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

SAP Approve Date: 08 May 2020

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

- Named persons or organizations associated with the study.
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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-164-1001

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

PHASE I

Version: 1.0

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Prepared by: PPD

Based on:

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1.1 Approval Signatures

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

2.0 TABLE OF CONTENTS

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3.0 LIST OF ABBREVIATIONS

ADA	antidrug antibody
ADC	antibody-drug conjugate
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	Area under the curve
BMI	body mass index
BUN	blood urea nitrogen
CI	confidence interval
CRF	case report form
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
EOT	end-of-treatment
GCC	guanylyl cyclase C
KM	Kaplan-Meier
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate
OS	overall survival
PD	progression of disease
PFS	progression-free survival
PK	pharmacokinetics
PT	Preferred term
PRO	patient-reported outcome
Q3wQ3W	once every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SOC	System organ class
TEAE	Treatment-emergent adverse event
ULN	upper limit of normal
WHODrug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objectives

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

4.2 Secondary Objectives

- 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 DCR, DOR, and PFS.

4.3 Exploratory Objectives

CCI

[redacted]

4.4 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. 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.

Only Part A of the study has been conducted (Figure 4.a).

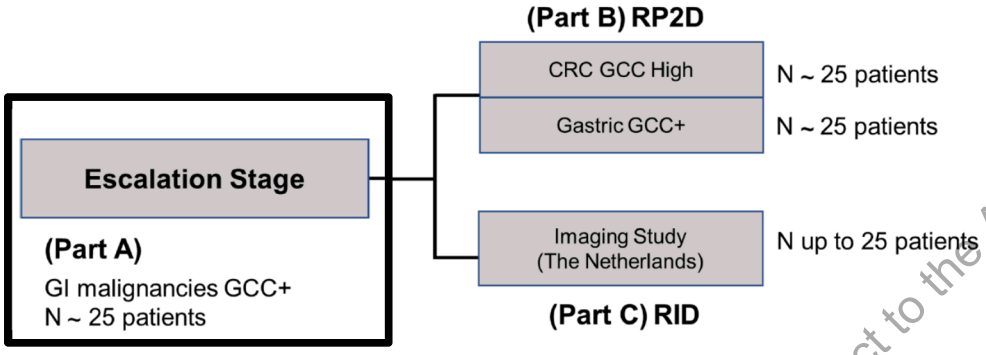
Once enrolled in the study, patients will receive TAK-164 IV administration on Day 1 of each 21-day cycle or Q3W. The starting TAK-164 dose will be 0.004 mg/kg Q3W and the maximal dose will not exceed 0.19 mg/kg Q3W following Protocol Amendment 05. To determine the MTD/RP2D and to guide the dose escalation portion of the study, a Bayesian model of modified toxicity probability interval (mTPI) will be used. DLTs occurring during 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.

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. DLTs

are defined in Protocol 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.

Figure 4.a Study Design for TAK-164-1001 Phase 1 First-in-Human



5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

- Number of patients with a DLT in Cycle 1.
- 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 or an alternate RP2D of TAK-164.

5.2 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 (CR+PR) as assessed by the investigator per modified Response Evaluation Criteria in Solid Tumors (RECIST, Version 1.1).
- DCR (CR+PR+SD).
- DOR.
- PFS.
- ADA in serum.

5.3 Exploratory Endpoints

CCI

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

It is anticipated that approximately 25 patients will be enrolled into Part A (escalation), following an mTPI model detailed in Protocol Section 8.3, to allow for dose finding across 7-8 different dose levels. The mTPI dosing schema will maximize patients treated at or near the MTD.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

All available efficacy and safety data will be included in data listings and tabulations. Data that are potentially spurious or erroneous will be examined under the auspices of standard data management operating procedures.

Where appropriate, variables will be summarized descriptively by study visit. For the categorical variables, the count and proportion of each possible value will be tabulated. The denominator for the proportion will be based on the number of subjects who provided non-missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be tabulated.

Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data.

Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

The summary tables will include each dose group and the total in the escalation stage (Part A).

No formal statistical hypothesis testing will be performed. All statistical analyses will be conducted using SAS® Version 9.4, or higher.

7.1.1 Study Definitions

7.1.2 Definition of Study Days

Study Day 1 is defined as the date on which a subject is administered their first dose of TAK-164. Other study days are defined relative to the Study Day 1, eg, Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1.

