drug

TAK-164, a novel ADC consists of a mAb that specifically targets GCC, linked to a cytotoxic DNA-damaging agent by a peptide linker. TAK-164 is designed to internalize into tumor cells and to release the cytotoxic agent, which binds to DNA, resulting in DNA damage due to alkylation, ultimately leading to apoptosis-driven cell death.

GCC is expressed throughout the GI tract and plays an important role in maintaining fluid ion homeostasis and genomic integrity in intestinal cells. GCC binds to the endogenous ligands, guanylin and uroguanylin, as well as to the heat-stable enterotoxin [45,46]. In normal epithelial cells, GCC is localized on the apical side of intestinal epithelium. This anatomically distinct location is accessible from the luminal side but not from the vascular compartment due to the presence of the epithelial tight junctions [47]. The anatomically distinct apical localization is altered in malignant intestinal cells in which normal tissue architecture and tight junctions are disrupted. Therefore, a systemic intravenous (IV) administration of TAK-164 targeting GCC should affect both primary and metastatic GI carcinoma without affecting normal epithelia (where GCC would not be accessible to the drug). By accessing malignant cells but not normal GI cells due to GCC localization and tight junctions, TAK-164 is expected to have improved treatment efficacy while minimizing toxicity of the treatment.

In a broad range of GI cancer cells expressing GCC, TAK-164 has demonstrated antitumor activity at picomolar range. Based on preclinical studies, TAK-164 is expected to have a manageable safety profile (as described in Section 4.6) when administered IV to patients. Preclinical studies have been completed to refine the flexibility of the dose and schedule of TAK-164 that could be adopted in the clinical setting to support administration of single-agent

TAK-164 as part of this study, as well as a subsequent combination study. Several pharmacodynamic biomarkers have been found to be modulated in response to single-agent TAK-164, as shown by nonclinical studies. These include [redacted]. Robust and long-lasting increases in both of these markers are observed in human tumor xenografts. The increases are sustained for longer than 24 hours in response to various doses of TAK-164. Studies which evaluated a range of response across a spectrum of tumor xenografts as well as baseline variability of GCC expression in human tumors have suggested that a majority of tumor models that responded to TAK-164 treatment generally had a GCC H-score of [redacted].

4.3 Preclinical Experience

Detailed information regarding the nonclinical pharmacology and toxicology of TAK-164 may be found in the Investigator's Brochure (IB).

4.3.1 Pharmacology

TAK-164 binds to GCC-expressing cells where the ADC is internalized and processed by lysosomal enzymes such as cathepsin B or other proteolytic enzymes releasing active catabolites that alkylate cellular DNA. Alkylation of the DNA results in DNA damage that can be measured by the pharmacodynamic marker [redacted] TAK-164 shows significant anti-proliferative selectivity between human embryonic kidney (HEK)-293 GCC Clone 2 and HEK-293 Vector cell lines. Likewise, TAK-164 also demonstrates selective potency relative to the nonbinding control ADC, [redacted].

Significant dose-dependent antitumor activity was demonstrated following a single IV administration of TAK-164 (payload concentration) in HEK-293 GCC Clone 2 human kidney tumor xenografts at [redacted] PHTX-09C primary human colon tumor xenografts at [redacted] PHTX-11C human primary colon tumor xenografts at [redacted] and PHTX-17C primary human colon xenograft model at [redacted] in female severe combined immunodeficiency (SCID) or nude mice.

The pharmacokinetic (PK) and pharmacodynamic properties of TAK-164 were investigated following a single IV administration in HEK-293 GCC 2 tumor-bearing female CB17 SCID mice. Pharmacodynamic analysis was measured via an immunohistochemistry (IHC) assay used to measure [redacted] xpression in tumor samples, indicating the presence or absence of double-stranded DNA breaks before and after TAK-164 treatment. For both total antibody (TAb) and conjugated antibody, the mean plasma concentration at 1 hour and mean plasma area under the concentration-time from time 0 to the last value in female CB17 SCID mice increased in a dose-proportional manner at [redacted] After a single IV administration of TAK-164, a dose-dependent relationship between TAK-164 treatment and an increase in DNA damage was measured by [redacted] IHC.

4.3.2 Safety Pharmacology

The 50% inhibitory concentration for the in vitro inhibitory effect of FGN849, the primary catabolite of TAK-164, on ionic currents in voltage-clamped HEK-293 cells that stably express the human ether-à-go-go-related gene (hERG) was estimated to be greater than 1 μM, the solubility limit. Consistent with in vitro monkey plasma stability results, plasma levels of FGN849 and sulfonated FGN849 (s-FGN849) were below the limit of quantification in monkeys in the 4-week Good Laboratory Practice (GLP)-compliant repeat-dose toxicity study at 1.6 μg/kg, 4.4 μg/kg, and 8.8 μg/kg once every 2 weeks (Q2W). Human and monkey in vitro plasma stability was similar and therefore the risk for circulating FGN849 and hERG inhibition in patients is low. Additionally, there were no TAK-164-related findings observed in cardiovascular, respiratory, or central nervous system (CNS) safety pharmacology parameters in the 4-week GLP-compliant repeat-dose toxicity study in cynomolgus monkeys at any dose.

4.3.3 PK

The nonclinical drug metabolism and PK studies performed support the IV administration of TAK-164 to achieve pharmacologic effect in humans. The PK properties and catabolism of TAK-164 have been studied in a series of comprehensive experiments in vitro and in vivo using tumor-bearing female SCID or nude mice, Sprague-Dawley rats, cynomolgus monkeys, and humans (in vitro only) with both unlabeled and tritium (^{3}H)-labeled ADC.

Catabolite/metabolite profiling data revealed that the hydrolysis product s-FGN849 and its disulfonyl derivative, FGN849, are the major circulating components in tumor-bearing mice after IV administration of [^{3}H]TAK-164 at 5 mg/kg. In tumor homogenates, s-FGN849 is a minor component and FGN849 is the major component. In vitro incubation of [^{3}H]TAK-164 with rat tritosomes and human cathepsin B revealed the formation of s-FGN849 and FGN849 as catabolites.

O-dealkylation and *O*-dealkylation and oxidation are 2 major metabolic pathways of FGN849 in rat, monkey, and human liver microsomes and recombinant cytochrome P450 enzyme (CYP) 3A4. Metabolites of FGN849 observed in human liver microsomes were also found in rat and monkey liver microsomes. FGN849 and s-FGN849 showed low apparent permeability in Caco-2 cells and appear to be P-glycoprotein (P-gp) and/or breast cancer resistance protein (BCRP) efflux pump substrates. There is a potential for drug-drug interaction (DDI) of the free payload, FGN849, with BCRP, P-gp, and CYP3A4 inhibitors and inducers.

In mice, rats, and monkeys, TAK-164 (both total and conjugated antibodies) had low clearance (CL) (<2.5 mL/h/kg) and low volume of distribution (Vd) (<100 mL/kg). Terminal disposition half-lives ($t_{1/2}$) ranged from 2 to 5 days. The exposure increased in a dose-proportional manner in the tested tolerable dose range in mice, rats, and monkeys. No marked sex-related differences were observed in TAK-164 PK in monkeys. The TAb PK of TAK-164 in mice, rats, and monkeys displayed similar PK profiles to the conjugated antibody at the earlier time points, indicating that direct release of payload from the antibody in the plasma was minimal. Trace amounts of the free payload, FGN849 (also known as IGN-P1-aniline), were detected in only 1 out of 238 samples at 6 hours post the dose of 4.4 μg/kg of TAK-164, and no s-FGN849 (also

known as s-IGN-P1-aniline) was detected in plasma samples in the GLP-compliant monkey toxicokineticstudy.

4.3.4 Toxicology

The toxicology studies with TAK-164 and FGN849, the primary catabolite of TAK-164, addressed the target tissues for toxicity, dose-limiting toxicity (DLT), noninvasive methods for monitoring of clinically relevant toxicities, and the reversibility of adverse effects. DLTs with TAK-164 were similar in rats (in which TAK-164 is not cross-reactive for GCC) and monkeys, and were consistent with the toxicity profile of FGN849 in rats at equivalent toxin doses indicating that the toxicity profile of TAK-164 in nontumor-bearing nonclinical species is driven by the payload. Findings in the repeat-dose monkey study on which the safe starting dose is based were similar in nature but observed with increased incidence and severity compared to the findings at the same dose level in the single-dose study. DLT with TAK-164 was associated with test article-related findings in the hematopoietic and lymphoid systems, skin at procedure-related sites (IV administration, blood collection, and/or restraint), and GI tract, with additional toxicity observed in the female reproductive system and acinar glandular tissues in monkeys. All target organ toxicities observed in the repeat-dose studies were generally monitorable and trending toward or completely reversible, or expected to be reversible following a 28-day recovery period.

4.4 Clinical Experience

This is the first-in-human study of TAK-164.

Potential safety concerns and/or biological activity could be extrapolated from toxicology findings (see Section 4.6) and data available for other ADCs; however, such extrapolation must be done with caution. It is important to note that antibody target specificity or selectivity and ADC linker activity may result in significantly different safety profiles between ADCs.

During the dose escalation phase of the study, serious and TAK-164-related hepatic toxicity was reported at dose of 0.25 mg/kg once every 3 weeks (Q3W); this led to a dose cap at 0.19 mg/kg Q3W.

4.5 Rationale for the Proposed Study

TAK-164, a novel ADC consists of a human mAb that specifically targets GCC, linked to a cytotoxic DNA-damaging agent by a peptide linker. TAK-164 is designed to internalize into tumor cells and to release the cytotoxic agent which binds to DNA, resulting in DNA damage due to alkylation, and ultimately leading to apoptosis-driven cell death.

GCC is expressed in a variety of GI tumors. Also, GCC is expressed throughout the GI tract where it is localized on the apical side of intestinal epithelium and plays an important role in maintaining fluid ion homeostasis. This anatomically distinct localization is accessible from the luminal side but not from the vascular compartment due to the presence of the epithelial tight junctions [43,44,46,48]. In malignant intestinal cells, the normal tissue architecture and tight junctions are disrupted. Therefore, a systemic IV administration of TAK-164 targeting GCC may reach this target in both primary and metastatic GI carcinoma without affecting normal epithelia

(where GCC would not be accessible to the drug). By accessing malignant cells but not normal GI cells due to GCC localization and tight junctions, TAK-164 is expected to have improved treatment efficacy while minimizing toxicity of the treatment.

In a broad range of GI cancer cells expressing GCC, TAK-164 has demonstrated antitumor activity in the picomolar range. Preclinical studies have been conducted to refine the flexibility of the dose and schedule of TAK-164 that could be adopted in the clinical setting to support administration of single-agent TAK-164 as part of this study, as well as a subsequent combination study. Several pharmacodynamic biomarkers have been found to be modulated in response to single-agent TAK-164, as shown by nonclinical studies. Those include CCI CCI. Studies which evaluated a range of responses across a spectrum of tumor xenografts have suggested that a majority of tumor models responsive to TAK-164 treatment generally had a GCC H-score of CC I. In human tumors, a variety of GCC expression levels have been detected with a broad range of H-scores up to CCI

The PK of TAK-164 in humans was predicted using an allometric scaling approach from TAK-164 PK in cynomolgus monkeys, an approach that has demonstrated success in predicting human PK for the TAK-264 program (previous name "MLN0264") that used the same GCC-targeted antibody, CCI. The predicted human CL, Vd, and plasma $t_{1/2}$ of TAK-164 using this method is approximately 1.02 mL/h/kg, 51.96 mL/kg, and 35 hours, respectively. No accumulation in plasma is expected with either a Q2W or a Q3W dosing schedule.

Translational dynamic PK-efficacy modeling (using data from GCC-expressing tumor xenograft models) and semi-mechanistic toxicity modeling (using neutrophil count data from cynomolgus monkeys) suggested that Q2W administration of TAK-164 would provide pharmacologically active exposures (with a projected dose range of 0.1 mg/kg to 0.25 mg/kg) with a clinically manageable safety profile (absolute neutrophil count [ANC] above Grade 3 neutropenia cutoff at nadir), making it a favorable schedule to evaluate in this study. However, emerging clinical safety data supports limiting the maximum dose to 0.19 mg/kg Q3W.

Based on overall nonclinical investigation, TAK-164 is expected to have a manageable safety profile when administered IV to patients. Significant findings emerging from preclinical studies are considered monitorable, reversible, and/or manageable in patients with GI malignancies.

Inclusively, these findings provide a rationale for clinical development of TAK-164.

Molecular imaging using immuno-PET (positron emission tomography) can be performed as a noninvasive assessment of radioisotope-labeled ADCs. Unlike conventional PK, immuno-PET gives detailed information on biodistribution and tumor uptake and may provide additional insights on relative dosing of a drug. A variety of antibodies and ADCs have been investigated in a wide range of different cancers including GI tumors such as colon cancer. Clinical applications of immuno-PET include improved staging before therapy [49,50].

Zirconium-89 (^{89}Zr) lends itself to visualizing the localization of ADCs as it resides largely in the target tissue following cellular internalization and has a $t_{1/2}$ (78 hours) that is suitable for centralized production and distribution [3]. On the basis of previous studies, we anticipate that the optimal time for a PET assessment of 37 MBq (1 mCi) of the ^{89}Zr-labeled antibody is likely

to be 2 to 7 days after injection. The Vrije Universiteit Medical Centre in Amsterdam has previously investigated ^{89}Zr-labeled antibodies and ADCs [51].

^{89}Zr-labeled TAK-164 can be used to evaluate GCC expression at a whole-body level and provides information about antibody biodistribution and tumor heterogeneity. Given variable GCC expression in patients with CRC and gastric cancer, we also anticipate a range of ^{89}Zr-TAK-164 tumor uptake in the patients enrolled in this study. Evaluating the relationship between ^{89}Zr-TAK-164 tumor uptake and 18-fluorodeoxyglucose (^{18}F-FDG)-PET uptake will be informative in determining the impact of GCC expression levels on response in these patient populations.

4.6 Potential Risks and Benefits

Based on nonclinical safety analyses of TAK-164 and published clinical data that derive from the investigation of similar ADCs and mAb therapies in general, potential risks of TAK-164 treatment include:

- Hepatotoxicity.
  - Increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin.
- Hematopoietic and lymphoid toxicity.
  - Decreased cellularity in bone marrow and lymphoid tissues with resultant decreases in red blood cell (RBC) mass, decreases in white blood cells (WBCs), and platelets with increased coagulation times.
- Potential predisposition to anemia, infection, sepsis, and/or spontaneous hemorrhage.
- Local skin toxicity, procedure-related sites.
  - Dermal/subcutaneous necrosis with ulceration present at IV administration and blood collection sites observed in monkeys, presumably due to accidental extravasation of TAK-164.
- Skin hyperpigmentation, focal to generalized.
  - Dark/black discoloration of the face, limbs and/or whole body with/without mild erosion or ulceration due to epidermal degeneration and increased melanin.
- GI toxicity.
  - Decreased appetite and mild body weight loss.
  - Atrophy of the GI mucosa (stomach through rectum) with loose stool.
- Reproductive toxicity.
  - Potential for infertility.

- Decreased acinar gland granulation.
  - Affected the pancreas (females only), salivary, and lacrimal glands of monkeys.
  - Possible association with mild bilateral conjunctivitis (though may also have been a result of skin effects in the conjunctiva).
- DDI with CYP3A4, P-gp, and BCRP modulators.
- Infusion-related reactions including anaphylaxis.

While toxicities potentially induced by TAK-164 could be severe, they will be managed by clinical monitoring and intervention to minimize potential risks. Nevertheless, the potential toxicities could become life-threatening. The potential risks of TAK-164 are based on findings from single- and repeat-dose nonclinical toxicology studies in monkeys and rats (in which TAK-164 is not cross-reactive for GCC). Adverse events (AEs) associated with TAK-164 may include any toxicity, comprised of those that were not observed in or predicted from the studies completed in monkeys and rats.

As with other mAb therapies, potential risk for immunogenicity cannot be excluded. Based on our TAK-264 (previous name "MLN0264") experience, where the same antibody was utilized (very low immunogenicity positivity), general screening/titer/confirmation/domain specificity immunogenicity assays will be performed but not the further antidrug antibody (ADA) characterization assay such as neutralization assay. The overall immunogenicity will be monitored closely in the study and the timing of implementing neutralization assay will be assessed at later phase for this product.

Patients will be monitored closely for anticipated DLTs (defined in Section 8.2) and more generalized observations as they are receiving this agent.

In order to limit the risks to patients, up to 3 patients will be enrolled at each new dose (although larger cohorts will be permissible if eligible patients are available, following discussions between the sponsor and the investigators), and observed through completion of the first cycle before additional patients are treated. In the dose escalation phase, there will be an interval of at least 7 days between dosing of the first 2 patients within a cohort; the interval between subsequent patients in the same cohort may be less than 7 days, but at least 1 day later. Additionally, a full DLT review period will be observed for Cycle 1 during dose escalation, before dosing a new (higher dose) cohort. Although therapeutic efficacy is a desired outcome of treatment with TAK-164, it is unknown whether patients will benefit from this study.

It is also noted that some patients may receive suboptimal doses of this drug, if it proves to be efficacious. In this dose escalation study, dose will be escalated by cohort. Intrapatient dose escalation is not planned. Although dose escalation will be based on observed DLTs in Cycle 1, safety/tolerability data beyond Cycle 1 will be integrated into the recommended phase 2 dose (RP2D) determination for the expansion phase.

Risk mitigation strategies for potential AEs include, but are not limited to strict application of the study inclusion and exclusion criteria, frequent monitoring of clinical and laboratory results,

guidelines for management and prophylaxis of potential toxicities, criteria for dose modification, and regular monitoring of AEs and serious adverse events (SAEs) by the sponsor.

TAK-164-related effects were observed after repeat doses in the ovaries, uterus, cervix, and vagina of sexually immature female monkeys. Effects were also observed in the prostate of sexually mature male rats (in which TAK-164 is not cross-reactive for GCC) at nontolerated dose levels. The effect of TAK-164 was not evaluated in sexually mature monkeys and because TAK-164 is a novel ADC cytotoxic agent with no prior human experience, patients considering having children in the future should consider autologous gamete cryopreservation prior to therapy with TAK-164.

^{89}Zr immuno-PET conjugates have been shown to be safe in more than 15 clinical studies if carefully characterized, demonstrated to be stable, and produced under Good Manufacturing Practice (GMP) conditions [3]. When considering the justification of application, a benefit-risk analysis must be performed. The Netherlands Commission on Radiation Dosimetry (NCS) provides a model for this (2016) based on Report 118 of The International Commission on Radiological Protection. The risk level according to this model is stated as Category II. The dose caused by a single administration of approximately 37 MBq ^{89}Zr-TAK-164 is estimated to be around 20 mSv on the basis of available dosimetry data on ^{89}Zr-labeled intact antibodies. Dosimetry will be performed to confirm exposure. After the injection, the patient can go home immediately without shielding. For 6 months after the study, male and female patients both are advised to prevent pregnancy. The risks associated with ^{89}Zr-TAK-164 seem minor, and although patients do not directly benefit from the PET imaging, these results will be valuable for understanding tumor uptake and biodistribution in relation to response and toxicity and will guide further prospective research. The modifications to TAK-164 with the radiolabeling process are considered minimal, so the toxicity profile is anticipated to be similar to that of unlabeled TAK-164 (internal in vitro data).

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

The benefits of this drug have not been established, because the efficacy of TAK-164 has not yet been characterized.

4.6.1 Radiation Burden for Patients in the Imaging Substudy (Part C, To Be Conducted in The Netherlands Only)

A single injection of approximately 37 to 40 MBq ^{89}Zr-TAK-164 is expected to result in a radiation burden of ~20 mSv [52,53]. For an ^{18}F-FDG injection compliant with the European Association of Nuclear Medicine (EANM) procedure guidelines [54] a typical dose of 200 MBq will result in a radiation burden of 4 mSv. In addition, every low-dose computed tomography (ldCT) scan adds 3 mSv to the radiation burden.

The first 6 patients will receive 2 injections of ^{89}Zr-TAK-164 followed by 5 PET scans (3 after the first and 2 after the second injection) resulting in a radiation dose of 55 mSv. Subsequent patients will receive 1 injection of ^{89}Zr-TAK-164 followed by 2 PET scans, resulting in a radiation dose of 26 mSv. After ^{89}Zr-TAK-164 administration, no shielding is required, and the

patient can go home immediately. It is recommended that prolonged physical contact with small children (hugging, holding for more than a few hours per day) is avoided in the days following injection of ^{89}Zr-TAK-164.

In addition, all patients will receive up to 3 injections of ^{18}F-FDG, each followed by a single ldCT scan, resulting in up to 21 mSv. In total, the radiation dose for the first 6 patients is expected to be approximately 76 mSv. For subsequent patients, the radiation dose is expected to be approximately 47 mSv.

The radiation dose is determined by dosimetry and optimized in approximately the first 6 patients (the dosimetry and imaging optimization [DIO] subgroup). In these patients, the optimal imaging parameter, including the optimal dose of ADC (≤RP2D) for imaging will be determined. Subsequent patients will be imaged at this optimal dose. 37 MBq of ^{89}Zr is the minimum level of activity that can be used per injection to support adequate quantitation. [52] There are no risk increasing/decreasing factors.

Justification of this study is provided through the intended benefit of mitigating serious diseases in the future (category 3b). In conclusion, the radiation burden for this study has been optimized, is justified, and falls within the dose limits as discussed in NCS-26/ICRP-62.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective is:

- To evaluate the safety of TAK-164 and to determine the maximum tolerated dose (MTD) and/or RP2D.

5.1.2 Secondary Objectives

Part A and part B secondary objectives are:

- To characterize the PK of TAK-164.
- To evaluate immunogenicity of TAK-164.
- To evaluate efficacy of TAK-164 as measured by overall response rate (ORR).
- To evaluate other efficacy measures such as disease control rate (DCR), which includes response (complete response [CR]+partial response [PR]) plus stable disease (SD), duration of response (DOR), and progression-free survival (PFS).

Part C (imaging substudy) secondary objectives are:

- To determine the biodistribution of ^{89}Zr-TAK-164 in patients with mCRC and/or metastatic gastric carcinomas.
- To determine the tumor targeting of ^{89}Zr-TAK-164.
- To determine dosimetry of ^{89}Zr-TAK-164.

5.1.3 Exploratory Objectives

CCI

[redacted]

CCI

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoints are:

- Number of patients with a DLT.
- Percentage of patients with AEs.
- Percentage of patients with Grade 3 or above AEs.
- Percentage of patients with drug-related AEs.
- Percentage of patients with drug-related Grade 3 or above AEs.
- Percentage of patients with SAEs.
- Percentage of patients with AEs leading to discontinuation.
- Percentage of participants who meet the markedly abnormal criteria for safety laboratory tests at least once postdose.
- Percentage of participants who meet the markedly abnormal criteria for vital sign measurements at least once postdose.
- MTD and/or an alternate RP2D of TAK-164.

5.2.2 Secondary Endpoints

- TAK-164 PK parameters: single-dose maximum (peak) concentration (C_{max}), single-dose first time of occurrence of maximum (peak) concentration (t_{max}), and area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}) during Cycle 1 Day 1 and Cycle 2 Day 1. In addition, observed concentration at the end of a dosing interval (C_{trough}) may be reported for other dosing days during which a single predose PK sample is collected.

- ORR as assessed by the investigator per modified RECIST version 1.1 [1].
- DCR.
- DOR.
- PFS.
- ADA in serum.

Additional imaging-specific secondary endpoints (part C only):

- Qualitative and quantitative (SUV) determination of patient-level biodistribution of ^{89}Zr-TAK-164 at all ^{89}Zr imaging time points.
- Qualitative and quantitative (SUV) determination of ^{89}Zr-TAK-164 uptake in tumor lesions identified with computed tomography (CT)/^{18}F-FDG-PET at all ^{89}Zr imaging time points.