7.1.3 Definition of Study Visit Windows

All data will be categorized based on the scheduled visit at which it is collected. These visit designators are predefined values that appear as part of the visit tab in the eCRF.

7.1.4 Conventions for Missing Adverse Event Dates

Missing or partial AE start dates will be imputed according to the following rules.

Table 7.a Imputation Rules for Missing AE Start Dates

Non-missing	Missing	Estimated
Month and Year	Day	Day of first dose date of STUDY DRUG, if month and year of onset date are the same as month and year of date of first dose. The last day of the month, if the month and year of onset date are before the month and year of date of first dose of STUDY DRUG. The first day of the month, if the month and year of onset date are after the month and year of date of first dose of STUDY DRUG.
Year	Day and Month	Day and month of first dose date of STUDY DRUG, if the year of onset date is the same as the year of date of first dose of STUDY DRUG. December 31st, if the year of onset date is prior to the year of date of first dose of STUDY DRUG. January 1st, if the year of onset date is after the year of date of first dose of STUDY DRUG.
	Day, Month and Year	Date of first dose of STUDY DRUG

Missing or partial AE stop dates will be imputed according to the following rules: if only the day is missing, use 15th of the month; if both month and day are missing, use June 30th. For a record with a complete start date and a partial stop date, if the estimated stop date would become earlier than the start date, the stop date will not be estimated.

If AE stop date is not missing and the AE stop date < estimated start date, let estimated onset date = AE stop date.

All dates presented in listings are recorded dates without imputation.

7.1.5 Conventions for Missing Concomitant Medication Dates

If only the day is missing, use 15th of the month; if both month and day are missing, use June 30th. For a record with a complete start date and a partial stop date, if the imputed stop date would become earlier than the start date, the stop date will not be estimated.

All dates presented in listings are recorded dates without imputation.

7.2 Analysis Sets

- Safety analysis set: Patients who receive at least 1 dose of TAK-164. The safety analysis set will be used for safety analyses, and for the primary analysis of PFS and OS
- 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 the modified RECIST, version 1.1, and at least 1 postbaseline response assessment. The response-evaluable analysis set will be used for the primary analysis of the response-related efficacy endpoints, eg, ORR, DCR, DOR.
- 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: Patients with a baseline immunogenicity assessment and at least 1 postbaseline immunogenicity assessment.

7.3 Disposition of Subjects

Disposition of patients includes the number and percentage of patients in each dose level, total dose escalation stage, along with a summary of the primary reason for discontinuation from study drug. All percentages will be based on the number of patients in the safety analysis set.

Subjects who failed the screening will be summarized in a separate table by age, gender, ethnicity, and race, as appropriate. Primary reasons for screen failure will also be summarized.

Protocol deviations will be identified. A listing will be generated for significant protocol deviations.

7.4 Demographic and Other Baseline Characteristics

Demographics will be summarized. Baseline demographic data to be evaluated will include age, sex, race, ethnicity, height, weight, and GCC score. Age will be calculated from date of birth to date of informed consent.

Throughout this study, baseline assessments are defined as those performed at the closest time before the start of study drug administration.

Baseline characteristics including baseline disease primary diagnosis, years since initial diagnosis, staging, Eastern Cooperative Oncology Group (ECOG) performance status, will be summarized.

7.5 Medical History and Concurrent Medical Conditions

Medical history will be presented in a by-patient listing, including the medical and surgical history, date of onset and the status (resolved or ongoing, if known.)

7.6 Medication History and Concomitant Medications

A summary table will present the numbers and percentages of patients who received prior therapy, including prior systemic anticancer therapy, prior radiation, prior surgery, and best response to the prior therapy if known.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking concomitant medications will be tabulated by WHO drug generic term for the safety analysis set, from the first dose of study treatment and through 30 days after the last dose of study drug, or to the start of subsequent anticancer therapy, whichever occurs first.