5.2.3 Exploratory Endpoints

CCI

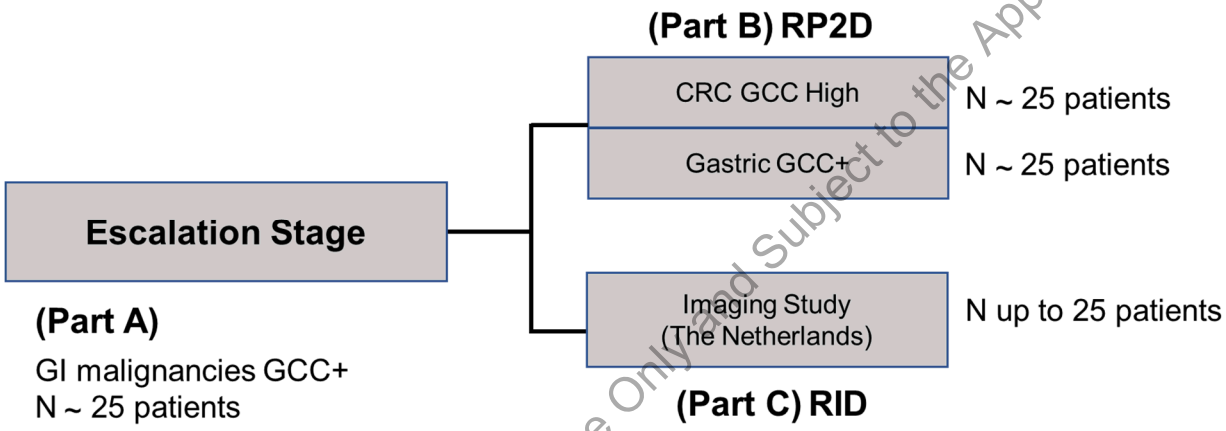
[redacted]

6.0 STUDY DESIGN

6.1 Overview of Study Design

This is a multicenter, nonrandomized, open-label, phase 1 study of TAK-164 in patients with advanced GI cancers expressing GCC for whom standard treatment is no longer effective or for whom there is no available standard therapy. The overall study design is presented in Figure 6.a. Part C is presented in greater detail in Figure 6.b.

Figure 6.a Study Design for TAK-164-1001 Phase 1 First-in-Human



CRC: colorectal carcinoma; GCC: guanylyl cyclase C; GI: gastrointestinal; RID: recommended imaging dose; RP2D: recommended phase 2 dose.

This study will be the first to administer TAK-164 to humans. For the dose escalation portion of the study, the patient population will consist of adults, aged 18 years or older, with various GI malignancies for whom standard treatment is no longer effective or for whom there is no available standard therapy. In the expanded cohort, enrollment will be limited to patients with CRC and gastric carcinoma. This study is designed to determine safety, tolerability, and PK and to determine an MTD and/or RP2D of TAK-164 that may be safely administered to patients with advanced GI cancer. The study will also define a therapeutic window of TAK-164 based on pharmacodynamics within the range of therapeutically relevant exposures. It is anticipated that approximately 100 patients could be enrolled, including the escalation (part A), the expansion phase (part B), and up to 25 patients in the imaging substudy (part C).

Once enrolled in the study, patients will receive TAK-164 IV administration on Day 1 of each 21-day cycle or Q3W. Note that for patients who continue on study to Cycle 3 and beyond, a window of ±3 days will be permitted for all doses.

The proposed schedule is based upon preclinical pharmacology and toxicology predictions of exposure-response. Triplicate electrocardiogram (ECG) data will be collected during dose escalation to assess the TAK-164 concentration-QT relationship. In the expansion portion of the study (part B), one schedule based on escalation results will be used to administer TAK-164 at

RP2D as informed by the data derived in the course of the dose escalation, including clinical considerations based on safety, PK, pharmacodynamic, antitumor response, and other relevant data.

Dose Escalation (Part A)

The starting TAK-164 dose will be 0.004 mg/kg Q3W and the maximal dose will not exceed 0.19 mg/kg Q3W. To determine the MTD/RP2D and to guide the dose escalation portion of the study, a method based on a Bayesian model of modified toxicity probability interval (mTPI) will be used. DLTs occurring during the first cycle of treatment (Cycle 1) at a given dose level will be evaluated and will affect decisions to dose-escalate. Although dose escalation and MTD will be estimated based on observed DLTs in Cycle 1, safety/tolerability data beyond Cycle 1 will be integrated into the RP2D determination for the expansion phase.

Expansion Cohorts (Part B)

Once the RP2D is established, up to 50 patients with CRC GCC high expression level (H-score ≥150) and patients with gastric carcinoma expressing GCC (H-score ≥10) will be included. A minimum of approximately 20 patients will be enrolled in each cohort.

The evaluation of tumor burden status will be performed as described in Appendix A. by CT or magnetic resonance imaging (MRI) according to modified RECIST, version 1.1 [1] in all patients participating in this study at treatment intervals of 2 cycles. Pharmacodynamic evaluation will be performed CCI [redacted] on tumor biopsies required to be obtained from a minimum of approximately 5 evaluable patients of the study.

All patients participating in this study who are judged by the investigator to be receiving clinical benefit will be permitted to remain on therapy until progression of disease (PD), unacceptable toxicity, or they choose to withdraw from the study.

Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0, effective date 27 November 2017 [55]. DLTs are defined in Section 8.2.

AEs will be assessed, and laboratory values, vital signs, and ECGs will be obtained to evaluate the safety and tolerability of TAK-164.

Part A and Part B

Serial blood samples for determination of the plasma concentration of TAK-164 mAb (conjugated and unconjugated), conjugated TAK-164 and FGN849 (free payload) will be obtained at prespecified time points as described in the Schedules of Events (Appendix A).

Relationships between plasma exposures of TAK-164 and GCC expression CCI [redacted] activation from tumor biopsies and/or blood-based biopsy samples will be assessed to determine if exposure-response relationships are estimable for target inhibition in relevant tissues.

To evaluate the presence of ADA, validated assays will be used to analyze blood samples collected from patients prior to dosing, as described in the Schedules of Events (Appendix A). These assays are capable of detecting binding antibodies to TAK-164; the ADA status for each

patient (positivity [transient, persistent], titer, and specificity) may be reported. Based on our TAK-264 experience (previous name "MLN0264") and because this is a phase 1 study, neutralizing ADA is not assessed. The impact of ADA on PK, safety, and efficacy will be explored in future studies.

Tumor tissue will be analyzed both during the escalation and expansion phases to investigate candidate biomarkers associated with tumor sensitivity and resistance to TAK-164. A retrospective analysis of GCC protein expression levels in tumor tissue (archival tissue or pretreatment biopsy) using a semiquantitative IHC assay will be done to determine correlations between protein levels of GCC in the tumor with clinical outcome. This will allow a better understanding of to what extent GCC protein expression may impact clinical responses. Tumor tissue may also be evaluated for genetic alterations, such as GCC, CCI [redacted] to determine the clinical benefit of TAK-164 in genetically-defined subpopulations and to investigate potential determinants of sensitivity or resistance to treatment. A buccal epithelial cell sample will be obtained on Cycle 1 Day 1 to generate germline DNA, to be used as a control sample for these analyses. Tumor biopsies may also be collected posttreatment from consenting patients who achieve at least a PR and then subsequently relapse, if considered advisable by the treating physician. Optionally, tumor biopsies from consenting patients who do not achieve a response and experience progression may also be collected, if considered advisable by the treating physician, to investigate correlations of candidate biomarkers associated with acquired resistance to clinical response. In a subset of patients, fresh pretreatment and posttreatment biopsies should be obtained to determine changes in the target engagement marker CCI [redacted].

CCI [redacted]

All patients participating in this study who are judged by the investigator to be receiving clinical benefit will be permitted to remain on therapy until they experience PD, unacceptable toxicity, or they choose to withdraw from the study.

Imaging Substudy (Part C, To Be Conducted in The Netherlands Only)

Up to 25 patients will be enrolled in the study in The Netherlands to determine the in vivo biodistribution and tumor targeting of ^{89}Zr-TAK-164 in patients with GCC-expressing mCRC and/or metastatic gastric carcinoma. In addition, the relationship of ^{89}Zr-TAK-164 tumor targeting with ^{18}F-FDG-PET–determined response and RECIST version 1.1 response, and the relationship of ^{89}Zr uptake with GCC expression in tumor tissues/other biomarkers, will be characterized.

Based on emerging data from the dose escalation phase (part A) and in agreement between the site investigator and sponsor, part C will be triggered at a dose that is considered safe and has treatment potential (recommended imaging dose [RID]).

Approximately 6 patients (including 3 dosimetry patients) will be enrolled for purposes of DIO. This DIO subgroup will receive ^{89}Zr-TAK-164 (mass dose <50% of the RID) 14 days before the first regularly scheduled study dose at Cycle 1 Day 1 (see Figure 6.b) and a second ^{89}Zr-TAK-164 administration on Cycle 1 Day 1 in combination with unlabeled TAK-164 at a maximum mass dose of 100% of the RID. Imaging will be performed 1 hour after end of infusion (EOI) of the first ^{89}Zr-TAK-164 administration for dosimetry in the first 3 patients, and for all patients at 2 time points between Day 2 and Day 7 after EOI. Imaging time points and mass dose of TAK-164 can be adjusted in order to optimize imaging conditions. Up to 19 additional patients will be enrolled into part C to receive a single dose of ^{89}Zr-TAK-164 at Cycle 1 Day 1 in addition to unlabeled TAK-164 as determined for optimal imaging. Once the RP2D of TAK-164 is determined, part C patients who have received TAK-164 at an RID lower than the RP2D of TAK-164 may dose-escalate to the RP2D in the absence of PD or unacceptable treatment-related toxicity at the investigator's discretion and with sponsor's approval. If the full RID/RP2D is not administered at Cycle 1 Day 1, the differential will be provided after the second image acquisition. Part C patients will continue treatment with the RID/RP2D of TAK-164 at Cycle 2 Day 1 and beyond (see Figure 6.c).

^{89}Zr-TAK-164 PET

Initially, approximately 6 patients (including 3 dosimetry patients) will be enrolled for DIO. This DIO subgroup will receive ^{89}Zr-TAK-164 (mass dose <50% of the RID) 14 days before the first regularly scheduled study dose at Cycle 1 Day 1 and a second ^{89}Zr-TAK-164 administration on Cycle 1 Day 1 in combination with unlabeled TAK-164 at a maximum mass dose of 100% of the RID. Imaging will be performed 1 hour after EOI of the first ^{89}Zr-TAK-164 administration for dosimetry in the first 3 patients and for all patients at 2 time points between Day 2 and Day 7 after EOI. Imaging time points and mass dose of TAK-164 can be adjusted to optimize imaging conditions. Qualitative and quantitative ($SUV_{mean,max}$) will be determined for all ^{89}Zr imaging time points (for further details, see Appendix A).

The ^{89}Zr-TAK-164 administration on Cycle 1 Day 1 will be in combination with variable amounts of unlabeled TAK-164 in the DIO subgroup, never exceeding the RID. This way, imaging conditions can be optimized by adding a variable mass dose of unlabeled TAK-164 to ^{89}Zr-TAK-164 administration to explore the presence of a potential sink, and by changing

imaging time points up to 7 days after EOI if required. When unlabeled TAK-164 is administered with ^{89}Zr-TAK-164 for imaging purposes, ^{89}Zr-TAK-164 will be administered within 2 hours after the EOI of unlabeled TAK-164.

Radiolabeled ^{89}Zr-TAK-164 will be administered IV. Unlabeled TAK-164 will be administered according to the Schedule of Assessments (Appendix A).

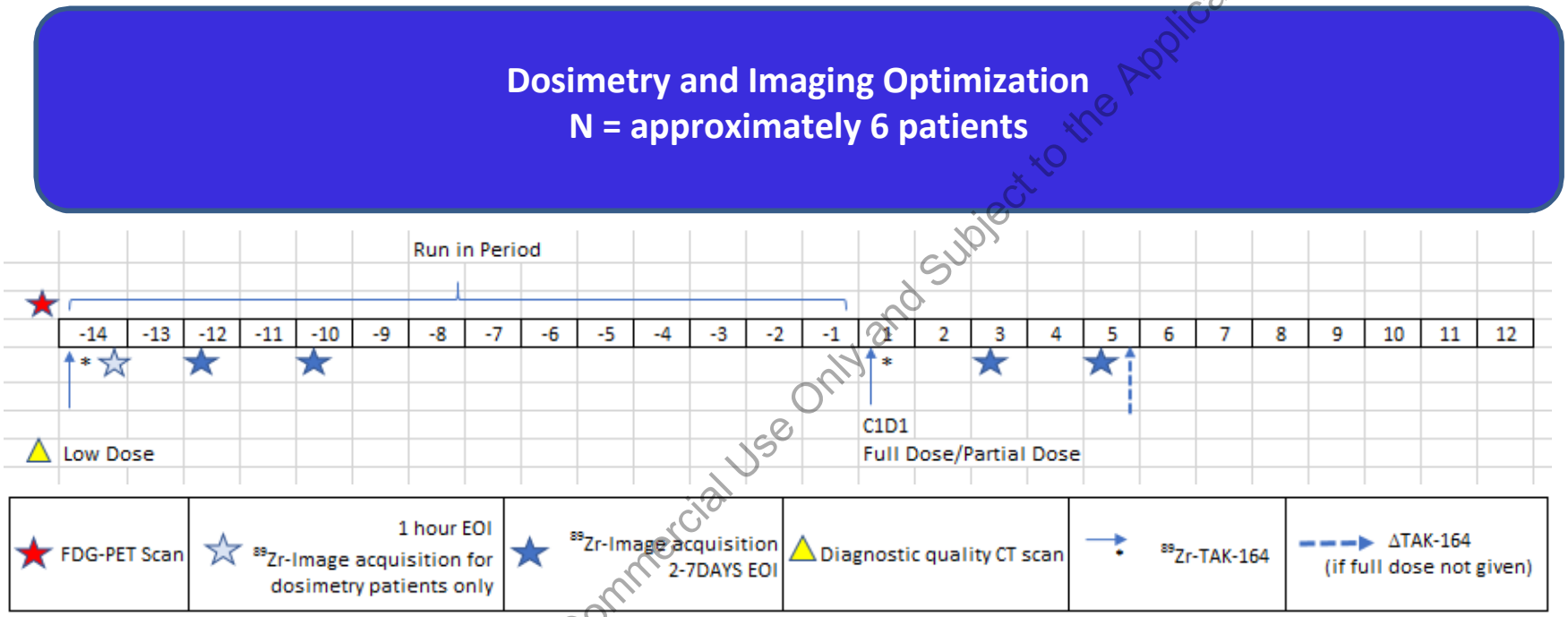
Subsequent dosing and CT scans for RECIST version 1.1 determination will be performed consistent with the expansion cohort regimen. A flow diagram is provided in Figure 6.b. Further details are available in the imaging manual.

^{18}F-FDG-PET

^{18}F-FDG-PET will be performed at baseline, on Cycle 2 Day 12, and again in patients who achieve SD or response (CR or PR) per RECIST 1.1 at Cycle 4 Day 21 (see Schedule of Assessments [Appendix A]). In patients who agree to a biopsy, the second ^{18}F-FDG-PET image will be acquired before the biopsy is taken on Cycle 2 Day 12. Evaluation of metabolic activity of the disease and scanner calibrations will fully comply with the EANM guidelines [54,56]. Briefly, patients will fast 6 hours before the radiotracer injection. Patients will be injected with 3 MBq/kg (±10%) ^{18}F-FDG. After 60 minutes (±5 minutes), a PET scan will be performed from skull base to mid-thigh. The dose of ^{18}F-FDG will be approximately 185 MBq (adapted by weight). Residual activity in the syringe will be measured and subtracted from the injected dose before calculations are done.

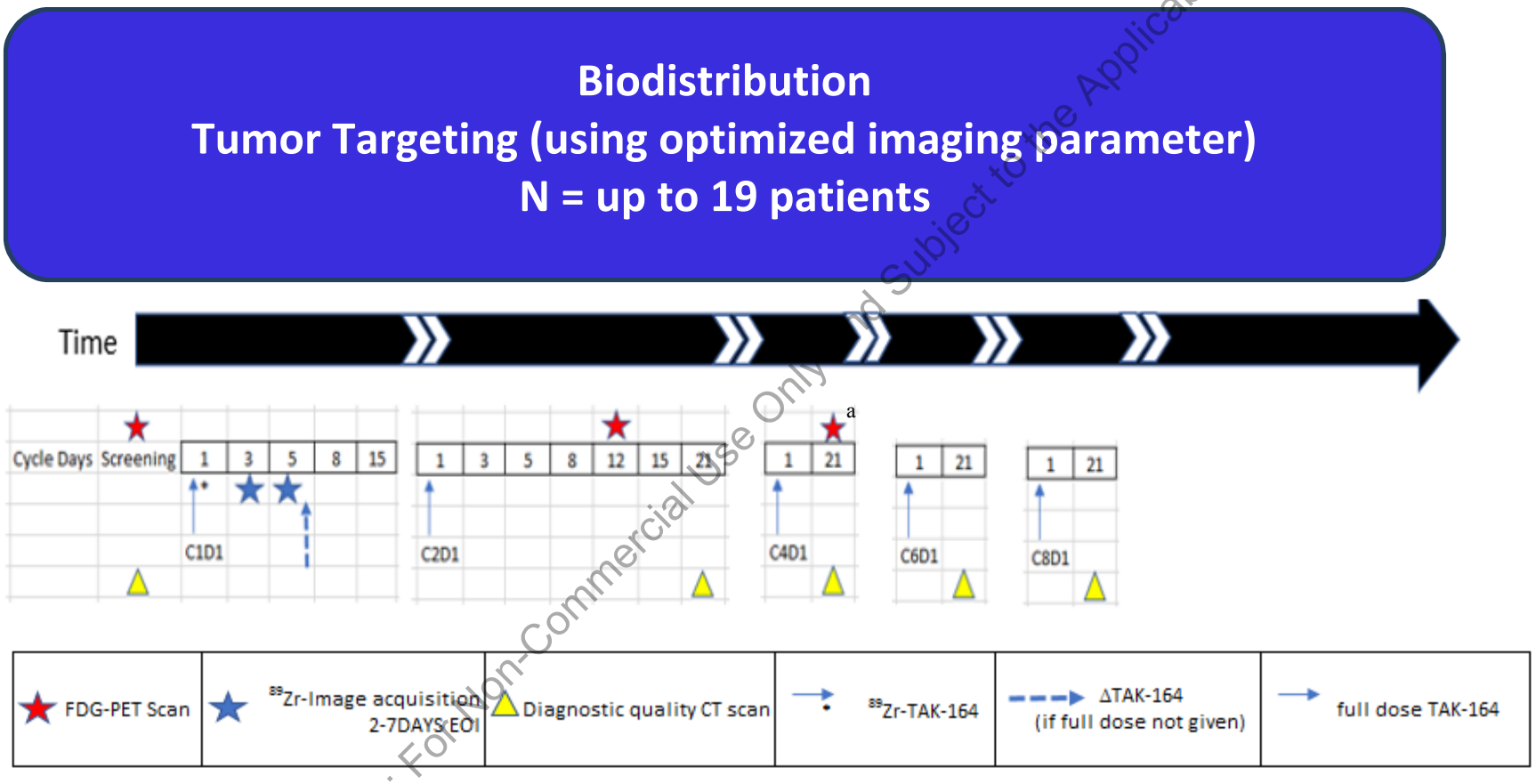
Data analysis will be performed to assess SUL_{mean}, SUL_{max}, SUL_{peak}, 70% volume of interest (VOI), and 50% VOI, normalized for serum glucose and body weight.

Figure 6.b Study Flow Diagram for Part C DIO Subgroup



^{89}Zr: zirconium-89; C: Cycle, CT: computed tomography; D: Day; DIO: dosimetry and imaging optimization; EOI: end of infusion; FDG: fluorodeoxyglucose; PET: positron emission tomography.

Figure 6.c Study Flow Diagram Part C Following DIO



[89]Zr: zirconium-89; C: Cycle, CR: complete response; CT: computed tomography; D: Day.; DIO: dosimetry and imaging optimization; EOI: end of infusion; FDG: fluorodeoxyglucose; PET: positron emission tomography; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors.
[a] Additional FDG-PET scan for patients with stable disease or response (CR or PR) according to RECIST 1.1.

6.2 Number of Patients

Approximately 100 patients will be enrolled in this study from approximately 5 study sites in the US and up to 2 sites in The Netherlands.

Approximately 25 patients will be enrolled in part A and up to 50 patients in part B which includes approximately 25 patients with CRC of high GCC expression level (with H-score ≥150) and approximately 25 patients with gastric carcinoma expressing GCC (with H-score ≥10). A minimum of approximately 20 patients will be enrolled in either cohort of the expansion portion of the study (part B).

Additional patients may be enrolled based on clinical judgment and the totality of clinical outcomes may be considered. Additional sites may be added globally for expansion.

Enrollment is defined as the time of initiation of the first dose of study drug.

Patients who are withdrawn from treatment during Cycle 1 for reasons other than DLTs will be replaced.

In part C, the imaging substudy, up to 25 patients will be enrolled.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients, including those who achieve a clinical response, may receive TAK-164 until they experience disease progression. Patients will discontinue treatment if they have an unacceptable TAK-164–related toxicity.

Patients will be followed for 30 days for safety. Radiographic evaluation will be conducted at treatment intervals of 2 cycles. The maximum duration of treatment is 12 cycles. All patients participating in this study who are judged by the investigator to be receiving clinical benefit will be permitted to remain on therapy until PD or they choose to withdraw from the study due to toxicity or other factors.

Follow-up visits for PFS, which will evaluate a response, will be conducted at the site every 3 months from last dose of study drug for patients who discontinue for reasons other than PD. Those follow-up visits will continue for up to 6 months or until PD, the start of alternative therapy, or conclusion of the study (whichever occurs first).

6.3.2 End of Study/Study Completion Definition and Planned Reporting

Primary Completion/Study Completion

The clinical study report analyses will be conducted after all patients enrolled in the study have had the opportunity to complete 4 cycles of treatment with TAK-164 or discontinued from study.

Study Completion

The estimated time frame for study completion is 43 months (18 months enrollment dose escalation + 12 months enrollment expansion cohorts + 12 cycles [approximately 12 months] of treatment + 1 month of follow-up).

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.

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
Primary:		
• Number of patients with a DLT.	Standard safety assessments	Up to 36 months
• Percentage of patients with AEs.	Standard safety assessments	Up to 36 months
• Percentage of patients with Grade 3 or above AEs.	Standard safety assessments	Up to 36 months
• Percentage of patients with drug-related AEs.	Standard safety assessments	Up to 36 months
• Percentage of patients with drug-related Grade 3 or above AEs.	Standard safety assessments	Up to 36 months
• Percentage of patients with SAEs.	Standard safety assessments	Up to 36 months
• Percentage of patients with AEs leading to discontinuation.	Standard safety assessments	Up to 36 months
• Percentage of participants who meet the markedly abnormal criteria for safety laboratory tests at least once postdose.	Standard safety assessments	Up to 36 months
• Percentage of participants who meet the markedly abnormal criteria for vital sign measurements at least once postdose.	Standard safety assessments	Up to 36 months
• MTD or an alternate RP2D of TAK-164.	Standard safety assessments	Up to 36 months
Secondary:		
• TAK-164 PK parameters: C_{max}, $t_{max,}$ and AUC_{last} during Cycle 1 Day 1 and Cycle 2 Day 1. In addition, C_{trough} may be reported for other dosing days during which a single predose PK sample is collected.	Standard PK parameters to allow determination of PK profile	Up to 36 months
• ORR as assessed by the investigator per modified RECIST version 1.1 [1].	ORR	Up to 36 months
• DCR.	DCR	Up to 36 months
• DOR.	DOR	Up to 36 months
• PFS.	PFS	Up to 36 months
• ADA levels in serum.	ADA levels in serum	Up to 36 months
• Qualitative and quantitative (SUV) determination of patient-level biodistribution	Biodistribution	At 1 hour after EOI for Dosimetry patients and

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
of ^{89}Zr-TAK-164 at all ^{89}Zr imaging time points.		2 instances from Day -13 to Day -9 (all of DIO subgroup) and 2 instances between Day 2 and Day 7 after EOI of ^{89}Zr (all patients in part C)
• Qualitative and quantitative (SUV) ^{89}Zr-TAK-164 uptake in tumor lesions were identified with CT/^{18}F-FDG-PET at all ^{89}Zr imaging time points.	• For qualitative: uptake levels in the tumor will be compared visually with the background. • For quantitative: mean, max, and peak lesions (SUVs). • For quantification in tumor lesions: mean, max, and peak SUL, TLG.	2 instances Day -13 to -8 (DIO patients only) and to 2 instances between Day 2 and Day 7 after end of ^{89}Zr infusion (all patients part C).

^{18}F-FDG: 18-fluorodeoxyglucose; ^{89}Zr: zirconium-89; ADA: antidrug antibody; AE: adverse event; AUC_{last}: area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration; C_{max}: single-dose maximum (peak) concentration; CT: computed tomography; C_{trough}: observed concentration at the end of a dosing interval; DCR: disease control rate; DIO: dosimetry and imaging optimization; DLT: dose-limiting toxicity; DOR: duration of response; EOI: end of infusion; MTD: maximum tolerated dose; ORR: overall response rate; PET: positron emission tomography; PFS: progression-free survival; PK: pharmacokinetic(s); RECIST: Response Evaluation Criteria in Solid Tumors; RP2D: recommended phase 2 dose; SAE: serious adverse event; SUL: standardized uptake value corrected for lean body mass; SUV: standardized uptake value; TLG: total lesion glycolysis; t_{max}: single-dose first time of occurrence of maximum (peak) concentration.

6.3.4 Total Study Duration

Patients will be evaluated at scheduled visits over the following study periods: screening, treatment, and EOT. Patients will discontinue treatment if they experience PD or unacceptable toxicities. The maximum duration of treatment, however, will be 12 cycles unless it is determined that a patient would derive benefit from continued therapy beyond 12 cycles as discussed with investigators and the sponsor. Patients will attend an EOT visit 30 days after the last dose of TAK-164 or just prior to the start of subsequent antineoplastic therapy, whichever occurs first.

It is anticipated that this study will last for approximately 43 months.

7.0 STUDY POPULATION

Male or female patients 18 years or older with histologic or cytologic evidence of measurable advanced and/or metastatic solid GI tumor that expresses GCC protein, for which standard treatment is no longer effective or for whom there is no available standard therapy (part A) or primary or metastatic CRC expressing high levels of GCC and gastric carcinoma expressing GCC (part B). Patients must have adequate bone marrow, liver, and renal function, Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1, a life expectancy of at least 12 weeks, and no serious preexisting medical or psychiatric conditions. A portion of patients from part A and part B should have tumors amenable for serial biopsy for pharmacodynamic assessment.

Inclusion and exclusion criteria for patients participating in part C (imaging substudy) are consistent with the criteria for the patients participating in parts A and B of the study as listed in Sections 7.1 and 7.2. In this substudy, patients with mCRC and patients with metastatic gastric carcinoma for whom standard treatment is no longer effective or for whom there is no available standard therapy can be included. A minimum of approximately 3 patients should have tumors suitable for biopsy and be willing to provide consent for pharmacodynamic assessment to investigate correlations of candidate biomarkers associated with acquired resistance to clinical response. In addition, patients will need to have at least 1 extrahepatic metastatic lesion ≥2 cm in the longest diameter.

7.1 Inclusion Criteria

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

1. Histologically or cytologically confirmed measurable advanced and/or metastatic solid GI tumor that expresses GCC protein (H-score ≥10), for which standard treatment is no longer effective or for whom there is no available standard therapy. For the escalation part of the study (part A), GI malignancies include, but are not limited to, mCRC, gastric carcinoma, esophageal carcinoma, small intestine cancer, and pancreatic cancer. The expansion part of the study (part B) is limited to patients with CRC expressing a high-level GCC (H-score ≥150) and gastric carcinoma (H-score ≥10). Part C includes patients with CRC and gastric carcinoma (H-score ≥10 for both indications).
    - Part B of the study will be limited to patients with 2 or 3 prior lines of systemic standard of care therapy.
2. Voluntary written consent must be obtained from the patient prior to enrollment in the study with the understanding that consent may be withdrawn by the patient at any time without consequences on receiving future medical care.
3. Male or female patients 18 years or older.
4. Adequate bone marrow function, defined as an ANC of $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and hemoglobin ≥9 g/dL. Receiving transfusions or hematopoietic growth factors to meet enrollment criteria is not allowed within 14 days preceding the first dose of study drug.

5. Adequate hepatic function with:
   - Total bilirubin (TBL) ≤1.5 × upper limit of normal (ULN).
   - Serum ALT and AST must be ≤2.5 × ULN (AST and ALT may be elevated up to 3 × ULN if the elevation can be reasonably ascribed to the presence of metastatic disease in liver).
   - Serum albumin ≥3.0 g/dL.
6. Adequate renal function as defined by creatinine CL ≥60 mL/min.
7. ECOG performance score of 0 or 1 (refer to Appendix D).
8. Life expectancy of at least 12 weeks.
9. Completion of prior chemotherapy, biologic therapy, immunotherapy, or radiation therapy at least 4 weeks prior to enrollment.
10. Resolution of all toxic effects of prior treatments (except alopecia) to Grade ≤1 NCI CTCAE, version 5.
11. Female patients who:
    - Are postmenopausal for at least 1 year before the screening visit, OR
    - Are surgically sterile, OR
    - If they are of childbearing potential, agree to practice one highly effective method of contraception and one additional effective (barrier) method (see Appendix F) at the same time, from the time of signing the informed consent through 90 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.)
12. Male patients, even if surgically sterilized (ie, status postvasectomy), who:
    - 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.)
13. Suitable peripheral venous access for the study drug administration and required blood sampling (ie, PK and pharmacodynamic sampling).

14. A portion of patients should have tumors amenable for biopsy and a willingness to provide consent for pharmacodynamic assessment.

Additionally, for part C (imaging substudy), patients must fulfill the following criteria:

15. At least 1 extrahepatic metastatic lesion ≥2 cm in the longest diameter.

7.2 Exclusion Criteria

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

1. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the screening period.
2. Serious preexisting medical or psychiatric conditions that, in the opinion of the investigator, would preclude participation in the study.
3. Chronic or active infection requiring systemic therapy, as well as a history of symptomatic viral infection which has not been fully cured (eg, HIV or viral hepatitis B or C).
4. Symptomatic CNS malignancy or metastasis. Screening of asymptomatic patients without history of CNS metastases is not required.
5. History of congestive heart failure with New York Heart Association class greater than 2 (Class 1 and 2 are eligible), unstable angina (within 3 months prior to study enrollment), recent myocardial infarction (within 6 months of study enrollment), transient ischemic attacks, stroke, arterial or venous vascular disease, or clinically significant symptomatic arrhythmia despite anti-arrhythmic therapy.
6. Corrected QT by Fridericia method (QTcF) interval >470 msec.
7. Treatment with anticancer chemotherapy or biologic therapy or with an experimental anticancer agent within 28 days of the initial dose of study drug.
8. Diagnosed or treated for another malignancy within 2 years before administration of the first dose of study drug, or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.
9. Patient has a history of severe allergic or anaphylactic reactions to recombinant proteins or excipients used in TAK-164 or ^{89}Zr-TAK-164 formulation.
10. Use of strong CYP3A inhibitors and CYP3A inducers or inhibitors or modulators of P-gp or BCRP within 1 week before the first dose of study drug (see Appendix E).
11. For patients enrolled in studies in which tumor biopsies are obtained:
    - Known bleeding diathesis or history of abnormal bleeding, or any other known coagulation abnormalities that would contraindicate the tumor biopsy procedure.
    - Ongoing therapy with any anticoagulant or antiplatelet agents (eg, aspirin, clopidogrel, heparin, or warfarin).

12. Patient has concurrent alcohol abuse or a history of drug-induced liver injury (DILI).

8.0 STUDY DRUG

8.1 Study Drug Administration

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

All patients in part A and part B will receive TAK-164 as a single infusion (see pharmacy manual for additional details). The study will contain a dose escalation phase (part A), an expansion cohort phase (part B), and an imaging substudy (part C).

Each 21-day treatment cycle will consist of a single dose on Day 1, followed by a rest period of 20 days.

Infusion of TAK-164 should occur in an area with resuscitating equipment and medications such as antihistamines, acetaminophen, corticosteroids, epinephrine, and bronchodilators readily available. Although no infusion-related reactions were observed with TAK-164 in cynomolgus monkeys, such a risk cannot be excluded, and in order to reduce potential risk the patients' vital signs must be monitored before, during, and at the end of administration of TAK-164. Treatment must be discontinued in patients who develop Grade 4 toxicity to TAK-164, unless in the opinion of the investigator and the project clinician treatment is in the patient's best interest. For all other grades of toxicity, based on the severity of infusion-related reactions potentially observed, the infusion rate may be decreased by 50% or discontinued, and signs and symptoms promptly treated with 1 or more of the medications detailed above (antihistamines, etc). Patients who develop mild to moderate infusion reactions or hypersensitivity (Grade 1 or 2) may receive premedication with 1 or more of the medications detailed above for subsequent doses as deemed appropriate by the investigator.

Routine prophylaxis for infusion-related reactions is not recommended for the first dose.

Patients will be observed at the clinical site for approximately 8 hours after the administration of the first dose and 2 hours after the administration of subsequent doses. The patient should be considered clinically stable by the investigator or designee before discharge.

The total amount of TAK-164 administered for each patient will be based on actual body weight (kg) as measured on Day 1 of Cycle 1. Dose calculations will be repeated at subsequent visits if the patient experiences a greater than 5% change in body weight since the last dose calculation.

As with other potentially toxic compounds, caution should be exercised in handling this drug. The use of gloves is recommended. Following topical exposure, events could include redness or blistering. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

For Patients in the Imaging Substudy (Part C, To Be Conducted in The Netherlands Only):

The dose of unlabeled TAK-164 to be administered to imaging substudy patients before ^{89}Zr-TAK-164 infusion will be determined by a multidisciplinary team at the clinical site in

agreement with the sponsor and the total amount of TAK-164 (labeled and unlabeled) will not exceed the RID/RP2D.

8.2 Definitions of DLT

Toxicity will be evaluated according to the NCI CTCAE, version 5, effective 27 November 2017 [55]. These criteria are provided in the study manual and are available online at ctep.cancer.gov/reporting/ctc.html. DLT will be defined as any of the following AEs that occur and are considered by the investigator to be related to therapy with TAK-164:

1. Grade 4 neutropenia (ANC <500 cells/mm^3).
2. Febrile neutropenia as characterized by an ANC <1000/mm^3 and a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour.
3. Grade 4 thrombocytopenia (platelets <25,000/mm^3).
4. Grade 3 or greater thrombocytopenia with clinically meaningful bleeding at any time.
5. Grade 3 or greater nausea and/or emesis that occurs despite the use of optimal anti-emetic prophylaxis. Optimal anti-emetic prophylaxis is defined as an anti-emetic regimen that employs both a 5-hydroxytryptamine 3 serotonin receptor (5-HT3) antagonist and a corticosteroid given in standard doses and according to standard schedules.
6. Grade 3 or greater diarrhea that occurs despite optimal supportive care measures.
7. Any other Grade 3 or greater nonhematologic toxicity with the following exceptions:
   - Brief (<1 week) Grade 3 fatigue.
8. Inability to start the next cycle of therapy due to treatment delay of more than 2 weeks because of a lack of adequate recovery of TAK-164–related hematological or nonhematologic toxicities.
9. Other TAK-164–related nonhematologic toxicities Grade 2 or greater that, in the opinion of the investigator, require a discontinuation of therapy with TAK-164.

Although DLTs may occur at any point during treatment, only DLTs occurring during Cycle 1 of treatment will necessarily influence decisions regarding dose escalation, expansion of a dose, or evaluation of intermediate doses. In part A, Cycle 1, toxicities requiring a dose hold for longer than 2 weeks or discontinuation will be considered a DLT.

Patients will be monitored through all cycles of therapy for treatment-related toxicities. AEs associated with TAK-164 may include any toxicity except those that are definitely attributable to another cause, such as disease progression.

8.3 Dose Escalation Rules

A dose escalation of TAK-164 will follow a mTPI study design. Up to 3 patients will be enrolled at dose cohort level 1 (0.004 mg/kg) in the first cycle. Thereafter, interval reassessment for dose

adjustment will be performed for subsequent patients, as described below per mTPI design. Each patient will be followed until PD, DLT, or until they choose to withdraw consent from the trial.

As described in Ji [2], the mTPI design is based on toxicity probabilities (p_T) for each dose level. These probabilities are sequentially updated with the data generated by tolerability of each patient beginning with the initial dose (dose level 1) and each subsequent patient.

Decision rules at each step are based on calculating the unit probability mass (UPM) of 3 intervals corresponding to underdosing, proper dosing, and overdosing a patient, in terms of toxicity. Specifically, the underdosing interval is defined as (0, targeted p_T - ε_1), the overdosing interval as (p_T + ε_2, 1), and the proper dosing interval as (p_T - ε_1, p_T + ε_2), where ε_1 and ε_2 are small fractions to account for the uncertainty around the true target toxicity. In this study, p_T is targeted at 25%, ε_1, ε_2 are both 5% to account for uncertainty.

The 3 dosing intervals are associated with 3 different dose escalation decisions. The underdosing interval corresponds to a dose escalation (E), overdosing corresponds to a dose de-escalation (D), and proper dosing corresponds to staying at the current dose (S). Given an interval and a probability distribution, the UPM of that interval is defined as the probability of the interval divided by the length of the interval. The mTPI design calculates the UPMs for the 3 dosing intervals, and the one with the largest UPM implies the corresponding dose-finding decision. That decision provides the dose level to be used for future patients. The mTPI dosing schema will maximize patients treated at or near the MTD and the MTD will be determined by using an isotonic regression to fit a function of observed probabilities of DLT at each dose level in this trial.

The dose escalation design is shown in Figure 8.a.

Figure 8.a TAK-164-1001 mTPI Decision Table

Number of Patients with DLTs	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
2		D	D	D	S	S	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E
3			DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	S	S	S	E	E	E	E	E	E
4				DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
5					DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	S	S	S	S
6						DU	DU	DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	S
7							DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S	S	S	S	S	S	S	S
8								DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S	S	S	S	S
9									DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S	S
10										DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
11											DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
12												DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
13													DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
14														DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
15															DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
16																DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
17																	DU	DU	DU	DU	DU	DU	DU	DU	DU
18																		DU	DU	DU	DU	DU	DU	DU	DU
19																			DU	DU	DU	DU	DU	DU	DU
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21																					DU	DU	DU	DU	DU
22																						DU	DU	DU	DU
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24																								DU	DU
25																									DU

Top row indicates the number of patients treated, first column indicates the number of patients with DLTs.
E: Escalate to the next higher dose, S: Stay at the same dose, D: De-escalate to the previous lower dose, DLT: dose-limiting toxicity; DU: De-escalate to the previous lower dose and the current dose or higher will never be used again; mTPI: modified toxicity probability interval.

Safety will be assessed throughout the study by monitoring AEs, vital signs, physical examinations, and clinical laboratory tests. Prior to escalating to the next dose level, a meeting

with the sponsor and investigators will be conducted, and they will review all data based on the clinical observations and laboratory tests. Based on medical judgment and the guidance of the statistical model, a decision will be made for each patient's next dose level, including dose increases or decrements as appropriate. In addition, the medical monitor and treating physician will consult in real time as needed based on clinical findings.

Note that depending on PK-defined exposure estimates, a dose level between the planned dose levels may be explored. In addition, based on safety/tolerability, alternative dosing schedules may be explored after discussion and concurrence with all lead investigators and the Takeda study clinician. However, no patients will receive a dose above 0.19 mg/kg Q3W.

The first cohort of patients is treated at the starting dose level (0.004 mg/kg).

- If the first cohort includes 2 patients and none of the patients experiences DLT, the dose level is escalated for the next cohort of patient (corresponding to "E" in Column 1 of the table).
- If 1 of the patients experiences DLT, the dose level remains the same, more patients will be added.
- If both patients experience DLT, the dosing at this level will be stopped, additional cohort of patients will be dosed at dose level -1 (0.002 mg/kg). If 2 or more DLTs are observed at the 0.002 mg/kg dose level, the study will be stopped.

When a cohort of patients completes the DLT observation period, the number of DLTs is determined, and the action (escalation, de-escalation, or remaining at the same level) for the next cohort of patients is determined based on the number of DLTs and number of patients at that dose level. For example, at dose level 3, if 1 DLT is observed in the first of 2 treated patients, the dose level remains same for additional patients until 7 patients are dosed at this level and only 1 DLT is observed. As shown in the table, the value in the row labeled "1" and the column labeled "7" indicates "E," corresponding to "Escalation" for the next cohort. This algorithm is followed until 25 patients have been accrued. The operating characteristics of this design are described in Section 13.1.1. Patients will be observed for 1 cycle at a given dose level for DLTs prior to additional patients enrolling at a higher dose in order to ensure safe dose escalation. Within each dose level, there will be a 7-day interval between the first and second patient and subsequent patients will be staggered by at least 1 day.

- Approximately 25 patients will be enrolled in the dose escalation. More patients may be enrolled based on clinical judgment. The starting dose of 0.004 mg/kg will be used to treat the first cohort of patients and the dose escalation schema will be followed, as planned. Data will be collected to determine PK and estimate variability throughout the tested dose range. Intrapatient dose escalation will not be allowed.
- MTD will be estimated based on observed DLTs using mTPI and clinical judgment.
- The investigator and study physician may diverge from the outlined dose escalation plan to select a lower dose than indicated as MTD based on tolerability beyond Cycle 1 or cumulative toxicity within Cycle 1 of less than DLT-defined toxicities.

- If Grade 2 toxicity or greater is seen at a defined dose level and the toxicity is considered by investigator as related to TAK-164 treatment, the dose escalation plan may be modified to allow a dose increase of no more than 25% of the prior dose.

Patients not receiving all doses of TAK-164 in Cycle 1 for reasons other than DLTs will be replaced within the cohort.

Q3W Schedule and Dose Levels:

- TAK-164 is administered on Day 1 of each 21-day cycle.
- Up to 3 initial patients per cohort will be enrolled at the starting dose of 0.004 mg/kg. Dose escalation is planned to proceed by evaluating patients at respective dose levels: 0.008 mg/kg, 0.016 mg/kg, 0.032 mg/kg, 0.064 mg/kg, 0.12 mg/kg, and 0.19 mg/kg.

MTD with a target toxicity of 25% is determined by mTPI (dose level of posterior mean toxicity closest to target toxicity, Section 8.3). Although dose escalation and MTD will be estimated based on observed DLTs in Cycle 1, safety/tolerability data beyond Cycle 1 will be integrated into the RP2D determination for the expansion phase.

In part C, the imaging substudy, the DIO subgroup will receive ^{89}Zr-TAK-164 (mass dose <50% of the RID) 14 days before the first regularly scheduled study dose at Cycle 1 Day 1 (see Figure 6.b) and a second ^{89}Zr-TAK-164 administration on Cycle 1 Day 1 in combination with unlabeled TAK-164 at a maximum mass dose of 100% of the RID. Imaging will be performed 1 hour after EOI of the first ^{89}Zr-TAK-164 administration for dosimetry in the first 3 patients, and for all patients at 2 time points between Day 2 and Day 7 after EOI. Imaging time points and mass dose of TAK-164 can be adjusted to optimize imaging conditions. Up to 19 additional patients will be enrolled into part C to receive a single dose of ^{89}Zr-TAK-164 at Cycle 1 Day 1 in addition to unlabeled TAK-164 as determined for optimal imaging. Once the RP2D of TAK-164 is determined, part C patients who have received TAK-164 at an RID lower than the RP2D of TAK-164 may dose-escalate to the RP2D in the absence of PD or unacceptable treatment-related toxicity at the investigator's discretion and with sponsor's approval. If the full RID/RP2D is not administered at Cycle 1 Day 1, the differential will be provided after the second image acquisition. Part C patients will continue treatment with the RID/RP2D of TAK-164 at Cycle 2 Day 1 and beyond (see Figure 6.c).

8.4 Dose Modification Guidelines

8.4.1 Criteria for Retreatment and Dose Delays and Modifications Delaying a Subsequent Treatment Cycle

Treatment with TAK-164 will be repeated each cycle, 21 days (Q3W schedule). Criteria for delaying treatment, modifying the dose, or discontinuing treatment in individual patients are outlined in Table 8.a and discussed below. Dose modification will apply to patients who complete Cycle 1 and are continuing on treatment. When a dose reduction of TAK-164 is required, no re-escalation of dose will be permitted. For the next cycle of treatment to begin, the patient must meet the following criteria:

- ANC must be ≥1500/mm^3.
- Platelet count must be ≥100,000/mm^3.
- Serum albumin level must be ≥3 g/dL.
- In addition, for therapy to resume, toxicity considered to be related to treatment with TAK-164 must have resolved to Grade ≤1, to the patient's baseline values, or to a level considered acceptable by the physician (eg, hypophosphatemia that can be managed by oral replacement). Also, the patient's nutritional status and organ function must be adequate, as assessed by the treating physician.

If the patient does not meet the above-cited criteria for retreatment, initiation of the next cycle of treatment should be delayed for 1 week. At the end of that time, the patient should be reevaluated to determine whether the criteria for retreatment have been met. If observed that the criteria for retreatment have been met, the treatment may continue at a reduced dose. If needed, the initiation of the next cycle of treatment should be delayed for 1 additional week. At 2 weeks if the treatment criteria are met, the dose may be reduced for at least 1 dose level for subsequent cycles. If a patient needs to delay treatment for a period greater than 2 weeks, that should trigger discontinuation from the study unless the treating physician considers it to be in the patient's best interest to continue study treatment and the sponsor agrees.

Table 8.a TAK-164 Recommended Dose Modification Criteria

General	
Occurrence	**Modification**
Any Grade >1 toxicity that does not resolve within 2 weeks of study drug being withheld.	Discontinuation [a]
HEMATOLOGIC TOXICITIES	
Adverse Event (Severity)	**Modification**
Neutropenia	
Grade 4 without fever.	Dose reduction [a]
Grade 3 or greater with fever (a single oral temperature of >38.3°C or a sustained temperature of ≥38°C for more than 1 hour).	Dose reduction [a]
Thrombocytopenia	
Grade 3 or greater with clinically meaningful bleeding at any time.	Dose reduction [a]
Anemia	
Grade 3 or greater.	Dose reduction [a]

Table 8.a TAK-164 Recommended Dose Modification Criteria

NONHEMATOLOGIC TOXICITIES	
Adverse Event (Severity)	**Modification**
Peripheral Neuropathy	
Grade 1 with pain or Grade 2.	Dose reduction [a]
Grade 2 with pain or Grade 3.	Dose interruption
Grade 4.	Discontinuation
All Other Grade 3 or Greater Nonhematologic Toxicities	
– Grade 3 nonhematologic toxicities attributed to study drug. [b,c]	Dose interruption with dose reduction [a]
– Grade 3 or greater nausea and/or emesis in the absence of optimal antiemetic therapy.	No dose modification required
– Grade 3 or greater diarrhea in the absence of optimal supportive therapy.	No dose modification required
– Grade 3 fatigue with duration <1 week.	No dose modification required
– Grade 4 nonhematologic toxicities. [a]	Discontinuation or dose interruption with dose reduction
– Grade 3 derangements of liver function tests.	Refer to discontinuation rules in Section 8.4.3
DLT	If, in the opinion of the investigator and the medical monitor it is in the patient's best interest to continue treatment with TAK-164, then the dose of TAK-164 should be reduced by at least 1 dose level with subsequent treatment after recovery of the toxicity or toxicities in question to Grade 1 or to baseline values. When a dose reduction of TAK-164 is required, no re-escalation will be permitted.

DLT: dose-limiting toxicity.
[a] Dose reduction will be dosing 1 level lower. If at scheduled start of next cycle, the toxicity has returned to Grade ≤1 or baseline, administer TAK-164 at a reduced dose. If toxicity has not resolved to Grade ≤1 or baseline within 1 week, delay treatment for an additional week. Once toxicity has recovered to Grade ≤1 or baseline (at 1 or 2 weeks), restart treatment at a reduced dose. Discontinue treatment if after 2 weeks the criteria for retreatment have not been met, unless the treating physician considers it to be in the patient's best interest to continue study treatment and the sponsor agrees.
[b] Except Grade 3 or greater nausea, vomiting, or diarrhea in absence of optimal antiemetic or supportive therapy, Grade 3 fatigue less than 1-week duration.
[c] Except Grade 3 derangements of liver function tests.

8.4.2 Criteria for Dose Reduction

The dose of TAK-164 should be reduced by at least 1 dose level (or by 50% if the patient is receiving the first dose level) if the patient has any of the following:

- Grade 4 neutropenia (ANC <500 cells/mm^3) lasting more than 7 consecutive days.

- Grade 3 or greater neutropenia with fever and/or infection, where a fever is defined as a single oral temperature of >38.3°C or a sustained temperature of ≥38°C for more than 1 hour. Grade 3 thrombocytopenia with clinically meaningful bleeding at any time.
- Grade 4 thrombocytopenia (platelet count <25,000/mm^3) lasting more than 7 consecutive days.
- Grade 3 nonhematologic toxicity (except liver function derangements) attributed to TAK-164 except for the following that do not require dose reduction:
  - Grade 3 or greater nausea and/or emesis in the absence of optimal antiemetic prophylaxis. (Optimal antiemetic prophylaxis is defined as an antiemetic regimen that employs both a 5-HT3 antagonist and a corticosteroid given in standard doses and according to standard schedules.)
  - Grade 3 or greater diarrhea that occurs in the absence of optimal supportive therapy.
  - Grade 3 fatigue lasting less than 1 week.
- Derangement of liver function tests (LFTs) will follow discontinuation rules in Section 8.4.3.

When a dose reduction of TAK-164 is required, no re-escalation of dose will be permitted.

8.4.3 Criteria for Discontinuation of TAK-164

Grade 4 nonhematologic toxicities will in general require that treatment with TAK-164 be permanently discontinued. Treatment delays of greater than 2 weeks for study drug-related toxicities require discontinuation from study treatment, unless the treating physician considers it to be in the patient's best interest to continue study treatment and the sponsor agrees.

Treatment with TAK-164 will also be permanently discontinued under the following conditions:

- ALT or AST >8 × ULN; OR
- ALT or AST >5 × ULN for more than 2 weeks; OR
- ALT or AST >3 × ULN and TBL >2 × ULN.

If, in the opinion of the investigator and the project clinician, it is in the patient's best interest to continue treatment with TAK-164, then the dose of TAK-164 should be reduced by at least 1 dose level (or by 50% if the patient is receiving the first dose level) after recovery of the toxicity or toxicities in question to Grade 1 or to baseline values.

If more than 2 dose reductions are required, TAK-164 should be discontinued. If, in the opinion of the investigator and the project clinician, it is in the patient's best interest to continue treatment with TAK-164, then the dose of TAK-164 should be reduced by at least 1 dose level for subsequent cycles of treatment after recovery of the toxicity or toxicities in question to Grade 1 or to baseline values. When a dose reduction of TAK-164 is required, no re-escalation of dose will be permitted.

8.5 Excluded Concomitant Medications and Procedures

During the course of the study, patients will be instructed not to take any additional medications (including over-the-counter products and supplements) without prior consultation with the investigator. At each visit, the investigator will ask the patient about any new medications he/she is or has taken while on study. All concomitant medications (defined as any medication given during the study) and significant nondrug therapies, including physical therapy and blood transfusions, should be recorded from signing of the informed consent form (ICF) through 28 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first.

The following medications and procedures are prohibited during the study:

- All concomitant chemotherapy, immunotherapy, and radiotherapy.
- Any investigational agent other than TAK-164, including agents that are commercially available for indications other than GI malignancies that are under investigation for the treatment of GI malignancies.
- Any antineoplastic treatment with activity against GI malignancies other than TAK-164.
- Strong CYP3A inhibitors (a list of CYP3A inhibitors and inducers is presented in Appendix E). Concurrent systemic administration of TAK-164 with strong inhibitors or inducers of CYP3A or inhibitors or modulators of P-gp or BCRP should be avoided in this study. Refer to Appendix E for a nonexhaustive list of medications, supplements, and food products that are strong inhibitors or inducers of CYP3A based on the US Food and Drug Administration (FDA) Draft Drug-Drug Interaction Guidance.
- Anticoagulant therapy (eg, aspirin, coumadin, heparin) that cannot be held for patients who will require a tumor biopsy.

If a patient experiences an AE, therapies required to manage the AE and control cancer symptoms are allowed according to standard clinical practice including palliative radiation (if, in the opinion of the investigator, there is no appropriate alternative treatment available). Such situations will be managed on a case-by-case basis and require medical monitor approval based on the risk/benefit for the patient. The discussion/approval should be documented in the study file and the patient should be closely monitored for potential toxicity.

8.6 Precautions and Restrictions

It is not known what effects TAK-164 has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, OR

- Surgically sterile, OR
- If they are of childbearing potential, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception at the same time, from the time of signing of the ICF through 90 days after the last dose of study drug (whichever is longer), 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.)

Male patients, even if surgically sterilized (ie, status postvasectomy) 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.)

8.7 Management of Clinical Events

Therapies that are required to manage AEs and control cancer symptoms are allowed based on standard clinical practice, unless specifically excluded. Supportive care agents, such as erythropoietin, granulocyte colony stimulating factor (G-CSF), blood products (RBC and platelet transfusions), and pain medications are permitted as needed per American Society of Hematology (ASH)/American Society of Clinical Oncology (ASCO) guidelines or local institutional practice. However, these agents should not be used in this study in a manner that would either help establish eligibility for the study or support escalation of study drug dose during dose escalation. If dose alterations are necessary as a result of the events detailed below, refer to Section 8.4.

8.7.1 Nausea- and/or Vomiting

This study will not initially employ prophylactic antiemetics before the first dose of the study drug during dose escalation. However, a patient who develops nausea and/or vomiting will be actively managed by employing optimal antiemetic treatment based on local standard practice. Additionally, antiemetics may be used prophylactically as clinically indicated following the occurrence of a first event of study drug-related or possibly related nausea and/or vomiting. An optimal antiemetic regimen is defined as one that employs both a 5-HT3 antagonist and a corticosteroid given in standard doses and according to standard schedules.

8.7.2 Anemia, Thrombocytopenia, and/or Neutropenia

Hemoglobin and blood counts should be monitored regularly as outlined in the Schedules of Events (Appendix A) with additional testing obtained according to standard clinical practice. Administration of TAK-164 should be modified per dose modification guidance in the protocol when anemia, thrombocytopenia, or neutropenia occur (see Table 8.a). RBC transfusion and use of erythropoietin to manage severe anemia, platelet transfusion to prevent and minimize bleeding in case of severe thrombocytopenia, and myeloid growth factor (eg, G-CSF, GM-CSF) support to treat severe and/or febrile neutropenia are permitted per ASH/ASCO guidelines, as necessary. However, it should be noted that prophylactic use of myeloid growth factors should be avoided during the first cycle of dose escalation.

8.7.3 Skin Lesions

Dermal and subcutaneous lesions with ulceration or necrosis represent a potential risk and are presumed associated with accidental extravasation. Local institutional guidelines must be applied to stress proper administration and prevention of accidental extravasation of TAK-164. Constant monitoring at the beginning and during infusion must be ensured. If extravasation occurs, the infusion must be discontinued immediately, and institutional guidelines applied. Treatment and monitoring of patients until symptoms resolve should be consistent with institutional standards and guidelines as appropriate. Patients should be instructed to report any discomfort, pain, or swelling at the infusion site.

8.7.4 Lacrimal Gland Secretion Alteration

Patients should be advised to report any discomfort with dry eye, if that should occur. Treatment and monitoring should be consistent with institutional standard and guidelines as appropriate.

8.7.5 Diarrhea

This study will not initially employ prophylactic antidiarrheals; however, there is no prohibition against their use in the management of a patient who develops diarrhea. Patients will be instructed to take antidiarrheal medication(s) at the physician's discretion until they are diarrhea-free for at least 12 hours. Fluid intake should be maintained to avoid dehydration.

8.7.6 Infusion-related Reactions

If such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension or hypertension, bronchospasm, or other symptoms. Treatment and monitoring of patients until symptoms resolve should be consistent with institutional standards and guidelines as appropriate. If Grade 3 and 4 infusion reactions occur, infusion should be discontinued immediately. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. The patient should be closely monitored until recovery of symptoms. The patient will be permanently discontinued from the trial. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the medical monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE, version 5.

As with other mAb therapies, potential risk for immunogenicity cannot be excluded. Based on our TAK-264 experience, where the same antibody was utilized (very low immunogenicity positivity), general screening/titer/confirmation/domain specificity immunogenicity assays will be performed but not the further ADA characterization assay such as neutralization assay. The overall immunogenicity will be monitored closely in the study and the timing of implementing neutralization assay will be assessed at later phase for this product.

8.7.7 Hepatotoxicity

It is recommended that patients treated with TAK-164 undergo periodic monitoring of LFTs as outlined in the Schedules of Events (Appendix A). These liver tests should be monitored closely throughout the study, and strict procedures for evaluation and/or discontinuation of patients with elevated liver tests that meet predefined criteria should be implemented. Additional testing and treatment should be implemented as per institutional standard of care.

If patients experience ALT or AST >3 × ULN or AST > ULN but ≤3 × ULN, and if this observation cannot be explained by concomitant disease or another alternative etiology, follow-up laboratory tests (at a minimum alkaline phosphatase [ALP], ALT, AST, and TBL) should be performed within a maximum of 48 hours.

8.8 Blinding and Unblinding

This is an open-label study.

8.9 Description of Investigational Agents

The drug product is TAK-164 for injection.

TAK-164 for injection is for IV administration only.

Full details are available in the IB.

8.10 Preparation, Reconstitution, and Dispensation

The reconstituted product will be administered by IV infusion over a defined period of time. Detailed reconstitution and dosage preparation instructions are provided in the Directions for Use located in the pharmacy manual.

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

TAK-164 is an anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling TAK-164.

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

8.11 Packaging and Labeling

All label information will fulfill requirements specified by local governing regulations. Additional details are provided in the pharmacy manual.

8.12 Storage, Handling, and Accountability

Complete receipt, inventory, accountability, reconciliation, and destruction records will be maintained for all used and unused study drug vials. A drug dispensing log, including records of drug received from the sponsor and drug dispensed to patients will be provided and kept at the study site. Disposal instructions are provided in the pharmacy manual.

8.13 Other Protocol-Specified Materials

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

8.14 Description of ^{89}Zr-TAK-164

Radiolabeling of TAK-164 with ^{89}Zr will be performed by the CCI [redacted] according to standard operating procedures. The process will be performed according to GMP standards. This production site has been inspected by the Dutch Health Care Inspectorate and is licensed to manufacture tracers for human use according to European Union guidelines.

8.15 Preparation of ^{89}Zr-TAK-164

^{89}Zr-TAK-164 will be prepared as described in the pharmacy manual and administered by IV at an anticipated dose of 0.5 to 2 mg at 37±10% MBq. The specific mass dose of ADC will be determined during the DIO phase of the imaging substudy.

The product should be used immediately. For specific instructions and information on expiry date, see the lead container.

8.16 ^{89}Zr-TAK-164 Administration

^{89}Zr-TAK-164 will be administered as an IV infusion over a period of up to 30 minutes with careful monitoring of potential infusion-related and all AEs. When unlabeled TAK-164 is to be administered on the same day as ^{89}Zr-TAK-164, the patients will receive 37±10% MBq of ^{89}Zr-TAK-164 (see pharmacy manual for details) within 2 hours after the infusion of unlabeled TAK-164 according to the registered label.

9.0 STUDY CONDUCT

This trial will be conducted in compliance with the protocol, GCP, applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

9.1 Study Personnel and Organizations

The contact information for the Takeda Study Monitor for this study, the central laboratory and any additional clinical laboratories, the contract research organization (CRO), and the coordinating investigator for each member state/country may be found in the study manual. A full list of investigators is available in the sponsor's investigator database.

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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC). It is not envisioned that prisoners (or other populations that might be subject to coercion or exploitation) will be enrolled into this study.

9.3 Treatment Group Assignments

This is a phase 1 study that incorporates a dose escalation phase and an expansion cohort phase at the MTD/RP2D. In the dose escalation phase, patients will be assigned a dose by cohort based on the dose escalation rules as described in Section 8.3. Patients with mCRC enrolled in the MTD/RP2D cohort during the dose escalation phase of the study will be counted as part of the total of expansion cohort patients. Up to 50 patients with CRC GCC high expression level and patients with gastric carcinoma will be assessed. A minimum of approximately 20 patients will be enrolled in either cohort. In addition, up to 25 patients will be enrolled in the imaging substudy in The Netherlands (part C).

9.4 Study Procedures

Each patient must sign and date an ICF before undergoing any study-specific procedures unless those procedures are performed as part of the patient's standard of care.

A detailed visit-by-visit schedule of study procedures is provided in the Schedules of Events (Appendix A).

Patients will be evaluated at scheduled visits over the following study periods: screening, treatment, and EOT. Evaluations during the screening period are to be conducted within 21 days before the first dose of TAK-164 except for prescreening of GCC, which may be completed prior to screening with appropriate patient consent. Procedures conducted during the screening period that are performed within 3 days of Cycle 1 Day 1 may also be used as the predose evaluation and do not need to be repeated, unless otherwise specified. For patients in the DIO subgroup of part C, all screening procedures must be completed before Day -14. It is recommended to consider prescreening patients' GCC expression while on prior treatment. All EOT evaluations

should occur approximately 30 days after the last dose of study drug, or prior to the start of subsequent antineoplastic therapy. Refer to the Schedules of Events (Appendix A) for timing of assessments. Additional details are provided as necessary in the sections that follow.

9.4.1 Informed Consent

Each patient, or the patient's legal representative, must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard medical care. Informed consent may be obtained more than 21 days before the first dose of study drug, provided that the patient is confirmed to be eligible per the inclusion/exclusion criteria. A separate informed consent may be given by patients for release of archived tumor tissue for GCC prescreening. If archival tissue is not available, patients can provide tumor biopsy samples after signing the ICF. Unless specifically stated, references to ICF or informed consent in this protocol refer to the ICF patients sign when enrolling in the study.

9.4.2 Inclusion/Exclusion Review

Inclusion and exclusion criteria will be reviewed during screening to ensure patient meets eligibility requirements.

9.4.3 Patient Demographics

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

9.4.4 Medical History

During the screening period, a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy and include a description of prior therapies for it. In addition, concomitant medications will be recorded as specified in Section 9.4.9.

9.4.5 Physical Examination

A physical examination will be completed per standard of care at the times specified in the Schedules of Events (Appendix A). Any clinically relevant findings are to be documented.

9.4.6 Height and Weight

Height will be measured only during screening. Body weight will be measured at the times specified in the Schedules of Events (Appendix A).

9.4.7 ECOG Performance Status

Performance status is to be assessed using the ECOG scale (see Appendix D for a description of the scale) at the times specified in the Schedules of Events (Appendix A).

9.4.8 Vital Signs

Vital sign measurements, including diastolic and systolic blood pressure, heart rate, and temperature, will be assessed as specified in the Schedules of Events (Appendix A).

9.4.9 Pregnancy Test

A serum pregnancy test will be obtained for women of childbearing potential at screening and at EOT. The screening results must be available and negative prior to enrollment. A urine pregnancy test will be obtained for women of childbearing potential on Day 1 of every cycle and a negative result must be confirmed prior to dosing.

Pregnancy tests may also be repeated during the study if requested by an IEC/IRB or if required by local regulations.

9.4.10 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the electronic case report form (eCRF) from signing of the ICF through the EOT visit or the start of subsequent antineoplastic therapy, whichever occurs first. See Section 8.5 for a list of medications and therapies that are prohibited during the study.

9.4.11 AEs

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

9.4.12 Enrollment

Enrollment is defined as the time of initiation of the first dose of study drug.

Procedures for completion of the enrollment information are described in the study manual.

9.4.13 Cardiac Monitoring

9.4.13.1 12-Lead ECGs and Left Ventricular Ejection Fraction

Left ventricular ejection fraction (LVEF) will be measured by an echocardiogram (ECHO) at the times listed in the Schedules of Events (Appendix A). If a patient develops signs or symptoms of congestive heart failure, TAK-164 administration should immediately be discontinued and LVEF measurement should be performed. ECHO will be performed for all patients in part A and the first 30 patients in part B. After the first 30 patients, if there are no clinical findings, ECHO will no longer be required.

Single 12-lead ECGs will be collected at screening (to assess eligibility) and for "safety" within 1 hour before TAK-164 administration (ie, start of the infusion). All other ECGs require triplicate 12-lead ECG recordings. Refer to the Schedules of Events (Appendix A) for the specific visits, timepoints, and type (ie, single vs triplicate recording) of ECGs that are required.

All ECGs will be centrally read and ECG parameters will include PR, QT, QTcF, QRS, and ventricular rate.

Any findings from ECGs collected after study drug administration will be captured as AEs if, in the opinion of the investigator, there has been a clinically significant change from baseline.

When the timing of a PK, biomarker, or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample.

9.4.13.2 Triplicate ECGs

Triplicate 12-lead ECG recordings matched with PK sampling are required at time points specified in the Schedules of Events (Appendix A) for a preliminary assessment of TAK-164 on QTcF interval. The triplicate ECG will be stored and submitted for central reading.

When triplicate ECGs overlap with safety ECGs, the triplicate ECG may be used for safety assessment.

9.4.14 Clinical Laboratory Evaluations

9.4.14.1 Clinical Chemistry, Hematology, and Urinalysis

Clinical laboratory evaluations will be performed locally as per the institutional standard of care.

Blood samples for analysis of the following clinical chemistry and hematological parameters and urine samples for urinalysis will be obtained as specified in the Schedules of Events (Appendix A).

Hematology

- Hemoglobin
- Hematocrit
- Platelet (count)
- Leukocytes with differential
- Neutrophils (ANC)

Coagulation

- Prothrombin time
- Activated partial thromboplastin time

Serum/Plasma Chemistry

- Blood urea nitrogen/urea
- Serum creatinine
- TBL
- Urate
- Phosphate
- Albumin
- ALP
- AST
- ALT
- Glucose
- Sodium
- Potassium
- Calcium
- Chloride
- Carbon dioxide
- Magnesium

Urinalysis

- pH
- Specific gravity
- Protein
- Ketones
- Bilirubin
- Occult blood
- Nitrite
- Urobilinogen
- Glucose
- Leukocytes

Hematology and serum chemistry samples may be taken up to 3 days prior to the visit, and coagulation testing and urinalysis may be conducted 24 hours prior to the visit. All results must be evaluated prior to dosing.

In order for a new cycle of treatment to begin, the patient's ANC must be ≥1500/mm^3, the platelet count must be ≥100,000/mm^3, and the patient's serum albumin level must be ≥3.0 g/dL.

Serum creatinine CL is to be estimated by the Cockcroft-Gault formula [57] as follows:

$$Estimated\ creatinine\ CL = [(140 - Age) * Mass(kg)\ ] / [72 * serum\ creatinine(mg/dL)]$$

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

As a backup creatinine CL can be determined based on 12 hours or 24 hours collection of urine specimen.

9.4.15 Disease Assessment

At screening, contrast-enhanced CT of thorax, abdomen, and pelvis should be performed. If an anatomic region cannot be adequately imaged by CT, MRI may be used instead. The same imaging modality utilized at screening for a particular site of disease must be used consistently throughout all subsequent disease assessments.

Objective assessments will be performed at screening, every 2 treatment cycles (42 days with a window of 3 days in advance), and at the EOT visit, as described in the Schedules of Events (Appendix A). Response assessment will be calendar-based regardless of treatment delays/interruptions. Objective assessments will be based on the modified RECIST criteria, version 1.1 (see Appendix G) [1]. When possible, the same qualified physician will interpret results to reduce variability. Radiographic images will be maintained at the site, and test results and physician's findings will be filed in patient source documents. In addition, all study images acquired for patients in part B and part C will be collected by a central imaging vendor and assessed in a blinded independent central review. The sites will transfer images to a central facility consistent with the guidance provided by the sponsor.

If the patient discontinues the study and has had a CT/MRI scan within 2 weeks of the EOT study visit, the CT/MRI scan does not need to be repeated.

9.4.16 Assessment of ^{89}Zr-TAK-164 PET Imaging (Part C, To Be Conducted in The Netherlands Only)

All PET/CT data will be reconstructed as described by Makris et al [58]. ^{89}Zr PET assessments will be performed under the supervision of a qualified nuclear medicine physician. Qualitative

uptake of ^{89}Zr-TAK-164 in tumor lesions will be described as present or absent above local background. Quantitative analysis will be performed to determine tissue uptake values expressed as SUV. The data will be reflective of the amount of TAK-164 administered and organ and tumor lesion(s) biodistribution and accumulation over time. SUV_{mean} will be reported for biodistribution to the different organs. Tumor target lesions will need to have a minimum diameter of 2 cm, to minimize potential partial volume effect, and must have a visual uptake above background activity. SUV mean, max, and peak will be reported for tumor lesions, with a maximum of 5 tumor lesions per organ/tumor site.

9.4.17 Assessment of ^{18}F-FDG-PET Imaging (Part C, To Be Conducted in The Netherlands Only)

Target lesions must have a minimum diameter of 1 cm on CT scan, to minimize potential partial volume effect, and must have an uptake above background activity. The background activity will be calculated in healthy liver tissue in a 3 × 3 cm VOI (using the following formula [1.5 × SUL_{mean} liver] + [2 × standard deviation SUL_{mean} liver]) or in the descending aorta in a 1 × 1 cm VOI (using the following formula (2 × SUL_{mean} descending thoracic aorta) + (2 × standard deviation SUL_{mean} descending thoracic aorta) in case of hepatic metastases according to Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) [59]. Tumor VOIs will be created manually and resized semiautomatically using a delineation tool that uses a 50% SUL_{peak} threshold with background correction.

At least 3 quantification units will be evaluated: SUL_{peak} within the tumor VOI (placed automatically to ensure that a sphere of approximately 1.2 cm diameter with the highest mean SUL will be captured), SUL_{max} (defined as the voxel with the highest SUL within the tumor VOI), metabolic tumor volume (MTV, this volume is defined with an isocontour VOI of 50% of SUL_{peak} with background correction), and TLG (defined as SUL_{mean} times MTV). Quantitative analysis of the PET images will be done for multiple tumor lesions (≤5 tumor lesions, ≤2 per organ) and for the metabolically most active target lesions per PET scan, as suggested in PERCIST [59].

9.4.18 Biomarker, PK, and Pharmacodynamic Samples

The primary specimen collection procedures are shown in Table 9.a. Additional handling and shipment of biomarker, PK, and pharmacodynamic samples are outlined in the laboratory manual.

Table 9.a TAK-164-1001: Primary Specimen Collection

Specimen Name in Schedule of Procedures	Primary Specimen	Primary Specimen Derivative 1	Description of Intended Use	Sample Collection
Fresh tumor tissue biopsy sample	Fresh tumor tissue	FFPE block FFPE slides	Biomarker measurements	• Mandatory if archival (banked) tumor tissue is not available. • Minimum of approximately 5 biopsy patients required for target engagement biomarker.
Archival (banked) tumor tissue sample [a]	FFPE block FFPE slides (unstained)	--	GCC evaluation and biomarker measurements	If not provided, patient must provide a fresh biopsy sample.
Buccal epithelial cells sample for DNA	Buccal DNA swab	DNA	Biomarker measurements	Mandatory
Serum sample for pharmacodynamics	Serum	--	Biomarker measurements	Mandatory
CCI				
Plasma sample for TAK-164 PK	Plasma	--	PK measurements	Mandatory
Plasma sample for FGN849 and s-FGN849	Plasma	--	PK measurements	Mandatory
Serum sample for immunogenicity	Serum	--	Immunogenicity evaluation	Mandatory
CCI				

FFPE: formalin-fixed paraffin-embedded; FGN849: free payload for TAK-164; GCC: guanylyl cyclase C; PK: pharmacokinetic; s-FGN849: sulfonated FGN849.
[a] A deidentified pathology report should be sent to the central lab with archival tumor tissue.
[b] Samples not collected for patients participating in part C.

9.4.18.1 Biomarker Samples

Blood samples will be collected via venipuncture or indwelling catheter at the time points detailed in the Schedules of Events (Appendix A) for concentration measurements of TAK-164 and biomarker assessments. The primary specimen collection is presented in Table 9.a.

Banked formalin-fixed paraffin-embedded tumor tissue or a minimum of 10 unstained slides of the tumor tissue (ie, tumor tissue obtained at the time of the patient's original diagnosis and/or at the time of subsequent procedures conducted as part of the patient's standard care) will be collected at screening to assess biomarkers implicated in the sensitivity or resistance to

TAK-164. The accompanying pathology report should be sent to the centralized testing lab. The tumor pathology block will be returned to the original site by the sponsor or designee. If the pathology block is not provided, submission of 10 unstained slides that have been immersed in paraffin after sectioning will be accepted. See the laboratory manual for details. Patients who cannot provide at least 10 histological slides from their diagnosis biopsy may undergo a new fresh tumor biopsy during screening (may be obtained up to 21 days prior to the first dose of study drug).

Effort should be made to take an additional optional biopsy when patients have relapsed. These samples are to be tested for the expression of GCC and other potential markers of tumor resistance.

In this study, several biomarkers will be assessed to test for correlation with safety CCI

[redacted]

9.4.18.2 PK Measurements

Serial plasma samples for PK analysis of TAK-164 will be collected during Cycle 1 Day 1 and Cycle 2 Day 1 of the 21-day dosing schedule. In addition, trough samples (ie, predose) will be collected at prespecified time points as described in the Schedules of Events (Appendix A). The primary purpose of collecting these samples is to measure the plasma concentrations of TAK-164 (conjugated and unconjugated antibody) and circulating plasma concentrations of FGN849 and s-FGN849 to characterize the PK of TAK-164, FGN849, and s-FGN849 after single- and multiple-dose administration. This information will also further inform the building of PK models to describe TAK-164 and FGN849 PK and such models will be used to predict TAK-164 and FGN849 plasma levels under different dosing scenarios to help select an appropriate dose/schedule of TAK-164. The dates and exact times of TAK-164 administration before collecting PK samples and the dates and exact times of postdose PK sample collections will be recorded in the eCRFs. These plasma samples may also be used for additional exploratory assessments if needed in the future.

9.4.18.3 Pharmacodynamic Measurements

Serum for Pharmacodynamic Measurement

Serum samples will be collected to monitor different pharmacodynamic biomarkers such as immune system response via cytokine/chemokine changes upon treatment. Collection of this sample will be at the time points described in the Schedules of Events (Appendix A). Instructions for processing and shipping of blood samples for serum pharmacodynamic measurements are provided in the laboratory manual.

Serum for Protein (Local) Measurements

Serum samples for protein will not be collected for patients participating in part C. For all other patients, samples will be collected to monitor changes in clinically established biomarkers such as carcinoembryonic antigen to assess relationship with clinical response. Collection of this sample will be at baseline (all cycles) and Day 8 (Cycle 2 only). Laboratory tests will be performed at the site.

CCI [redacted]

9.4.19 DNA Measurements

Buccal epithelial cells at baseline or at screening will be collected via swab as detailed in the Schedules of Events (Appendix A) as a germline control sample for DNA mutation analysis from banked tumor and/or fresh tumor biopsies.

9.4.20 Banked Tumor and/or Fresh Tumor Biopsy Specimen Measurements

GCC expression is evaluated by using IHC, as conducted by a central laboratory. An H-score will be used for GCC assessment and enrollment. Patients with GCC H-score ≥10 will be eligible for enrollment. An H-score ≥ 150 will be used for assigning patients to a GCC high group. In addition, status of MSI may be analyzed on banked tumor and/or fresh tumor biopsies. Collection of tumor biopsies at baseline and following treatment with TAK-164 is highly encouraged to monitor expression of GCC CCI [redacted]. A viable fresh baseline biopsy and a viable posttreatment biopsy will be collected during dose escalation in a minimum of approximately 5 patients participating in parts A and B, and approximately 3 patients participating in part C. A baseline biopsy and posttreatment biopsy will be collected to assess target engagement and the tumor microenvironment. The specific anatomical location of the biopsy before resection must be specified.

CCI [redacted]

9.4.22 Immunogenicity Sample Collection

Blood samples will be collected to evaluate immunogenicity as indicated in the Schedules of Events (Appendix A). Serum samples will then be prepared and analyzed in the validated ADA assays.

9.5 Completion of Study Treatment (for Individual Patients)

Patients will be considered to have completed study treatment if they complete 12 cycles of treatment with TAK-164, or if they experience PD. Patients will be considered to have completed study treatment if they discontinued study drug for any reason as outlined in Section 8.4.3.

9.6 Discontinuation of Treatment with Study Drug and Patient Replacement

Patients will be informed that they have the right to discontinue study treatment at any time for any reason, without prejudice to their medical care.

Treatment with study drug may be discontinued for any of the following reasons:

- AE.
- Protocol deviation.
- PD.
- Symptomatic deterioration.
- Study terminated by sponsor.
- Withdrawal by patient.
- Lost to follow-up.
- Other.

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

Patients who are withdrawn from treatment during Cycle 1 for reasons other than DLT will be replaced.

Note that some patients may discontinue study drug for reasons other than PD before completing the full treatment course; these will remain in the study for posttreatment assessments as outlined in the Schedules of Events (Appendix A) until PD occurs.

9.7 Study Compliance

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

9.8 Posttreatment Follow-up Assessments (PFS)

Patients who stop treatment for any reason other than PD will continue to be followed for PFS. The PFS follow-up visits, including imaging, should be conducted at the site every 3 months from last dose of study drug for up to 6 months or until PD, the start of alternative therapy, or conclusion of the study (whichever occurs first).

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

10.1.2 AE Definition

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

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

Disease progression should not be captured as an AE.

10.1.3 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, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events

include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 5, effective date 27 Nov 2017 [55]. 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 WBC count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.1.4 AESI Definition

An AESI is an AE of scientific and medical concern specific to the compound or program for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them, and instructions regarding how and when AESIs should be reported to Takeda are provided in Section 10.2 along with a list of AESIs.

10.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

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

If information not available at the time of the first report becomes available at a later date, then the investigator will transmit a follow-up EDC SAE report (or a paper-based SAE form if an EDC SAE report is not feasible) or provide other documentation immediately within 24 hours of

receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

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

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

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

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

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

AESI Reporting:

The below aminotransferase test results will be treated as AESIs.

- ALT or AST >3 × ULN.
- ALT or AST >ULN but ≤ 3 × ULN which cannot be explained by concomitant disease or another alternative etiology.

All AESIs will be reported to Takeda Global Pharmacovigilance in an expedited manner irrespective of the event's seriousness or causal relationship. Further, patients will be advised to promptly report signs and symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. The investigator must contact the medical monitor within 24 hours to discuss further management of the patient and refer to management of hepatotoxicity in Section 8.7.7.

10.3 Monitoring of AEs and Period of Observation

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

- AEs will be reported from the signing of informed consent through 30 days after administration of the last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first, and recorded in the eCRFs.
- SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the signing of informed consent through 30 days after administration of the last dose of study drug 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).

- AESIs will be reported and monitored in the same way as SAEs (see above).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by sending a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee. The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately 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.

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 below.

A medication error is a preventable event that involves an identifiable patient and that 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 phone numbers or email addresses provided below.

Call center	Phone number	Email	Fax
DLSS	1-844-662-8532 Non-toll-free number: 1-510-740-1273	GlobalOncologyMedinfo@takeda.com	1-800-881-6092

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or 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 European Medicines Agency, investigators, and IRBs or 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 an expedited report within 7 days for fatal and life-threatening events and 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, clinical endpoint committee, or adjudication committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. If selected for coding, AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities. Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 eCRFs

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

The sponsor or its designee will supply investigative sites with access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, 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 designees) 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 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 its designee will be permitted to review the patient's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

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

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator and the head of the institution 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 prior to database lock for the final analysis. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

Deviations from the statistical analyses outlined in this protocol will be indicated in the SAP; any further modifications will be noted in the final clinical study report (part A and part B). Part C analyses will be reported in a clinical study report addendum.

13.1.1 Dose Escalation (Part A)

The mTPI study design by Ji [2] will be utilized to determine MTD. The mTPI design is based on p_T for each dose level. These probabilities are sequentially updated with the data generated by DLT of each cohort beginning with the initial dose (dose level 1) and each subsequent cohort of patient.

Decision rules at each step are based on calculating the UPM of 3 intervals corresponding to underdosing, proper dosing, and overdosing a patient, in terms of toxicity. Specifically, the underdosing interval is defined as $(0, p_T - \varepsilon_1)$, the overdosing interval as $(p_T + \varepsilon_2, 1)$, and the proper dosing interval as $(p_T - \varepsilon_1, p_T + \varepsilon_2)$, where ε_1 and ε_1 are small fractions to account for the uncertainty around the true target toxicity. In this study, p_T is targeted at 25%, $\varepsilon_1, \varepsilon_2$ are both 5% to account for uncertainty.

The 3 dosing intervals are associated with 3 different dose escalation decisions. The underdosing interval corresponds to a dose escalation (E), overdosing corresponds to a dose de-escalation (D), and proper dosing corresponds to staying at the current dose (S). Given an interval and a probability distribution, the UPM of that interval is defined as the probability of the interval divided by the length of the interval. The mTPI design calculates the UPMs for the 3 dosing intervals, and the one with the largest UPM implies the corresponding dose-finding decision. That decision provides the dose level to be used for future patients. Approximately 25 patients will be enrolled. The enrollment in part A will be stopped when prespecified sample size of 25 patients is reached, unless recommended otherwise based on clinical judgment, as discussed with the sponsor and the investigators. The mTPI dosing schema will maximize patients treated at or near the MTD and the MTD will be determined by using an isotonic regression to fit a function of observed probabilities of DLT at each dose level in this trial. Excessive toxicity (probability of DLT level exceeds 25% is greater than 95%) will prevent the escalation to next or higher dose levels and early termination of part A.

Assumptions upon which the mTPI design will be operating include an acceptable DLT rate of 25% based on preliminary data of TAK-164 as a single agent. As discussed above, approximately 25 patients will be dosed from starting dose using the Q3W schedule. The schedule will follow the same dose schema and mTPI table using different starting doses.

Simulation to evaluate the operating characteristics of mTPI was performed based on the proposed dose levels. Four scenarios of the assumed true DLT rates at each dose level were included to represent various distributions of toxicity. Average cohort size of 2 was used. Simulation was performed 5000 iterations for each scenario. Scenario details are shown in Table 13.a.

Table 13.a TAK-164-1001: Scenarios With Simulated True DLT Rate at Each Dose Level

	Proposed Dose Levels (mg/kg)							
	0.004	**0.008**	**0.016**	**0.032**	**0.045**	**0.060**	**0.080**	**0.106**
Scenario	**Simulated True DLT Rate Observed at Each Dose Level**							
1	0.01	0.02	0.03	0.04	0.05	0.25	0.5	0.6
2	0.05	0.15	0.25	0.3	0.35	0.4	0.6	0.8
3	0.15	0.18	0.2	0.23	0.27	0.3	0.3	0.35
4	0.05	0.2	0.3	0.45	0.6	0.8	0.9	0.95

DLT: dose-limiting toxicity.

Simulation results for scenario 1 are shown in Table 13.b for illustrative purposes. Under this scenario, MTD is selected at dose level 0.060 mg/kg, with probability of 56.4%.

Table 13.b TAK-164-1001: Simulation Results of Scenario 1

Target Toxicity Prob. = 0.25		**Selection Prob.**	**# of Patients Treated**	**# of Toxicities**
Dose Level (mg/kg)	**True Tox Prob.**	**mTPI**	**mTPI**	**mTPI**
0.004	0.01	0	2.1	0
0.008	0.02	0	2.3	0
0.016	0.03	0.3%	2.5	0.1
0.032	0.04	1.1%	2.6	0.1
0.045	0.05	33.5%	4.2	0.2
0.060	0.25	56.4%	8.3	2.1
0.080	0.5	8.3%	3.4	1.7
0.106	0.6	0.4%	0.7	0.4

mTPI: modified toxicity probability interval; Prob: probability; Tox: toxicity.

Individual scenario results are not included further, while summarized simulation results are shown in Table 13.c. Probabilities of selecting the true MTD are 49.9% - 82.5%. The probabilities of selecting dose-over-MTD or no selection are generally low with 4.5% to 13.1% and 0% to 3.9%.

Table 13.c TAK-164-1001: Operating Characteristics for Dose Escalation using mTPI

Scenario	MTD Selection Prob (%)	Toxicity Prob (%)	Select Dose-over-MTD Prob (%)	No Selection Prob (%)
1	56.4	17.8	8.7	0
2	49.9	21.9	13.1	0.1
3	51.5	20.6	8.4	3.9
4	82.5	23.0	4.5	0.1

MTD: maximum tolerated dose; mTPI: modified toxicity probability interval; Prob: probability.

13.1.2 Dose Expansion (Part B)

Up to 50 patients with CRC, which includes GCC high expression level (H-score ≥150) and patients with gastric carcinoma (H-score ≥10) will be assessed. A minimum of approximately 20 patients will be enrolled in either cohort.

Analysis sets that may be used are defined as below:

Safety analysis set: Patients who receive at least 1 dose of TAK-164. The safety analysis set will be used for safety analyses.

DLT analysis set: Patients who complete Cycle 1 or experience a DLT in Cycle 1. The DLT analysis set will be used to determine the MTD.

Response-Evaluable analysis set: Patients who receive at least 1 dose of TAK-164, have measurable disease at baseline based on modified RECIST, version 1.1 [1], and at least 1 postbaseline response assessment.

Plasma PK analysis set: Patients with sufficient dosing and PK data to reliably estimate PK parameters will be used for PK analyses.

Pharmacodynamic analysis set: Patients who receive at least 1 dose of TAK-164 and at least 1 target engagement biomarker assessment.

Immunogenicity-Evaluable analysis set: Analysis will be based on available data from patients with a baseline assessment and at least 1 postbaseline immunogenicity assessment.

13.1.3 Imaging Substudy (Part C, To Be Conducted in The Netherlands Only)

The imaging analysis set includes patients with at least one ^{89}Zr-TAK-164 PET scan. Results of ^{89}Zr-TAK-164 PET and ^{18}F-FDG-PET scan will be summarized using descriptive statistics for the total analysis set or by baseline, dose, and disease characteristics.

All patients who receive any amount of ^{89}Zr-TAK-164 will be included in the safety analyses. Safety will be assessed with summaries of AEs, changes in laboratory test results, and changes in vital signs. The in vivo biodistribution and tumor targeting of ^{89}Zr-TAK-164 will be evaluated using summary statistics of SUV by organ/tumor lesion, TAK-164 dose, and imaging time point.

Correlations between imaging variables, pharmacodynamic markers, and clinical response will be explored.

Efficacy endpoints will be summarized, and the correlation with imaging outputs may be explored. The results of part C will be summarized in a clinical study report addendum.

13.1.4 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by dose levels of TAK-164, expansion cohorts, and substudy part C. Data to be evaluated will include at least age, sex, race, weight, height, GCC score, etc. Components of disease severity assessment in additional to relevant patient and disease assessments and laboratory parameters will be presented if appropriate.

13.1.5 Efficacy Analysis

Assessment of tumor response will be according to modified RECIST, version 1.1 [1].

Dose Escalation (Part A)

There is no efficacy endpoint in the dose escalation portion of the study.

Patients with overall response in the dose escalation will be presented in a listing.

Dose Expansion (Part B)

Efficacy endpoints for the dose expansion includes ORR, defined as CR + PR. The estimate of ORR will be presented with 2-sided 80% exact binomial CIs for overall and patients of each cohort. The number and percentage of patients in each response category will be tabulated for overall and patients of each cohort. ORR will be analyzed based on the response-evaluable analysis set.

Efficacy analyses in part B also include DCR (CR+PR+SD), PFS, and DOR. DCR is defined as CR+PR+SD. The estimate of the DCR will be presented with 2-sided 80% exact binomial confidence intervals (CIs) for overall and patients of each cohort. The number and percentage of patients in each response category will be tabulated for each treatment arm based on RECIST, version 1.1 [1]. DCR will be analyzed based on the response-evaluable analysis set.

PFS is defined as the time from the date of the first dose TAK-164 to the date of first documentation of PD or death due to any cause, whichever occurs first. The censoring method will be described in the SAP. PFS will be tested based on the safety analysis set. The Kaplan-Meier survival curves, 25th, 50th (median), and 75th percentiles (if estimable), along with their 2-sided 95% CIs, will also be provided for overall patients or each cohort, if applicable.

DOR is defined as the time from the date of first documentation of a response to the date of first documentation of PD or death, whichever is earlier. Patients without documentation of PD or death at the time of analysis will be censored at the date of their last response assessment that is SD or better.

DOR will be analyzed using the Kaplan-Meier method for overall and patients of or each cohort, if applicable, along with their 2-sided 95% CIs, will also be provided for all patients or each cohort, if applicable. DOR will be analyzed based on the responders in the Response-Evaluable analysis set.

In the imaging substudy (part C), efficacy endpoints are assessed. Patient efficacy will be summarized, and the correlation with imaging outputs may be explored.

Further details of the efficacy analysis can be found in the SAP.

13.1.6 PK Analysis

PK Analysis

Individual and mean plasma concentration data will be plotted over time. Descriptive statistics will be presented for plasma PK parameters including (but not limited to) C_{max}, t_{max}, area under the plasma concentration versus time curve from time 0 to time t (AUC_t), area under the concentration-time curve from time 0 to infinity (AUC_{inf}), $t_{1/2}$, CL, V_d, etc.

PK data collected in this study are intended to additionally contribute to population PK modeling. These models may be used to predict TAK-164 PK in different dosing scenarios to further support the selection of a recommended phase-2 dose of TAK-164. The population PK analyses may include data collected in additional TAK-164 clinical studies. The analysis plan for population PK modeling will be separately developed and the results of such modeling will not be presented in the clinical study report for this study but will be presented in a separate report.

PK/QTcF Analysis

The relationship between plasma TAK-164 concentration and QTcF interval will be analyzed using mixed effects modeling based on centrally over-read ECG interval data. It is expected that the relationship between plasma TAK-164 concentrations and change from baseline (predose) values of QTcF will be described using a direct linear concentration-effect relationship; however, the selection of the final model and mathematical form of the concentration-effect relationship will be based on graphical assessment of the data (eg, visual examination of observed concentration-effect plots to rule out a hysteresis secondary to time-delayed effects on QTcF) and exploration of alternate structural models (eg, maximum effect attributed to the drug models). The analysis plan for the PK-QTcF modeling will be developed separately and the results of this analysis may not be included in the clinical study report for this study but will be presented in a separate report.

13.1.7 Biomarker Analysis

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[redacted]

13.1.8 Immunogenicity Analyses

The proportion of patients with positive ADA (transient and persistent, titer, and specificity) during the study will be summarized. The effect of immunogenicity on PK, and safety will be examined.

Analysis will be based on available data from patients with a baseline assessment and at least 1 postbaseline immunogenicity assessment. Summaries will be provided separately for each study phase and by dose, as applicable. The incidence of immunogenicity will be calculated. The impact of anti–TAK-164 antibodies on the PK profile, pharmacodynamic profile, and clinical safety will be evaluated, if possible.

13.1.9 Safety Analysis

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the safety population. Exposure to study treatment and reasons for discontinuation will be tabulated.

Treatment-emergent adverse events (TEAEs) that occur after administration of the first dose of study drug and through 30 days after the last dose of study drug will be tabulated.

AEs will be tabulated according to the Medical Dictionary for Regulatory Activities and will include the following categories:

- DLTs.
- TEAEs.
- Grade 3 or higher TEAEs.
- Drug-related TEAEs.
- Grade 3 or higher, drug-related, TEAEs.
- SAEs.
- TEAEs leading to dose reduction.
- TEAEs leading to discontinuation.
- Abnormal laboratory tests.
- Abnormal vital sign measurements.

A listing of TEAEs resulting in study drug discontinuation will be provided.

Additional safety analyses may be determined at any time without prejudice to most clearly enumerate rates of toxicities and to further define the safety profile of study drugs.

13.2 Interim Analysis and Criteria for Early Termination

No formal interim analysis is planned for this study.

13.3 Determination of Sample Size

It is anticipated that approximately 100 patients will be enrolled, combining dose escalation for determination of MTD and/or RP2D in part A and dose expansion in part B, as well as up to 25 additional patients will be enrolled in part C imaging substudy.

The mTPI will be used for dose escalation as detailed in Section 8.3. Approximately 25 patients with Q3W schedules will be enrolled during part A.

In part B, the sample size is estimated for CRC and gastric cancer separately. For CRC, assuming a targeted ORR of 16% with a 2-sided exact 80% CI such that the lower limit is greater than 5%, approximately 25 response-evaluable patients will provide close to 60% power to observe at least 4 responses, ie, 4/25 = 16%; exact 80% CI (7.2%, 29.5%). For gastric cancer, assuming a targeted ORR of 20% with a 2-sided exact 80% CI such that the lower limit is greater than 10%, approximately 25 response-evaluable patients will provide close to 60% power to observe at least 5 responses, ie, 5/25 = 20%; exact 80% CI (10.1%, 34.0%). Approximately 50 response-evaluable patients in total need to be enrolled in part B. Additional patients may be enrolled based on clinical judgment and the totality of clinical outcomes may be considered.

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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. 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 (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, patient medical records, informed consent documentation, documentation of patient authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that 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 EC, 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 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 FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should

be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, patients) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix 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 state and federal/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 due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the 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/or 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 exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives notification no protocol activities, including screening may occur.

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

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

15.2 Patient Information, Informed Consent, and Patient Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the patient's personal and personal health information for purposes of conducting the study. The ICF and the patient information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and if applicable, the patient authorization form. The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to 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. In the event the patient is not capable of rendering adequate written informed consent, then the patient's legally acceptable representative may provide such consent for the patient in accordance with applicable laws and regulations.

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

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

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

15.3 Patient Confidentiality

The sponsor and designees affirm and uphold the principle of the patient's right to protection against invasion of privacy. Throughout this study, a patient's source data will only be linked to the sponsor's clinical study database or documentation 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, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the patient's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a patient's study participation, and autopsy reports. Access to a patient's original medical records requires the specific authorization of the patient as part of the informed consent process (see Section 15.2).

Copies of any patient source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, patient name, address, and other identifier fields not collected on the patient's [e]CRF).

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/or 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

In order 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 in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

As needed, Takeda and Investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Takeda may assist participants or potential participants to find 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 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 or other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.4.4 Data Sharing

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

15.5 Insurance and Compensation for Injury

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

16.0 REFERENCES

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Appendix A Schedules of Events [21-Day Cycle - Q3W Schedule]

Table A-1 Schedule of Events for Parts A and B – Cycles 1 and 2

	Screening	Cycles 1 and 2							
	Day -21 to Day -1	Day 1 Predose	Day 1 Postdose	Day 2	Days 3 and 4	Day 8	Day 15	Day 21	EOT [a]
Informed Consent [b]	X								
Inclusion/Exclusion Review	X								
Demographics	X								
Medical History	X								
Complete Physical Examination	X								X
Symptom-Directed Physical Examination		X							
Height	X								
Weight		X				X	X		
ECOG Performance Status	X	X					X		X
Vital Signs	X	X	X [c]			X	X		X
Pregnancy Test [d]	X	X							X
TAK-164 Administration		X							
Concomitant Medications and Procedures	Concomitant medications and procedures will be recorded (eCRF) from signing of the ICF through the EOT visit or the start of subsequent antineoplastic therapy, whichever occurs first.								
AEs	AEs will be recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.								
SAEs, AESIs	SAEs and AESIs will be reported from signing of ICF through 30 days after last dose of study drug even if the patient starts nonprotocol therapy.								
12-Lead ECG [e]	X	X	X	X	X	X	X		
Echocardiography (LVEF)	X [f]								

Continued on next page.

	Screening	Cycles 1 and 2							
	Day -21 to Day -1	**Day 1 Predose**	**Day 1 Postdose**	**Day 2**	**Days 3 and 4**	**Day 8**	**Day 15**	**Day 21**	**EOT [a]**
Samples/Laboratory Assessments									
Hematology	X	X [g]				X [g]	X [g]		X
Chemistry	X	X [g]				X [g]	X [g]		X
Coagulation	X	X [h]				X	X		X
Urinalysis	X	X [h]							X
Disease Assessment (CT/MRI Scan/RECIST)	X							X [i]	X
CCI [redacted]									

AE: adverse event; AESI: adverse event of special interest; ANC: absolute neutrophil count; CT: computed tomography; CCI [redacted]; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; eCRF: electronic case report form; EOT: End of Treatment; GCC: guanylyl cyclase C; ICF: informed consent form; LVEF: left ventricular ejection fraction; MRI: magnetic resonance imaging; PK: pharmacokinetic; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: serious adverse event.

[a] The EOT visit will occur approximately 30 days after the last dose of study drug or prior to the start of subsequent antineoplastic therapy.

[b] Informed consent may be obtained prior to the start of the screening period (Day -21). A separate consent may be obtained for the release of archival tumor tissue for the evaluation of GCC expression prior to screening.

[c] Vital signs will be obtained on Day 1 at 5 and 15 minutes after start of infusion, and upon completion of the infusion for Cycles 1 and 2 (and the following cycles). Every effort should be made to obtain vital signs according to these time points. However, a ±3-minute window is acceptable.

[d] A serum pregnancy test will be obtained for women of childbearing potential at screening and at EOT. The screening results must be available and negative prior to enrollment. A urine pregnancy test will be obtained for women of childbearing potential on Day 1 of every cycle and a negative result must be confirmed prior to dosing. Pregnancy tests may also be repeated during the study if requested by an IEC/IRB or if required by local regulations.

[e] A single 12 lead ECG will be collected at screening to assess eligibility. Triplicate 12-lead ECG recordings will be required at the time points specified in Table A-4 and Table A-5 for part A and B, respectively. See Section 9.4.13 for details.

[f] LVEFs will be performed during the screening period and every 4 cycles (Cycles 4, 8, and 12, etc).

[g] Samples may be taken up to 3 days prior to visit. Results must be evaluated prior to dosing. In order for a new cycle of treatment to begin, the patient's ANC must be ≥1500/mm^3 and the platelet count must be ≥100,000/mm^3, and the patient's serum albumin level must be ≥3.0 g/dL.

[h] May be taken up to 24 hours prior to visit. Results must be evaluated prior to dosing.

[I] RECIST response assessments will be performed at screening, every 2 treatment cycles (42 days with a window of 3 days in advance), and at the EOT visit. Response assessment will be calendar-based regardless of treatment delays/interruptions. If the patient discontinues the study and has had a CT/MRI scan within 2 weeks of the EOT study visit, the CT/MRI scan does not need to be repeated. Every effort should be made to maintain the same imaging modality (CT or MRI) throughout the study in each individual patient.

[j] CCI [redacted]

Table A-2 Schedule of Events for Parts A and B – Cycles 3+

	Subsequent Cycles (Cycles 3+)				
	Day 1 Predose	**Day 1 Postdose**	**Day 21 (±3 days)**	**EOT [a]**	**PFS FU**
Complete Physical Examination				X	X
Symptom-Directed Physical Examination	X				
Weight	X				
ECOG Performance Status	X			X	X
Vital Signs	X	X [b]		X	X
Pregnancy Test [c]	X			X	
TAK-164 Administration	X [d]				
Concomitant Medications and Procedures	Concomitant medications and procedures will be recorded (eCRF) from signing of the ICF through the EOT visit or the start of subsequent antineoplastic therapy, whichever occurs first.				
AEs	AEs will be recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.				
SAEs, AESIs	SAEs and AESIs will be reported from signing of ICF through 30 days after last dose of study drug even if the patient starts nonprotocol therapy.				
12-Lead ECG [e]	X	X			
Echocardiography (LVEF)			X [f]		
Samples/Laboratory Assessments					
Hematology	X [g]			X	X
Chemistry	X [g]			X	
Coagulation	X [h]			X	
Urinalysis	X [h]			X	
Disease Assessment (CT/MRI Scan/RECIST)			X [i]	X	X
Biomarker/PK Sample Collection [j]	X	X		X	

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AE: adverse event; AESI: adverse event of special interest; ANC: absolute neutrophil count; CT: computed axial tomography; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; eCRF: electronic case report form; EOT: End-of-Treatment; FU: follow-up; ICF: informed consent form; LVEF: left ventricular ejection fraction; MRI: magnetic resonance imaging; PFS: Posttreatment Follow-up Assessments; PK: pharmacokinetic; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: serious adverse events.

[a] The EOT visit will occur approximately 30 days after the last dose of study drug or prior to the start of subsequent antineoplastic therapy.

[b] Vital signs will be obtained on Day 1 at 5 and 15 minutes after start of infusion, and upon completion of the infusion for Cycles 3 and beyond. Every effort should be made to obtain vital signs according to these time points. However, a ± 3-minute window is acceptable.

[c] A serum pregnancy test will be obtained for women of childbearing potential at screening and at EOT. The screening results must be available and negative prior to enrollment. A urine pregnancy test will be obtained for women of childbearing potential on Day 1 of every cycle and a negative result must be confirmed prior to dosing. Pregnancy tests may also be repeated during the study if requested by an IEC/IRB or if required by local regulations.

[d] A window of ±3 days will be permitted.

[e] Triplicate 12-lead ECG recordings will be required at the time points specified in Table A-4 and Table A-5 for part A and B, respectively. Beginning Cycle 6, a single 12-lead ECG is required predose. Patients should be in supine rest position for at least 5 minutes before the initiation of the ECG(s).

[f] LVEFs will be performed during the screening period and every 4 cycles (Cycles 4, 8, and 12, etc.).

[g] Samples may be taken up to 3 days prior to visit. Results must be evaluated prior to dosing. For a new cycle of treatment to begin, the patient's ANC must be $\geq 1500/mm^3$ and the platelet count must be $\geq 100{,}000/mm^3$, and the patient's serum albumin level must be ≥3.0 g/dL.

[h] May be taken up to 24 hours prior to visit. Results must be evaluated prior to dosing.

[i] RECIST response assessments will be performed at screening, every 2 treatment cycles (42 days with a window of 3 days in advance), and at the EOT visit. Response assessment will be calendar-based regardless of treatment delays/interruptions. If the patient discontinues the study and has had a CT/MRI scan within 2 weeks of the EOT study visit, the CT/MRI scan does not need to be repeated.

[j] Refer to Table A-3, Table A-4, and Table A-5 for full details on the part A and B Biomarker/ PK sample collection schema.

Table A-3 Biomarker Sample Collection for Parts A and B

	Screening	Cycles 1 and 2							Cycles 3+		
	Day -21 to Day -1	Day 1 Predose	Day 1 Postdose	Day 2	Day 3	Day 4	Day 8	Day 15	Day 1 Predose	Day 1 Postdose	EOT [a]
Fresh Tumor Tissue Biopsy sample [b]	X [c]						X [c,d]				X [b]
Archival (Banked) Tumor Tissue Sample [e]	X										
Buccal Epithelial Cells Sample for DNA		X [f]									
Serum Sample for Pharmacodynamics		X					X		X [g]		X
Serum Sample for Protein (Local)		X					X [h]		X [i]		
CCI [redacted]											
Plasma Sample for TAK-164 PK [k]		X	X	X [l]	X [l]	X [l]	X	X	X	X	
Plasma Sample for FGN849 and s-FGN849 PK [k]		X	X	X [l]	X [l]	X [l]	X	X	X	X	
CCI [redacted]											
Serum Sample for Immunogenicity		X [n]						X [n]	X [n]		X

Continued on next page.

ADA: antidrug antibody; CCI [redacted]; EOT: end-of-treatment; FGN849: free payload for TAK-164; GCC: guanylyl cyclase C; IHC: immunohistochemistry; PK: pharmacokinetics; s FGN849: sulfonated FGN849.

[a] The EOT visit will occur approximately 30 days after the last dose of study drug or prior to the start of subsequent antineoplastic therapy.

[b] Fresh tumor biopsies may be collected from consenting patients who achieve at least a partial response and then subsequently relapse, if considered advisable by the treating physician. Optionally, tumor biopsies from consenting patients who do not achieve a response and experience progression could be collected also, if considered advisable by the treating physician.

[c] Paired tumor tissue biopsies (pre- and postdose) are required in a minimum of approximately 5 patients. The specific anatomical location of the biopsy before resection must be specified.

[d] Cycle 2 Day 8 (+4 days) only.

[e] If archival tissue is not available for GCC evaluation by IHC, as assessed by a central laboratory, the patient may consent to provide biopsy tissue.

[f] Cycle 1 only.

[g] Cycle 3 only.

[h] Cycle 2 only.

[i] To be taken on Cycle 3 and then every other cycle after (Cycle 5, Cycle 7, etc).

[j] Cycle 5 only.

[k] PK blood draws will be performed according to the schedule presented in Table A-4 and Table A-5 for part A and B, respectively.

[l] Applicable to part A, only.

[m] CCI [redacted].

[n] ADA samples are taken predose on Day 1 of every cycle; an additional Day 15 sample will be taken for Cycle 1 only (no other cycles).

Table A-4 Serial PK and ECG Collection Schedule for Part A

Cycle 1 And Cycle 2	Day 1		Day 2		Day 3		Day 4		Day 8		Day 15	
	Triplicate ECG [a,b]	PK [c]	Triplicate ECG [a,b]	PK [c]	Triplicate ECG [a,b]	PK [c]	Triplicate ECG [a,b]	PK [c]	Triplicate ECG [a,b]	PK [c]	Triplicate ECG [a,b,d]	PK [c,d]
Predose (within 60 min before start of infusion)	X3	X1										
EOI [e]	X3	X1										
1 hour after EOI (±10 min)	X3	X1										
2 hours after EOI (±20 min)	X3	X1										
4 hours after EOI (±30 min)	X3	X1										
6 hours after EOI (±30 min)	X3	X1										
24 hours after EOI (±2 hour)			X3	X1								
48 hours after EOI (±2 hour)					X3	X1						
72 hours after EOI (±4 hour)							X3	X1				
168 hours after EOI (±6 hour)									X3	X1		
336 hours after EOI (±6 hour)											X3	X1
Cycle 3 and Beyond												
Predose (within 60 min before start of infusion)	X3 [f]	X1										
EOI [e]	X3 [f]	X1										

Continued on next page.

ECG: electrocardiogram; EOI: end of infusion; FGN849: free payload for TAK-164; PK: pharmacokinetic; s-FGN849: sulfonated FGN849.
[a] Triplicate 12-lead ECG measurements are to be performed with the patient in supine position. Patients should have been in supine rest position for at least 5 minutes prior to initiation of ECG collections. Each ECG measurement of the triplicate collection should be recorded at 2- to 3-minute intervals.
When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample. The triplicate ECG measurements should be completed immediately before the corresponding PK blood draw.
[b] The triplicate ECG collections can also be used as safety ECGs when the collections times for these ECGs coincide.
[c] Blood samples for plasma sample for TAK-164, FGN849, and s-FGN849 PK should be taken from the contralateral arm to that used for the TAK-164 infusion. Refer to laboratory manual for further instructions.
[d] Triplicate ECG and PK collections of Cycle 1 Day 15 and Cycle 2 Day 15 correspond to 336 hours after Cycle 1 Day 1 and Cycle 2 Day 1 infusions, respectively.
[e] At EOI, the collection of triplicate ECG should be initiated within 5 min prior to completion of TAK-164 infusion (i.e. not 5 min prior to EOI line flush). Each triplicate ECG should be collected at 2-3 min intervals with all 3 ECGs collected within a total 10 min window (i.e.,5 min prior to completion of TAK-164 infusion and 5 min after completion of TAK-164 infusion). The EOI PK sample should be collected immediately after the third ECG has been collected. EOI PK is in relation to TAK-164 infusion and not infusion line flush.
[f] Triplicate ECGs on Cycle 3 and beyond will be collected up to and including Cycle 5.

Table A-5 Part B Sparse PK and ECG Collection

	Day 1		Day 8		Day 15	
Cycle 1 and Cycle 2	**Triplicate ECG [a,b]**	**PK [c]**	**Triplicate ECG [a,b]**	**PK [c]**	**Triplicate ECG [a,b,d]**	**PK [c,d]**
Predose (within 60 min before start of infusion)	X3	X1				
EOI [e]	X3	X1				
1-2 hours after EOI	X3	X1				
168 hours after EOI (±6 h)			X3	X1		
336 hours after EOI (±6 h)					X3	X1
Cycle 3 and Beyond						
Predose (within 60 min before start of infusion)	X3 [f]	X1				
EOI [e]	X3 [f]	X1				

ECG: electrocardiogram; EOI: end of infusion; IV: intravenous; PK: pharmacokinetics.
When TAK164 is administered via a peripheral vein, blood samples for PK should be collected from the arm contralateral (ie, opposite) to the arm used for IV infusion.
When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample.
The triplicate ECG measurements should be completed immediately before the corresponding PK blood draw.
[a] Triplicate 12-lead ECG measurements are to be performed with the patient in supine position. Patients should have been in supine rest position for at least 5 min before initiation of ECG collections. Each ECG measurement of the triplicate collection should be recorded at 2- to 3-minute intervals.
[b] The triplicate ECG collections can also be used as safety ECGs when the collections times for these ECGs coincide.
[c] Blood samples for PK should be taken from the contralateral arm to that used for the TAK-164 infusion. Refer to laboratory manual for further instructions.
[d] Triplicate ECG and PK collections of Cycle 1 Day 15 and Cycle 2 Day 15 correspond to 336 hours after Cycle 1 Day 1 and Cycle 2 Day 1 infusions, respectively.
[e] At EOI, the collection of triplicate ECG should be initiated within 5 min prior to completion of TAK-164 infusion (i.e. **not** 5 min prior to EOI line flush). Each triplicate ECG should be collected at 2-3 min intervals with all 3 ECGs collected within a total 10 min window (i.e., 5 min prior to completion of TAK-164 infusion and 5 min after completion of TAK-164 infusion). The EOI PK sample should be collected immediately after the third ECG has been collected. EOI PK is in relation to TAK-164 infusion and **not** infusion line flush.
[f] Triplicate ECGs on Cycle 3 and beyond will be collected up to and including Cycle 5.

Table A-6 Part C (Imaging Substudy, DIO Patients Only) Schedule of Events for 14-Day Run-in Period

	Screening		Run-in Period: Day -14 to Day -1			
	Day -21 to Day -15	Day -14 Predose	Day -14 Postdose	Day -12 (-13 to -11)	Day -10 (-10 to -8)	Day -7
Informed consent [a]	X					
Inclusion/exclusion review	X					
Demographics	X					
Medical history	X					
Complete physical exam	X					
Symptom-directed physical exam		X				
Height	X					
Weight		X				X
ECOG performance status	X	X				
Vital signs	X	X	X [b]			X
Pregnancy test [c]	X	X				
^{89}Zr-TAK-164 administration		X [d]				
Concomitant medications and procedures	Concomitant medications and procedures will be recorded (eCRF) from signing of the ICF through the EOT visit or the start of subsequent antineoplastic therapy, whichever occurs first.					
AEs	AEs will be recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.					
SAEs, AESIs	SAEs and AESIs will be reported from signing of the ICF through 30 days after last dose of study drug even if the patient starts nonprotocol therapy.					
12-Lead ECG [e]	X	X	X			
^{89}Zr-TAK-164 PET scan			X [f]	X [g]	X [g]	
^{18}F-FDG-PET [h]	X					
Disease assessment (CT/MRI scan/RECIST)	X					
Hematology	X	X [i]				X [i]
Chemistry	X	X [i]				X [i]

	Screening		Run-in Period: Day -14 to Day -1			
	Day -21 to Day -15	**Day -14 Predose**	**Day -14 Postdose**	**Day -12 (-13 to -11)**	**Day -10 (-10 to -8)**	**Day -7**
Coagulation	X	X [J]				X [J]
Urinalysis	X	X [J]				
Archival (banked) tumor tissue sample	X [k]					
Fresh Tumor Tissue Biopsy sample	X [k]					
Buccal Epithelial Cells Sample for DNA	X					
Serum sample for Pharmacodynamics		X				
CCI						
Plasma sample for TAK-164 PK [l]		X	X	X	X	
Plasma sample for FGN849 and s-FGN849 PK [l]		X	X	X	X	

[18]F-FDG: 18-fluorodeoxyglucose; [89]Zr: zirconium-89; AE: adverse event; AESI: adverse event of special interest; CT: computed tomography; DIO: dosimetry and imaging optimization; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; eCRF: electronic case report form; EOT: End-of-Treatment; FGN849: free payload for TAK-164; GCC: guanylyl cyclase C; ICF: informed consent form; IHC: immunohistochemistry; MRI: magnetic resonance imaging; PET: positron emission tomography; PK: pharmacokinetic; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: serious adverse event; s-FGN849; sulfonated free payload for TAK-164.

[a] Informed consent may be obtained before the start of the screening period (Day -21). A separate consent may be obtained for the release of archival tumor tissue for the evaluation of GCC expression before screening.

[b] Vital signs will be obtained on Day -14 at 5 and 15 minutes after start of infusion, and upon completion of the infusion. Every effort should be made to obtain vital signs according to these time points; however, a ±3-minute window is acceptable.

[c] A serum pregnancy test will be obtained for women of childbearing potential at screening and at EOT. The screening results must be available and negative before enrollment. A urine pregnancy test will be obtained for women of childbearing potential on Day -14, and a negative result must be confirmed before dosing. Pregnancy tests may also be repeated during the study if requested by an independent ethics committee/institutional review board or if required by local regulations.

[d] [89]Zr-labeled TAK-164. Record infusion start and stop times and amount of administered in eCRF.

[e] A single 12-lead ECG will be collected at screening to assess eligibility. Triplicate 12-lead ECG recordings will be required at the time points specified in Table A-10.

[f] 1 hour after the EOI of the [89]Zr-labeled TAK-164. Dosimetry patients only.

[g] Imaging window maybe adjusted for imaging optimization purposes.

[h] Patients are required to fast for 6 hours before the FDG radiotracer injection.

[i] Samples may be taken ≤3 days before visit.

[j] May be taken ≤24 hours before visit. Results must be evaluated before dosing.

[k] If archival tissue is not available for GCC evaluation by IHC as assessed by a central laboratory, the patient may consent to provide biopsy tissue.

[l] Refer to Table A-10 for full details on the PK sample collection scheme.

Table A-7 Part C (Imaging Substudy) Schedule of Events for Cycle 1

	Screening [f]		Cycle 1						
	Day -21 to Day -1	Day 1 Predose	Day 1 Postdose	Day 3 (Day 2 to Day 4)	Day 5 (Day 5 to Day 7)	Day 8	Day 15	EOT [a]	PFS FU [b]
Informed consent [c]	X [d]								
Inclusion/exclusion review	X [d]								
Demographics	X [d]								
Medical history	X [d]								
Complete physical exam	X [d]							X	X
Symptom-directed physical exam		X							
Height	X [d]								
Weight		X				X	X		
ECOG performance status	X	X					X	X	X
Vital signs	X	X	X [e]		X	X	X	X	X
Pregnancy test [f]	X	X						X	
^{89}Zr-TAK-164 administration		X [g]							
TAK-164 administration		X [h]			X [i]				
Concomitant medications and procedures	Concomitant medications and procedures will be recorded (eCRF) from signing of the ICF through the EOT visit or the start of subsequent antineoplastic therapy, whichever occurs first.								
AEs	AEs will be recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.								
SAEs, AESIs	SAEs and AESIs will be reported from signing of ICF through 30 days after last dose of study drug even if the patient starts nonprotocol therapy.								
12-Lead ECG [j]	X	X	X			X	X		
^{89}Zr-TAK-164 PET scan				X	X				
^{18}F-FDG-PET [k]	X [d]								
Disease assessment (CT/MRI scan/RECIST)	X [d]							X [l]	X [l]

	Screening [f]		Cycle 1						
	Day -21 to Day -1	Day 1 Predose	Day 1 Postdose	Day 3 (Day 2 to Day 4)	Day 5 (Day 5 to Day 7)	Day 8	Day 15	EOT [a]	PFS FU [b]
Hematology	X	X [m]				X [m]	X [m]	X	X
Chemistry	X	X [m]				X [m]	X [m]	X	
Coagulation	X	X [n]				X [n]	X [n]	X	
Urinalysis	X	X [n]						X	
Fresh tumor tissue biopsy sample	X [o,d]								
Archival (banked) tumor tissue sample	X [p,d]								
Buccal Epithelial Cells Sample for DNA	X [d]								
Serum samples for pharmacodynamics		X				X		X	
CCI									
Plasma sample for TAK-164 PK		X	X	X	X	X	X		
Plasma sample for FGN849 and s-FGN849 PK [q]		X	X	X	X	X	X		
Serum sample for immunogenicity		X					X	X	

[18]F-FDG: 18-fluorodeoxyglucose; [89]Zr: zirconium-89; AE: adverse event; AESI: adverse event of special interest; CT: computed tomography; DIO: dosimetry and imaging optimization; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; eCRF: electronic case report form; EOT: End-of-Treatment; FGN849: free payload for TAK-164; FU: follow-up; GCC: guanylyl cyclase C; ICF: informed consent form; IHC: immunohistochemistry; MRI: magnetic resonance imaging; PET: positron emission tomography; PFS: progression-free survival; PK: pharmacokinetic; RECIST: Response Evaluation Criteria in Solid Tumors; RID: recommended imaging dose; SAE: serious adverse event; s-FGN849: sulfonated free payload for TAK-164.

[f] DIO patients have already completed some screening events or events do not apply to them, as indicated in footnote (d).

[a] The EOT visit will occur approximately 30 days after the last dose of study drug or before the start of subsequent antineoplastic therapy.

[b] Performed at 3-month intervals.

[c] Informed consent may be obtained before the start of the screening period (Day -21). A separate consent may be obtained for the release of archival tumor tissue for the evaluation of GCC expression before screening.

[d] Excluding DIO patients.

[e] Vital signs will be obtained on Day 1 at 5 and 15 minutes after start of infusion, and upon completion of the infusion. Every effort should be made to obtain vital signs according to these time points; however, a ±3-minute window is acceptable.

[f] A serum pregnancy test will be obtained for women of childbearing potential at screening and at EOT. The screening results must be available and negative before enrollment. A

urine pregnancy test will be obtained for women of childbearing potential on Day 1 of every cycle, and a negative result must be confirmed before dosing. Pregnancy tests may also be repeated during the study if requested by an independent ethics committee/institutional review board or if required by local regulations.

[g] ^{89}Zr-labeled TAK-164 will be administered within 2 h post end of infusion of unlabeled TAK-164. Record time and amount of administration in eCRF.

[h] Patients in the DIO group will receive ^{89}Zr-TAK-164 in combination with variable amounts of unlabeled TAK-164 at a maximum dose ≤RID. Subsequent patients receive unlabeled TAK-164 as determined for optimal imaging. Record infusion start and stop times and amount of administered in eCRF.

[i] Administration of additional unlabeled TAK-164, if necessary to achieve a full dose (record time and amount of administration in eCRF), following the ^{89}Zr PET acquisition.

[j] A single 12-lead ECG will be collected at screening to assess eligibility. Triplicate 12-lead ECG recordings will be required at the time points specified in Table A-10.

[k] Patients are required to fast for 6 hours before the FDG radiotracer injection.

[l] Patients who progress will not have further CT (nor EOT or PFS FU).

[m] To be collected ≤3 days before visit.

[n] May be taken ≤24 hours before visit. Results must be evaluated before dosing.

[o] Pre- and post-treatment biopsies required in approximately 3 patients. The predose biopsies may be taken during screening or on Cycle 1 Day 1 predose. The specific anatomical location of the biopsy before resection must be specified.

[p] If archival tissue is not available for GCC evaluation by IHC, as assessed by a central laboratory, the patient may consent to provide biopsy tissue.

[q] Refer to Table A-10 for full details on the PK sample collection scheme.

Table A-8 Part C (Imaging Substudy) Schedule of Events for Cycle 2

	Cycle 2							
	Day 1 Predose	**Day 1 Postdose**	**Day 8 (±3 days)**	**Day 12 (±1 Day)**	**Day 15 (±3 days)**	**Day 21 (±3 days)**	**EOT [a]**	**PFS FU [b]**
Complete physical exam							X	X
Symptom-directed physical exam	X							
Weight	X		X		X			
ECOG performance status	X						X	X
Vital signs	X	X [c]			X		X	X
Pregnancy test [d]	X						X	
TAK-164 administration	X							
Concomitant medications and procedures	Concomitant medications and procedures will be recorded (eCRF) from signing of the ICF through the EOT visit or the start of subsequent antineoplastic therapy, whichever occurs first.							
AEs	AEs will be recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.							
SAEs, AESIs	SAEs and AESIs will be reported from signing of ICF through 30 days after last dose of study drug even if the patient starts nonprotocol therapy.							
12-Lead ECG [e]	X	X	X		X			
^{18}F-FDG-PET [f]				X [g]				
Disease assessment (CT/MRI scan/RECIST)						X [h]	X [h]	X [h]
Hematology		X [i]	X		X		X	X
Chemistry		X [i]	X		X		X	

	Cycle 2							
	Day 1 Predose	**Day 1 Postdose**	**Day 8 (±3 days)**	**Day 12 (±1 Day)**	**Day 15 (±3 days)**	**Day 21 (±3 days)**	**EOT [a]**	**PFS FU [b]**
Coagulation		X [j]	X [j]		X [j]		X	
Urinalysis		X [j]					X	
Fresh tumor tissue biopsy sample				X [k]				
Serum sample for pharmacodynamics	X		X				X	
CCI								
Plasma sample for TAK-164 PK [l]	X	X	X		X			
Plasma sample for FGN849 and s-FGN849 PK [l]	X	X	X		X			
Serum sample for immunogenicity	X						X	

^{18}F-FDG: 18-fluorodeoxyglucose; AE: adverse event; AESI: adverse event of special interest; CT: computed tomography; DIO: dosimetry and imaging optimization; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; eCRF: electronic case report form; EOT: End-of-Treatment; FGN849: free payload for TAK-164; FU: follow-up; ICF: informed consent form; MRI: magnetic resonance imaging; PET: positron emission tomography; PFS: progression-free survival; PK: pharmacokinetic; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: serious adverse event; s-FGN849: sulfonated free payload for TAK-164.

[a] The EOT visit will occur approximately 30 days after the last dose of study drug or before the start of subsequent antineoplastic therapy.

[b] Performed at 3-month intervals.

[c] Vital signs will be obtained on Day 1 at 5 and 15 minutes after start of infusion, and upon completion of the infusion. Every effort should be made to obtain vital signs according to these time points; however, a ±3-minute window is acceptable.

[d] A serum pregnancy test will be obtained for women of childbearing potential at screening and at EOT. A urine pregnancy test will be obtained for women of childbearing potential on Day 1 of every cycle, and a negative result must be confirmed before dosing. Pregnancy tests may also be repeated during the study if requested by an independent ethics committee/institutional review board or if required by local regulations.

[e] Triplicate 12-lead ECG recordings will be required at the time points specified in Table A-10.

[f] Patients are required to fast for 6 hours before the FDG radiotracer injection.

[g] For patients who provide a fresh tumor biopsy in Cycle 2, the ^{18}F-FDG-PET image is to be acquired before the biopsy. The specific anatomical location of the biopsy before resection must be specified.

[h] RECIST response assessments will be performed at screening, every 2 treatment cycles (42 days with a window of 3 days in advance), and at the EOT visit. Response assessment will be calendar-based regardless of treatment delays/interruptions. If the patient discontinues the study and had a CT/MRI scan within 2 weeks of the EOT study visit, the CT/MRI scan does not need to be repeated. Every effort should be made to maintain the same imaging modality (CT or MRI) throughout the study in each individual patient. Patients who progress will not have further CT (nor EOT or PFS).
[I] To be collected ≤3 days before visit.
[j] May be taken up to 24 hours before visit. Results must be evaluated before dosing.
[k] Pre- and post-treatment biopsies are required in a minimum of approximately 3 patients, excluding patients in the DIO. The predose biopsies will be requested to be taken on Day -21 to Day 1 predose. Also, the postdose biopsies will be requested to be taken after the PET scan scheduled for Cycle 2 Day 12 (±1 day). The specific anatomical location of the biopsy before resection must be specified.
[l] Refer to Table A-10 for full details on the PK sample collection scheme.

Table A-9 Part C (Imaging Substudy) Schedule of Events for Cycle 3+ (21-Day Cycle)

	Cycle 3+				
	Day 1 Predose	Day 1 Postdose	Day 21 (±3 days)	EOT [a]	PFS FU
Complete physical exam				X	X
Symptom-directed physical exam	X				
Weight	X				
ECOG performance status	X			X	X
Vital signs	X	X [b]		X	X
Pregnancy test [c]	X			X	
TAK-164 administration	X				
Concomitant medications and procedures	Concomitant medications and procedures will be recorded (eCRF) from signing of the ICF through the EOT visit or the start of subsequent antineoplastic therapy, whichever occurs first.				
AEs	AEs will be recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.				
SAEs, AESIs	SAEs and AESIs will be reported from signing of ICF through 30 days after last dose of study drug even if the patient starts nonprotocol therapy.				
12-Lead ECG [d]	X	X			
^{18}F-FDG-PET [e]			X [f]		
Disease assessment (CT/MRI scan/RECIST)			X [g,h]	X [h]	X [h]
Hematology	X [i]			X	X
Chemistry	X [i]			X	
Coagulation	X [j]			X	
Urinalysis	X [j]			X	
Serum sample for pharmacodynamics	X [k]			X	
CCI [redacted]					
Plasma sample for TAK-164 PK [m]	X	X			
Plasma sample for FGN849 and s-FGN849 PK [m]	X	X			
Serum sample for immunogenicity	X			X	

^{18}F-FDG: 18-fluorodeoxyglucose; AE: adverse event; AESI: adverse event of special interest; CR: complete response; CT: computed axial tomography; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; eCRF: electronic case report form; EOT: End-of-Treatment; FGN849: free payload for TAK-164; FU: follow-up; ICF: informed consent form; MRI: magnetic resonance imaging; PET: positron emission tomography; PFS: progression-free survival; PK: pharmacokinetic; PR:

partial response; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: serious adverse event; s-FGN849: sulfonated free payload for TAK-164.

[a] The EOT visit will occur approximately 30 days after the last dose of study drug or before the start of subsequent antineoplastic therapy.

[b] Vital signs will be obtained on Day 1 at 5 and 15 minutes after start of infusion, and upon completion of the infusion. Every effort should be made to obtain vital signs according to these time points; however, a ±3-minute window is acceptable.

[c] A serum pregnancy test will be obtained for women of childbearing potential at EOT. A urine pregnancy test will be obtained for women of childbearing potential on Day 1 of every cycle, and a negative result must be confirmed before dosing. Pregnancy tests may also be repeated during the study if requested by an independent ethics committee/institutional review board or if required by local regulations.

[d] Triplicate 12-lead ECG recordings will be required at the time points specified in Table A-10.

[e] Patients are required to fast for 6 hours before the FDG radiotracer injection.

[f] For patients with stable disease or response (CR or PR) according to RECIST 1.1 Cycle 4 Day 21 (-3 days).

[g] RECIST response assessments will be performed at screening, every 2 treatment cycles (42 days with a window of 3 days in advance), and at the EOT visit. Response assessment will be calendar-based regardless of treatment delays/interruptions. If the patient discontinues the study and had a CT/MRI scan within 2 weeks of the EOT study visit, the CT/MRI scan does not need to be repeated. Every effort should be made to maintain the same imaging modality (CT or MRI) throughout the study in each individual patient.

[h] Following documented progression, patients will not have further CT (nor EOT or PFS).

[I] Samples may be taken up to 3 days before visit.

[j] May be taken up to 24 hours before visit. Results must be evaluated before dosing.

[k] Cycle 3 only.

[l] Cycle 5 only.

[m] Refer to Table A-10 for full details on the PK sample collection scheme.

Table A-10 Part C Sparse PK and ECG Collection

Run-in Period [g]	Day -14		Day -12 (-13 to -11)	Day -10 (-10 to -8)	Day 1		Day 3 [a]	Day 5 [b]	Day 8 [c]		Day 15 [d]	
	Triplicate ECG [e]	PK [f]	PK [f]	PK [f]	Triplicate ECG [e]	PK [f]	PK [f]	PK [f]	Triplicate ECG [e]	PK [f]	Triplicate ECG [e]	PK [f]
Predose (within 60 min before start of infusion)	X3	X1										
EOI [h]	X3	X1										
Pre-imaging (within 60 min before start of imaging)			X1 [i]	X1 [i]								
Cycle 1 and Cycle 2												
Predose (within 60 min before start of infusion)					X3	X1						
EOI [h]					X3	X1						
1-2 hours after EOI					X3	X1						
Pre-imaging (within 60 min before start of imaging)							X1 [i]	X1 [i]				
168 hours after EOI [j]									X3	X1		
336 hours after EOI [k]											X3	X1
Cycle 3 and Beyond												
Predose (within 60 min before start of infusion)					X3 [l]	X1						
EOI [h]					X3 [l]	X1						

[89]Zr: zirconium-89; DIO: dosimetry and imaging optimization; ECG: electrocardiogram; EOI: end of infusion; FGN849: free payload for TAK-164; IV: intravenous; PET: positron emission tomography; PK: pharmacokinetics; s-FGN849: sulfonated free payload for TAK-164.
When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample. The triplicate ECG measurements should be completed immediately before the corresponding PK blood draw.
[a] Day 3 (Days 2 to 4) for Cycle 1 only, no samples collected for Cycle 2.
[b] Day 5 (Days 5 to 7) for Cycle 1 only; no samples collected for Cycle 2.
[c] Day 8 for Cycle 1; Day 8 (±3 days), for Cycle 2.

[d] Day 15 for Cycle 1; Day 15 (±3 days), for Cycle 2.
[e] Triplicate 12-lead ECG measurements are to be performed with the patient in supine position. Patients should have been in supine rest position for at least 5 min before initiation of ECG collections. Each ECG measurement of the triplicate collection should be recorded at 2- to 3-minute intervals. The triplicate ECG collections can also be used as safety ECGs when the collections times for these ECGs coincide.
[f] Blood samples for TAK-164, FGN849, and s-FGN849 PK should be taken from the contralateral arm to that used for the TAK-164 infusion. Refer to laboratory manual for further instructions.
[g] Only applies to DIO patients.
[h] At EOI, the collection of triplicate ECG should be initiated within 5 min prior to completion of TAK-164 infusion (i.e. **not** 5 min prior to EOI line flush). Each triplicate ECG should be collected at 2-3 min intervals with all 3 ECGs collected within a total 10 min window (i.e., 5 min prior to completion of TAK-164 infusion and 5 min after completion of TAK-164 infusion). The EOI PK sample should be collected immediately after the third ECG has been collected. EOI PK is in relation to TAK-164 infusion and **not** infusion line flush.
[i] Within 60 min before start ^{89}Zr-TAK-164 PET scan.
[j] Day 8 PK sample should be taken at 168 hours after EOI (±6 h) for Cycle 1, and 168 hours after EOI (±72 h) for Cycle 2.
[k] Day 15 PK sample should be taken at 336 hours after EOI (±6 h) for Cycle 1, and 336 hours after EOI (±72 h) for Cycle 2.
[l] Triplicate ECGs on Cycle 3 and beyond will be collected up to and including Cycle 5.

Appendix B Responsibilities of the Investigator

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

The investigator agrees to assume the following responsibilities 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, prior to 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 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 consent, as outlined in CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each patient who participates in the study and document the date of consent in the patient's medical chart. Valid informed 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 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.

Appendix C Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, 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.

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 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.

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 investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix D 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, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American Journal of Clinical Oncology 1982;5(6):649-55.
ECOG: Eastern Cooperative Oncology Group.

Appendix E Inhibitors and Inducers

Note that the list of strong CYP3A inhibitors or inducers is not exhaustive and is based on the FDA Draft DDI Guidance (Sources: fda.gov/downloads/Drugs/Guidance Compliance Regulatory Information/Guidances/UCM292362.pdf and fda.gov/Drugs/Development Approval Process/Development Resources/ Drug Interactions Labeling/ucm080499.htm). If a medication, supplement, or food/beverage is suspected or known to be a strong CYP3A inhibitor or inducer but is not on the list, then its use must be approved on a case-by-case basis by the medical monitor after consultation with the clinical pharmacologist and assessment of the relative benefit and risk.

Table A-11 Strong CYP3A Inhibitors and Inducers

Strong and Moderate CYP3A4 Inhibitors	Clinically Significant Strong Enzyme Inducers	Inhibitors of P-gp and/or BCRP
Strong CYP3A4 Inhibitors:	carbamazepine	**P-gp Inhibitors:**
boceprevir	rifabutin	itraconazole
ketoconazole	St John's wort	lopinavir/ritonavir
ritonavir	phenobarbital	telaprevir
clarithromycin	rifampin	clarithromycin
lopinavir/ritonavir	phenytoin	ritonavir
saquinavir	rifapentine	ketoconazole
conivaptan	avasimibe	indinavir/ritonavir
mibefradil		conivaptan
telaprevir		
grapefruit juice		**BCRP Inhibitors:**
nefazodone		cyclosporine
telithromycin		elacridar
indinavir		eltrombopag
nelfinavir		gefitinib
voriconazole		
itraconazole		
posaconazole		
Moderate CYP3A4 inhibitors:		
amprenavir		
aprepitant		
atazanavir		
ciprofloxacin		
crizotinib		
darunavir/ritonavir		
diltiazem		
erythromycin		
fluconazole		
fosamprenavir		
grapefruit juice		
imatinib		
verapamil		

BCRP: breast cancer resistance protein; CYP: cytochrome P450; P-gp: P-glycoprotein.

Appendix F Methods of Contraception Considered to be Effective

Acceptable Methods Considered Highly Effective

Birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [a]:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation [a]:
  - Oral
  - Injectable
  - Implantable [b]
- Intrauterine device (IUD) [b]
- Intrauterine hormone-releasing system [b]
- Bilateral tubal occlusion [b]
- Vasectomised partner [b,c]
- Sexual abstinence [d]

Methods That Are Considered Less Highly Effective

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide [e]
- Cap, diaphragm or sponge with spermicide [e]

Source: European Heads of Medicines Agencies (HMA) Clinical Trial Facilitation Group (CTFG); see hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf.

[a] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.

[b] Contraception methods that in the context of this guidance are considered to have low user dependency.

[c] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential participant of the study and that the vasectomised partner has received medical assessment of the surgical success.

[d] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

[e] A combination of male condom with either cap, diaphragm or sponge with spermicide (double-barrier methods) are also considered acceptable, but not highly effective, birth control methods.

Appendix G Response Evaluation Criteria in Solid Tumors (version 1.1)

All sites of disease, target and nontarget lesions must be assessed at baseline. Objective disease status is to be recorded at each evaluation using the response categories and definitions provided in this section.

All sites of measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for reproducible repeated measurements. Measurements must be provided for target site of measurable lesions.

Confirmation of response is not required, as response is not the primary endpoint of this study.

Table A-12 Disease Response Criteria for Target and Nontarget Lesions

Evaluation of Target Lesions	
CR:	Disappearance of all target lesions and any pathological lymph nodes must have reduction in short axis to <10 mm
PR:	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
PD:	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started and at least 5 mm increase or the appearance of 1 or more new lesions
SD:	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started
Evaluation of Nontarget Lesions	
CR:	Disappearance of all nontarget lesions, all lymph nodes must be nonpathological in size (<10 mm short axis), and normalization of tumor marker level
Incomplete Response/ SD:	Persistence of 1 or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits
PD:	Appearance of 1 or more new lesions and/or unequivocal progression of existing nontarget lesions

Source: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.[1]
CR: complete response; LD: longest diameter; PD: progression of disease; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors; SD: stable disease.

The following table summarizes the overall response status calculation at each time point for patients who have measurable disease per RECIST at baseline.

Table A-13 Time Point Response: Patients With Target (± Nontarget) Disease

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
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

Source: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.[1]
CR: complete response; NE: not evaluable; PD: progression of disease; PR: partial response; SD: stable disease.

The following table summarizes the overall response status calculation at each time point for patients who have nonmeasureable (therefore nontarget) disease at baseline.

Table A-14 Time Point Response: Patients With Nontarget Disease Only

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Source: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.[1]
CR: complete response; NE: not evaluable PD: progression of disease; SD: stable disease.
[a] 'Non-CR/non-PD' is preferred over 'stable disease' for nontarget disease because SD is increasingly used as endpoint for assessment of efficacy in some trial so to assign this category when no lesions can be measured is not advised.

Appendix H Detailed Description of Amendments to Text

The primary section(s) of the protocol affected by the changes in Amendment 05 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: The future maximal TAK-164 dose was limited to 0.19 mg/kg Q3W.

The primary changes occur in Sections 4.5 Rationale for the Proposed Study, 6.1 Overview of Study Design, and 8.3 Dose Escalation Rules:

Initial wording:	Section 4.5 Rationale for the Proposed Study The PK of TAK-164 in humans was predicted using an allometric scaling approach from TAK 164 PK in cynomolgus monkeys, an approach that has demonstrated success in predicting human PK for the TAK-264 program (previous name "MLN0264") that used the same GCC-targeted antibody, 5F9. The predicted human CL), volume of distribution (Vd) and plasma t1/2 of TAK-164 using this method is approximately 1.02 mL/h/kg, 51.96 mL/kg, and 35 hours, respectively. No accumulation in plasma is expected with either a Q2W or an every 3-week (Q3W) dosing schedule. Q3W and Q2W dosing schedules will be evaluated to allow for flexibility in combination with other agents that are administered at their respective schedules. Translational dynamic PK-efficacy modeling (using data from GCC-expressing tumor xenograft models) and semi-mechanistic toxicity modeling (using neutrophil count data from cynomolgus monkeys) suggested that Q2W administration of TAK-164 would provide pharmacologically active exposures (with a projected dose range of 0.1 mg/kg to 0.25 mg/kg) with a clinically manageable safety profile (absolute neutrophil count [ANC] above Grade 3 neutropenia cutoff at nadir), making it a favorable schedule to evaluate in this study. Q3W schedule: administration of TAK-164 on Day 1 of 21-day cycles.
Amended wording:	Section 4.5 Rationale for the Proposed Study The PK of TAK-164 in humans was predicted using an allometric scaling approach from TAK 164 PK in cynomolgus monkeys, an approach that has demonstrated success in predicting human PK for the TAK-264 program (previous name "MLN0264") that used the same GCC-targeted antibody, 5F9. The predicted human ~~clearance (~~CL~~)~~, ~~volume of distribution (~~Vd~~)~~ and plasma t1/2 of TAK-164 using this method is approximately 1.02 mL/h/kg, 51.96 mL/kg, and 35 hours, respectively. No accumulation in plasma is expected with either a Q2W or ~~an every 3-week (~~a Q3W~~)~~ dosing schedule. ~~Q3W and Q2W dosing schedules will be evaluated to allow for flexibility in combination with other agents that are~~

	~~administered at their respective schedules.~~ Translational dynamic PK-efficacy modeling (using data from GCC-expressing tumor xenograft models) and semi-mechanistic toxicity modeling (using neutrophil count data from cynomolgus monkeys) suggested that Q2W administration of TAK-164 would provide pharmacologically active exposures (with a projected dose range of 0.1 mg/kg to 0.25 mg/kg) with a clinically manageable safety profile (absolute neutrophil count [ANC] above Grade 3 neutropenia cutoff at nadir), making it a favorable schedule to evaluate in this study. **However, emerging clinical safety data supports limiting the maximum dose to 0.19 mg/kg Q3W.** ~~Q3W schedule: administration of TAK-164 on Day 1 of 21-day cycles.~~
Initial wording:	Section 6.1 Overview of Study Design **Dose Escalation (Part A)** The starting TAK-164 dose will be 0.004 mg/kg. The evaluation of tumor burden status will be performed as described in Appendix A. by CT or magnetic resonance imaging (MRI) according to modified RECIST, Version 1.1 [1] in all patients participating in this study at treatment intervals of 2 cycles. Pharmacodynamic evaluation will be performed by assessing the target marker CCI [redacted] on tumor biopsies required to be obtained from a minimum of approximately 5 evaluable patients starting at dose level 6 (0.12 mg/kg) of the study.
Amended wording:	Section 6.1 Overview of Study Design **Dose Escalation (Part A)** The starting TAK-164 dose will be 0.004 mg/kg **Q3W and the maximal dose will not exceed 0.19 mg/kg Q3W.** The evaluation of tumor burden status will be performed as described in Appendix A. by CT or magnetic resonance imaging (MRI) according to modified RECIST, ~~V~~version 1.1 [1] in all patients participating in this study at treatment intervals of 2 cycles. Pharmacodynamic evaluation will be performed by assessing the target marker CCI [redacted] on tumor biopsies required to be obtained from a minimum of approximately 5 evaluable patients ~~starting at dose level 6 (0.12 mg/kg)~~ of the study.

Initial wording:

Section 8.3 Dose Escalation Rules

Note that depending on PK-defined exposure estimates, a dose level between the planned dose levels may be explored. In addition, based on safety during the escalation phase, intermediate doses between those outlined may be explored after discussion and concurrence with all lead investigators and the Takeda study clinician.

Q3W Schedule and Dose Levels:

- TAK-164 is administered on Day 1 of each 21-day cycle.
- Up to 3 initial patients per cohort will be enrolled at the starting dose of 0.004 mg/kg. Dose escalation is planned to proceed by evaluating patients at respective dose levels: 0.008 mg/kg, 0.016 mg/kg, 0.032 mg/kg, 0.064 mg/kg, 0.12 mg/kg, 0.19 mg/kg. Further respective dose increments may continue including 0.25 mg/kg and 0.32mg/kg until one of the following occurs:
  - Unacceptable toxicity is observed or suggested by mTPI.
  - The escalation may be stopped upon a completion of enrollment of all patients planned to participate in the dose escalation part of the study or based on clinical judgment supported by medical observations.

Amended wording:

Section 8.3 Dose Escalation Rules

Note that depending on PK-defined exposure estimates, a dose level between the planned dose levels may be explored. In addition, based on safety ~~during the escalation phase, intermediate doses between those outlined~~**/tolerability, alternative dosing schedules** may be explored after discussion and concurrence with all lead investigators and the Takeda study clinician. **However, no patients will receive a dose above 0.19 mg/kg Q3W.**

Q3W Schedule and Dose Levels:

- TAK-164 is administered on Day 1 of each 21-day cycle.
- Up to 3 initial patients per cohort will be enrolled at the starting dose of 0.004 mg/kg. Dose escalation is planned to proceed by evaluating patients at respective dose levels: 0.008 mg/kg, 0.016 mg/kg, 0.032 mg/kg, 0.064 mg/kg, 0.12 mg/kg, **and** 0.19 mg/kg. ~~Further respective dose increments may continue including 0.25 mg/kg and 0.32mg/kg~~

~~until one of the following occurs:~~

- ~~Unacceptable toxicity is observed or suggested by mTPI.~~
- ~~The escalation may be stopped upon a completion of enrollment of all patients planned to participate in the dose escalation part of the study or based on clinical judgment supported by medical observations.~~

Rationale for Change: In preliminary clinical data, serious and life-threatening hepatotoxicity was reported at a dose level of 0.25 mg/kg Q3W and was considered related to TAK-164 treatment; therefore, the maximum dose was limited for patient safety.

The following sections also contain this change:

2.0 STUDY SUMMARY

Appendix A Schedules of Events [21-Day Cycle - Q3W Schedule]

Change 2: Hepatotoxicity was added as a potential risk. An enhanced liver safety management plan was implemented.

The primary changes occur in Sections 4.6 Potential Risks and Benefits, 7.2 Exclusion Criteria, 8.4.1 Criteria for Retreatment and Dose Delays and Modifications Delaying a Subsequent Treatment Cycle, 8.4.2 Criteria for Dose Reduction, 8.4.3 Criteria for Discontinuation of TAK-164, and 8.7.7 Hepatotoxicity:

Added text: Section 4.6 Potential Risks and Benefits

- **Hepatotoxicity.**
  - **Increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin.**

Added text: Section 7.2 Exclusion Criteria

12. Patient has concurrent alcohol abuse or a history of drug-induced liver injury (DILI).

Description of change: Section 8.4.1 Criteria for Retreatment and Dose Delays and Modifications Delaying a Subsequent Treatment Cycle

Table 8.a TAK-164 Recommended Dose Modification Criteria was modified to recommend following the discontinuation rules in Section 8.4.3 for Grade 3 derangements of liver function tests. A footnote was also added to Grade 3 nonhematologic toxicities attributed to study drug to clarify that dose interruption with dose reductions(s) does not apply to Grade 3 derangements of liver function tests.

Added text:

Section 8.4.2 Criteria for Dose Reduction

The dose of TAK-164 should be reduced by at least 1 dose level (or by 50% if the patient is receiving the first dose level) if the patient has any of the following:

- Grade 4 neutropenia (ANC <500 cells/mm^3) lasting more than 7 consecutive days.
- Grade 3 or greater neutropenia with fever and/or infection, where a fever is defined as a single oral temperature of >38.3°C or a sustained temperature of ≥38°C for more than 1 hour. Grade 3 thrombocytopenia with clinically meaningful bleeding at any time.
- Grade 4 thrombocytopenia (platelet count <25,000/mm^3) lasting more than 7 consecutive days.
- Grade 3 nonhematologic toxicity **(except liver function derangements)** attributed to TAK-164 except for the following that do not require dose reduction:
- Grade 3 or greater nausea and/or emesis in the absence of optimal antiemetic prophylaxis. (Optimal antiemetic prophylaxis is defined as an antiemetic regimen that employs both a 5-HT3 antagonist and a corticosteroid given in standard doses and according to standard schedules.)
- Grade 3 or greater diarrhea that occurs in the absence of optimal supportive therapy.
- Grade 3 fatigue lasting less than 1 week.
- **Derangement of liver function tests (LFTs) will follow discontinuation rules in Section 8.4.3.**

When a dose reduction of TAK-164 is required, no re-escalation of dose will be permitted.

Added text:

Section 8.4.3 Criteria for Discontinuation of TAK-164

Treatment with TAK-164 will also be discontinued under the following conditions:

- **ALT or AST >8 × ULN; OR**
- **ALT or AST >5 × ULN for more than 2 weeks; OR**
- **ALT or AST >3 × ULN and TBL >2 × ULN.**

Added text:	Section 8.7.7 Hepatotoxicity **It is recommended that patients treated with TAK-164 undergo periodic monitoring of LFTs as outlined in the Schedules of Events (Appendix A). These liver tests should be monitored closely throughout the study, and strict procedures for evaluation and/or discontinuation of patients with elevated liver tests that meet predefined criteria should be implemented. Additional testing and treatment should be implemented as per institutional standard of care.** **If patients experience ALT or AST >3 × ULN or AST > ULN but ≤3 × ULN, and if this observation cannot be explained by concomitant disease or another alternative etiology, follow-up laboratory tests (at a minimum alkaline phosphatase [ALP], ALT, AST, and TBL) should be performed within a maximum of 48 hours.**

Rationale for Change: In preliminary clinical data, hepatotoxicity was causally assessed as related to TAK-164, which warranted addition of hepatotoxicity as a potential risk with TAK 164. Concurrent abuse of alcohol or a history of DILI would diminish liver reserve, the ability to recover, and potentially worsen the consequences of DILI, and are, therefore, added as an exclusion criterion.

The following sections also contain this change:

2.0 STUDY SUMMARY

10.2 Procedures for Recording and Reporting AEs and SAEs

Change 3: Clarified that safety/tolerability data beyond Cycle 1 will be integrated into the RP2D determination for the expansion phase.

The primary change occurs in Section 6.1 Overview of Study Design:

Added text:	Section 6.1 Overview of Study Design **Although dose escalation and MTD will be estimated based on observed DLTs in Cycle 1, safety/tolerability data beyond Cycle 1 will be integrated into the RP2D determination for the expansion phase.**

Rationale for Change: In preliminary clinical data, serious hepatotoxicity occurred after the cycle 2 administration of TAK-164; therefore, late-onset safety signals will be integrated for tolerability assessment.

The following sections also contain this change:

2.0 STUDY SUMMARY

4.6 Potential Risks and Benefits

8.3 Dose Escalation Rules

Change 4: Limited prior lines of therapy to 2 or 3 lines in the expansion phase (part B).

The primary change occurs in Section 7.1 Inclusion Criteria, Inclusion criterion #1:

Added Wording:	• **Part B of the study will be limited to patients with 2 or 3 prior lines of systemic standard of care therapy.**

Rationale for Change: In preliminary data, potential clinical benefit has been observed, with some patients being on study treatment for up to 8 cycles with tumor shrinkage. Most of the patients who started TAK-164 treatment had previously progressed on multiple prior lines of treatment. The ORR assessment of TAK-164 in the previously planned part B can be confounded by multiple factors in a heterogenous prior treatment background.

Section 2.0 STUDY SUMMARY also contains this change.

Change 5: Clarified that patients will be enrolled at the RID in the imaging substudy (part C).

The primary change occurs in Section 6.1 Overview of Study Design:

Description of change:	Figure 6.a was updated to clarify that the Imaging Study (part C) would be dosed at the RID, and part B would be dosed at the RP2D. The red timeline at the top of the figure was removed.
Initial wording:	Section 6.1 Overview of Study Design **Imaging Substudy (Part C)** Up to 25 patients will be enrolled in the study in the Netherlands to determine the in vivo biodistribution and tumor targeting of ^{89}Zr-TAK-164 in patients with mCRC and/or metastatic gastric carcinoma. In addition, the relationship of ^{89}Zr-TAK-164 tumor targeting with ^{18}F-FDG-PET–determined response and RECIST version 1.1 response, and the relationship of ^{89}Zr uptake with GCC expression in tumor tissues/other biomarkers, will be characterized. Once the MTD/RP2D is established, approximately 6 patients (including 3 dosimetry patients) will be enrolled for purposes of dosimetry and imaging optimization (DIO). This DIO subgroup will receive ^{89}Zr-TAK-164 (mass dose <50% of the MTD/RP2D) 14 days before the first regularly scheduled study dose at Cycle 1 Day 1 (see Figure 6.b) and a second ^{89}Zr-TAK-164 administration on Cycle 1 Day 1 in combination with unlabeled TAK-164 at a maximum mass dose of 100% of the

MTD/RP2D. Imaging will be performed 1 hour after end of infusion (EOI) of the first ^{89}Zr-TAK-164 administration for dosimetry in the first 3 patients, and for all patients at 2 time points between Day 2 and Day 7 after EOI. Imaging time points and mass dose of TAK-164 can be adjusted in order to optimize imaging conditions. Up to 19 additional patients will be enrolled into Part C to receive a single dose of ^{89}Zr-TAK-164 at Cycle 1 Day 1 in addition to unlabeled TAK-164 as determined for optimal imaging. If the full MTD/RP2D is not administered at Cycle 1 Day 1, the differential will be provided after the second image acquisition. Part C patients will continue treatment with the MTD/RP2D of TAK-164 at Cycle 2 Day 1 and beyond (see Figure 6.c).

^{89}Zr-TAK-164 PET

Initially, approximately 6 patients (including 3 dosimetry patients) will be enrolled for DIO. This DIO subgroup will receive ^{89}Zr-TAK-164 (mass dose <50% of the MTD/RP2D) 14 days before the first regularly scheduled study dose at Cycle 1 Day 1 and a second ^{89}Zr-TAK-164 administration on Cycle 1 Day 1 in combination with unlabeled TAK-164 at a maximum mass dose of 100% of the MTD/RP2D. Imaging will be performed 1 hour after EOI of the first ^{89}Zr-TAK-164 administration for dosimetry in the first 3 patients and for all patients at 2 time points between Day 2 and Day 7 after EOI. Imaging time points and mass dose of TAK-164 can be adjusted to optimize imaging conditions. Qualitative and quantitative ($SUV_{mean,max}$) will be determined for all ^{89}Zr imaging time points (for further details, see Appendix A).

The ^{89}Zr-TAK-164 administration on Cycle 1 Day 1 will be in combination with variable amounts of unlabeled TAK-164 in the DIO subgroup, never exceeding the MTD/RP2D. This way, imaging conditions can be optimized by adding a variable mass dose of unlabeled TAK-164 to ^{89}Zr-TAK-164 administration to explore the presence of a potential sink, and by changing imaging time points up to 7 days after EOI if required. When unlabeled TAK-164 is administered with ^{89}Zr-TAK-164 for imaging purposes, ^{89}Zr-TAK-164 will be administered within 2 hours after the EOI of unlabeled TAK-164.

Amended wording:

Section 6.1 Overview of Study Design

Imaging Substudy (Part C, To Be Conducted in The Netherlands Only)

Up to 25 patients will be enrolled in the study in The Netherlands to determine the in vivo biodistribution and tumor targeting of ^{89}Zr-TAK-164 in patients with **GCC-expressing** mCRC and/or metastatic gastric carcinoma. In addition, the relationship of ^{89}Zr-TAK-164 tumor targeting

with ^{18}F-FDG-PET–determined response and RECIST version 1.1 response, and the relationship of ^{89}Zr uptake with GCC expression in tumor tissues/other biomarkers, will be characterized.

~~Once the MTD/RP2D is established~~**Based on emerging data from the dose escalation phase (part A) and in agreement between the site investigator and sponsor, part C will be triggered at a dose that is considered safe and has treatment potential (recommended imaging dose [RID]).**

~~, a~~**A**pproximately 6 patients (including 3 dosimetry patients) will be enrolled for purposes of ~~dosimetry and imaging optimization (~~DIO~~)~~. This DIO subgroup will receive ^{89}Zr-TAK-164 (mass dose <50% of the ~~MTD/RP2D~~**RID**) 14 days before the first regularly scheduled study dose at Cycle 1 Day 1 (see Figure 6.b) and a second ^{89}Zr-TAK-164 administration on Cycle 1 Day 1 in combination with unlabeled TAK-164 at a maximum mass dose of 100% of the ~~MTD/RP2D~~**RID**. Imaging will be performed 1 hour after end of infusion (EOI) of the first ^{89}Zr-TAK-164 administration for dosimetry in the first 3 patients, and for all patients at 2 time points between Day 2 and Day 7 after EOI. Imaging time points and mass dose of TAK-164 can be adjusted in order to optimize imaging conditions. Up to 19 additional patients will be enrolled into part C to receive a single dose of ^{89}Zr-TAK-164 at Cycle 1 Day 1 in addition to unlabeled TAK-164 as determined for optimal imaging. **Once the RP2D of TAK-164 is determined, part C patients who have received TAK-164 at an RID lower than the RP2D of TAK-164 may dose-escalate to the RP2D in the absence of PD or unacceptable treatment-related toxicity at the investigator's discretion and with sponsor's approval.** If the full ~~MTD~~**RID**/RP2D is not administered at Cycle 1 Day 1, the differential will be provided after the second image acquisition. Part C patients will continue treatment with the ~~MTD~~**RID**/RP2D of TAK-164 at Cycle 2 Day 1 and beyond (see Figure 6.c).

^{89}Zr-TAK-164 PET

Initially, approximately 6 patients (including 3 dosimetry patients) will be enrolled for DIO. This DIO subgroup will receive ^{89}Zr-TAK-164 (mass dose <50% of the ~~MTD/RP2D~~**RID**) 14 days before the first regularly scheduled study dose at Cycle 1 Day 1 and a second ^{89}Zr-TAK-164 administration on Cycle 1 Day 1 in combination with unlabeled TAK-164 at a maximum mass dose of 100% of the ~~MTD/RP2D~~**RID**. Imaging will be performed 1 hour after EOI of the first ^{89}Zr-TAK-164 administration for dosimetry in the first 3 patients and for all patients at 2 time points between Day 2 and Day 7 after EOI. Imaging time points and mass dose of TAK-164 can be adjusted to optimize imaging conditions. Qualitative

and quantitative ($SUV_{mean,max}$) will be determined for all ^{89}Zr imaging time points (for further details, see Appendix A).

The ^{89}Zr-TAK-164 administration on Cycle 1 Day 1 will be in combination with variable amounts of unlabeled TAK-164 in the DIO subgroup, never exceeding the ~~MTD/RP2D~~**RID**. This way, imaging conditions can be optimized by adding a variable mass dose of unlabeled TAK-164 to ^{89}Zr-TAK-164 administration to explore the presence of a potential sink, and by changing imaging time points up to 7 days after EOI if required. When unlabeled TAK-164 is administered with ^{89}Zr-TAK-164 for imaging purposes, ^{89}Zr-TAK-164 will be administered within 2 hours after the EOI of unlabeled TAK-164.

Rationale for Change: This change allows for the start of the imaging substudy as soon as a dose is determined that is considered safe and likely to have a therapeutic effect.

The following sections also contain this change:

2.0 STUDY SUMMARY

8.1 Study Drug Administration

8.3 Dose Escalation Rules

Appendix A Schedules of Events [21-Day Cycle - Q3W Schedule]

Change 6: Clarified that part C will be conducted in The Netherlands only.

The primary change occurs in Section 6.1 Overview of Study Design:

Added text: Imaging Substudy (Part C**, To Be Conducted in The Netherlands Only**)

Rationale for Change: The location of part C was specified in additional parts of the document for greater clarity.

The following sections also contain this change:

2.0 STUDY SUMMARY

4.6.1 Radiation Burden for Patients in the Imaging Substudy (Part C, To Be Conducted in The Netherlands Only)

8.1 Study Drug Administration

9.4.16 Assessment of $^{89Zr\text{-}TAK\text{-}164}$ PET Imaging (Part C, To Be Conducted in The Netherlands Only)

9.4.17 Assessment of $^{18F\text{-}FDG\text{-}PET}$ Imaging (Part C, To Be Conducted in The Netherlands Only)

13.1.3 Imaging Substudy (Part C, To Be Conducted in The Netherlands Only)

Change 7: Clarified that gastric carcinoma patients in part B and colorectal or gastric carcinoma patients in part C must express guanylyl cyclase C (GCC) with an H-score of ≥10.

The primary change occurs in Section 7.1 Inclusion Criteria, Inclusion criterion #1:

Initial wording:	1. Histologically or cytologically confirmed measurable advanced and/or metastatic solid GI tumor that expresses GCC protein (H-score ~~>~~10), for which standard treatment is no longer effective or for whom there is no available standard therapy. For the escalation part of the study (Part A), GI malignancies include, but are not limited to, mCRC, gastric carcinoma, esophageal carcinoma, small intestine cancer, and pancreatic cancer. The expansion part of the study (Part B) is limited to patients with CRC expressing a high level GCC (H-score 150 and higher) and gastric carcinoma. Part C includes patients with CRC and gastric carcinoma.
Amended wording:	1. Histologically or cytologically confirmed measurable advanced and/or metastatic solid GI tumor that expresses GCC protein (H-score ~~>~~≥10), for which standard treatment is no longer effective or for whom there is no available standard therapy. For the escalation part of the study (part A), GI malignancies include, but are not limited to, mCRC, gastric carcinoma, esophageal carcinoma, small intestine cancer, and pancreatic cancer. The expansion part of the study (part B) is limited to patients with CRC expressing a high-level GCC (H-score ≥150~~ and higher~~) and gastric carcinoma **(H-score ≥10)**. Part C includes patients with CRC and gastric carcinoma **(H-score ≥10 for both indications)**.

Rationale for Change: This change clarifies the GCC thresholds for patients in parts B and C for both CRC and gastric cancer. H-scores were added to the document in several places for clarity.

The following sections also contain this change:

2.0 STUDY SUMMARY

6.1 Overview of Study Design

6.2 Number of Patients

9.3 Treatment Group Assignments

13.1.2 Dose Expansion (Part B)

Change 8: Clinical laboratory directives were updated to reflect local capabilities.

The primary change occurs in Sections 9.4.14.1 Clinical Chemistry, Hematology, and Urinalysis, 9.4.18 Biomarker, PK, and Pharmacodynamic Samples, and 9.4.18.3 Pharmacodynamic Measurements:

Initial wording:	*9.4.14.1 Clinical Chemistry, Hematology, and Urinalysis* Clinical laboratory evaluations will be performed locally. Additional handling and shipment of clinical laboratory samples will be outlined in the Laboratory Manual.
Amended wording:	*9.4.14.1 Clinical Chemistry, Hematology, and Urinalysis* Clinical laboratory evaluations will be performed locally~~. Additional handling and shipment of clinical laboratory samples will be outlined in the Laboratory Manual.~~ **as per the institutional standard of care.**
Added text:	9.4.18 Biomarker, PK, and Pharmacodynamic Samples The primary specimen collection procedures are shown in Table 9.a. **Additional handling and shipment of biomarker, PK, and pharmacodynamic samples are outlined in the laboratory manual.**
Deleted text:	9.4.18.3 Pharmacodynamic Measurements *Serum for Protein (Local) Measurements* Serum samples for protein will not be collected for patients participating in part C. For all other patients, samples will be collected to monitor changes in clinically established biomarkers such as carcinoembryonic antigen to assess relationship with clinical response. Collection of this sample will be at baseline (all cycles) and Day 8 (Cycle 2 only). ~~Instructions for collection will be detailed in the Laboratory Manual.~~ Laboratory tests will be performed at the site. CCI [redacted]

Rationale for Change: Changes were made to clarify that clinical chemistry, hematology, and urinalysis assessments are performed locally, and therefore, no instructions for handling and shipment will be in the laboratory manual. Biomarkers, PK, and pharmacodynamics assessments

are performed centrally and therefore, instructions for handling and shipment are in the laboratory manual.

Change 9: Clarified protocol for biopsy.

The primary change occurs in Section 9.4.20 Banked Tumor and/or Fresh Tumor Biopsy Specimen Measurements:

Initial wording:	9.4.20 Banked Tumor and/or Fresh Tumor Biopsy Specimen Measurements GCC expression is evaluated by using IHC, as conducted by a central laboratory. An H-score will be used for GCC assessment and enrollment. Patients with GCC H-score ≥10 will be eligible for enrollment. An H-score ≥ 150 will be used for assigning patients to a GCC high group. In addition, CCI [redacted]. Collection of tumor biopsies at baseline and following treatment with TAK-164 is highly encouraged to monitor expression of GCC and CCI [redacted]. A viable fresh baseline biopsy and a viable posttreatment biopsy will be collected during dose escalation starting at dose level 0.12 mg/kg and beyond in a minimum of approximately 5 patients and up to 10 patients participating in Parts A and B, and approximately 3 patients participating in Part C. A baseline biopsy and posttreatment biopsy will be collected to assess target engagement and the tumor microenvironment.
Amended wording:	9.4.20 Banked Tumor and/or Fresh Tumor Biopsy Specimen Measurements GCC expression is evaluated by using IHC, as conducted by a central laboratory. An H-score will be used for GCC assessment and enrollment. Patients with GCC H-score ≥10 will be eligible for enrollment. An H-score ≥ 150 will be used for assigning patients to a GCC high group. In addition, CCI [redacted] may be analyzed on banked tumor and/or fresh tumor biopsies. Collection of tumor biopsies at baseline and following treatment with TAK-164 is highly encouraged to monitor expression of GCC and CCI [redacted]. A viable fresh baseline biopsy and a viable posttreatment biopsy will be collected during dose escalation ~~starting at dose level 0.12 mg/kg and beyond~~ in a minimum of approximately 5 patients ~~and up to 10 patients~~ participating in parts A and B, and approximately 3 patients participating in part C. A baseline biopsy and posttreatment biopsy will be collected to assess target engagement and the tumor microenvironment. **The specific anatomical location of the biopsy before resection must be specified.**

Rationale for Change: A requirement to record the location of the biopsy was added because annotation of the location of the biopsy is critical for downstream analyses. In addition, the number of patients was clarified as a minimum of approximately 5 with no limit on the number of patients biopsied to ensure the biopsies could meet study goals.

The following sections also contain this change:

2.0 STUDY SUMMARY

6.1 Overview of Study Design

Appendix A Schedules of Events [21-Day Cycle - Q3W Schedule]Appendix A

Change 10: Added definition and requirements for monitoring and reporting adverse events of special interest (AESIs).

The primary change occurs in Sections 10.1.4 AESI Definition, 10.2 Procedures for Recording and Reporting AEs and SAEs, 10.3 Monitoring of AEs and Period of Observation:

Added text:	Section 10.1.4 AESI Definition **An AESI is an AE of scientific and medical concern specific to the compound or program for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them, and instructions regarding how and when AESIs should be reported to Takeda are provided in Section 10.2 along with a list of AESIs.**
Added text:	Section 10.2 Procedures for Recording and Reporting AEs and SAEs **AESI Reporting:** **The below aminotransferase test results will be treated as AESIs.** **ALT or AST >3 × ULN.** **ALT or AST >ULN but ≤ 3 × ULN, which cannot be explained by concomitant disease or another alternative etiology.** **All AESIs will be reported to Takeda Global Pharmacovigilance in an expedited manner irrespective of the event's seriousness or causal relationship. Further, patients will be advised to promptly report signs and symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. The investigator must contact the medical monitor within 24 hours to discuss further management of the patient and refer to management of hepatotoxicity in Section 8.7.7.**

Added text:

10.3 Monitoring of AEs and Period of Observation

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

- AEs will be reported from the signing of informed consent through 30 days after administration of the last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first, and recorded in the eCRFs.
- SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the signing of informed consent through 30 days after administration of the last dose of study drug 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).
- **AESIs will be reported and monitored in the same way as SAEs (see above).**

Rationale for Change: Hepatotoxicity is considered an AESI as this event is considered a potential risk with TAK-164. Reporting AESIs is critical for safety monitoring of liver toxicity and for further characterization of the safety profile of TAK-164.

The following sections also contain this change:

9.4.11 AEs

Appendix A Schedules of Events [21-Day Cycle - Q3W Schedule]Appendix A

Change 11: Clarified procedure for collection of electrocardiograms (ECGs) at the end of infusion (EOI).

The primary change occurs in Appendix A Schedules of Events [21-Day Cycle - Q3W Schedule]Appendix A:

Description of change:

A footnote was added to the tables below:

Table A-4 Serial PK and ECG Collection Schedule for Part A

Table A-5 Part B Sparse PK and ECG Collection

Table A-10 Part C Sparse PK and ECG Collection

At EOI, the collection of triplicate ECG should be initiated within 5 min prior to completion of TAK-164 infusion (i.e. not 5 min prior to EOI line flush). Each triplicate ECG should be collected at 2-3 min intervals with all 3 ECGs collected within a total 10 min window (i.e.,

	5 min prior to completion of TAK-164 infusion and 5 min after completion of TAK-164 infusion). The EOI PK sample should be collected immediately after the third ECG has been collected. EOI PK is in relation to TAK-164 infusion and not infusion line flush.

Rationale for Change: Additional details were added to clarify the procedure of collecting triplicate ECGs at the end of drug infusion to facilitate consistent measurements.

Change 12: Updated Response Evaluation Criteria in Solid Tumors (RECIST) per RECIST version 1.1 guidelines.

The primary change occurs in Appendix G Response Evaluation Criteria in Solid Tumors (version 1.1):

Description of change:	In Table A-12 Disease Response Criteria for Target and Nontarget Lesions, the disease response criteria were updated. For evaluation of target lesions: CR: Disappearance of all target lesions **and any pathological lymph nodes must have reduction in short axis to <10 mm** PD: At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started **and at least 5 mm increase** or the appearance of 1 or more new lesions For evaluation of nontarget lesions: CR: Disappearance of all nontarget lesions, **all lymph nodes must be nonpathological in size (<10 mm short axis),** and normalization of tumor marker level

Rationale for Change: Criteria were updated to reflect the disease response criteria per RECIST version 1.1 guidance.

Change 13: Clarified that the specific mass dose of antibody-drug conjugate (ADC) will be determined during the dosimetry and imaging optimization (DIO) phase of the imaging substudy.

The primary change occurs in Section 8.15 Preparation of ^{89}Zr-TAK-164.

Added text:	^{89}Zr-TAK-164 will be prepared as described in the pharmacy manual and administered by IV at an anticipated dose of 0.5 to 2 mg at 37±10% MBq. **The specific mass dose of ADC will be determined during the DIO phase of the imaging substudy.**

Rationale for Change: This sentence was added to provide greater clarity into when the ADC specific mass dose will be determined.

Change 14: Clarified the timing of disease assessments.

The primary change occurs in Section 9.4.15 Disease Assessment:

Initial wording:	Objective assessments will be performed at the end of every other cycle starting with Cycle 2 (ie, Cycles 2, 4, 6, etc) and at the EOT visit, as described in the Schedules of Events (Appendix A). Objective assessments will be based on the modified RECIST criteria, Version 1.1 (see Appendix G) [1]. Imaging and assessment may be conducted up to 3 days in advance of the regular periodic assessment day. When possible, the same qualified physician will interpret results to reduce variability. Radiographic images will be maintained at the site, and test results and physician's findings will be filed in patient source documents. In addition, all study images acquired for patients in Part B and Part C will be collected by a central imaging vendor and assessed in a blinded independent central review. The sites will transfer images to a central facility consistent with the guidance provided by the Sponsor.
Amended wording:	Objective assessments will be performed ~~at the end of every other cycle starting with Cycle 2 (ie, Cycles 2, 4, 6, etc~~) **at screening, every 2 treatment cycles (42 days with a window of 3 days in advance)**, and at the EOT visit, as described in the Schedules of Events (Appendix A). **Response assessment will be calendar-based regardless of treatment delays/interruptions.** Objective assessments will be based on the modified RECIST criteria, version 1.1 (see Appendix G) [1]. ~~Imaging and assessment may be conducted up to 3 days in advance of the regular periodic assessment day.~~ When possible, the same qualified physician will interpret results to reduce variability. Radiographic images will be maintained at the site, and test results and physician's findings will be filed in patient source documents. In addition, all study images acquired for patients in part B and part C will be collected by a central imaging vendor and assessed in a blinded independent central review. The sites will transfer images to a central facility consistent with the guidance provided by the sponsor.

Rationale for Change: The protocol was edited to clarify that disease response assessments will be calendar-based, not cycle-based, due to the potential of dosing delays or interruptions.

Appendix A Schedules of Events [21-Day Cycle - Q3W Schedule] also contains this change.

Change 15: Moved a section of text regarding part C from Section 13.1.6 to Section 13.1.3.

The primary change occurs in Sections 13.1.3 Imaging Substudy (Part C, To Be Conducted in The Netherlands Only) and 13.1.6 PK Analysis:

Description of change:	The text below was moved from Section 13.1.6 to Section 13.1.3: **Efficacy endpoints will be summarized, and the correlation with imaging outputs may be explored. The results of part C will be summarized in a clinical study report addendum.**

Rationale for Change: This text was moved into a more appropriate section.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Approval	04-Sep-2019 23:54 UTC
	Clinical Approval	05-Sep-2019 00:26 UTC
	Biostatistics Approval	05-Sep-2019 01:12 UTC
	Clinical Pharmacology Approval	05-Sep-2019 10:14 UTC
	Nonclinical Scientist Approval	05-Sep-2019 12:26 UTC