7.7 Study Drug Exposure and Compliance

The exposure to TAK-164 will be characterized separately by: Number of Treated Cycles, Number of Cumulative Treatment Cycles ((≥1, ≥2, …, ≥6, and ≥10 cycles), Duration of Treatment (weeks) and Cumulative Dose. is defined as time from the first study dose to 21 days after the last study dose: [(last dose date +21) – first dose date]. after the last study dose, duration of treatment is defined as [date of death – first dose date +1]. Cumulative Dose will be summarized and listed in mg for TAK-164.

for TAK-164 as:

$$100\% \times \frac{\text{cummulative dose (mg)/ duration of treatment (day)}}{\text{initial prescribed dose (mg) / (number of treatment cycles} \times 21)}$$

Relative dose intensity will be summarized by each cycle and overall.

Action on study drug (dose reduced, interrupted, and withdrawn) will be summarized by each cycle and total for each dose level, and for overall in the safety analysis set.

7.8 Efficacy Analysis

All efficacy analyses will be based on investigator assessments. Investigators will assess response using the modified RECIST v1.1. The response-evaluable analysis set will be used for the primary analysis of ORR, DCR, DOR, whereas the safety analysis set will be used for the primary analysis of PFS and OS.

7.8.1 Primary Efficacy Endpoint(s)

Not applicable

7.8.2 Secondary Efficacy Endpoint(s)

ORR is defined as the proportion of patients who have achieved a CR or PR and will be summarized using the Response-Evaluable population by dose level and overall. Estimates of the ORR will be presented with 2-sided 95% exact binomial confidence intervals (CIs).

Disease control rate (DCR) is the proportion of patients who have had a best response of CR, PR, or SD. DCR will be summarized using the Response-Evaluable population. The number and percentage of patients falling into each response category (e.g., CR, PR, and SD) will be tabulated descriptively with 2-sided 95% exact CIs.

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 due to any cause, whichever occurs first. 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, prior to receipt of subsequent anticancer therapy, if applicable. DOR will be analyzed based on the responders in the Response-Evaluable analysis set.

PFS is defined as the time from the date of first study drug administration to the day of first documented PD or death due to any cause, whichever occurs first. PFS will be censored at the last response assessment that is SD or better, prior to receipt of subsequent anticancer therapy, if applicable. The primary analysis of PFS will be based on the safety analysis set.

OS will be calculated from the date of first study drug administration to the date of patient death due to any cause. Patients without documentation of death at time of the analysis will be censored as of the date the patient was last known to be alive, or the data cutoff date, whichever is earlier. The primary analysis of OS will be based on the safety analysis set.

In general, time-to-event endpoints (DOR, PFS, and OS) will be analyzed using the Kaplan-Meier method and results will be summarized by the 25th, 50th, and 75th percentiles, if estimable, with associated 2-sided 95% CIs. KM plots will be generated with regard to the respective analysis sets and meaningful subsets.

7.8.3 Additional Efficacy Endpoint(s)

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

Individual and mean plasma concentration data will be plotted over time. Descriptive statistics will be presented for plasma concentration and the PK parameters including, but not limited to C_{max}, t_{max}, area under the plasma concentration from time 0 to time of the last quantifiable concentration (AUC_{last}) during C1D1 and C2D1, $t_{1/2}$, CL, Vd, C_{trough}, etc.

7.9.2 Pharmacodynamic Analysis

Pharmacodynamic evaluation will be performed by assessing the target marker [redacted] on tumor biopsies required to be obtained from a minimum of approximately 5 evaluable patients of the study (pre- and postdose paired). Patients with GCC H-score ≥10 will be eligible for enrollment with an H-score ≥ 150 deemed GCC High. Baseline expression of GCC protein and [redacted] and the percent change from baseline will be listed for individual patients, and also summarized with descriptive statistics based on the pharmacodynamic analysis set. These biomarkers may be evaluated in correlation to dose, PK exposure, other pharmacodynamic measures, and response as appropriate. Alternatively, the expression of GCC and [redacted] might be used as a surrogate marker. Circulating tumor DNA in plasma may be explored in DNA mutation analysis including gene mutation, total mutation burden, MSI status, and DNA damage repair gene signatures.

Descriptive statistics, graphical methods, and statistical modeling, as appropriate, will be used to explore various biomarkers. The results of pharmacodynamic analysis may or may not be completed as part of this study assessment; hence, will be reported separately from the clinical study report.

7.10 Other Outcomes

7.10.1 Immunogenicity

The proportion of patients with positive ADA (transient or persistent, ADA titer: high/low) during the study will be summarized. Analysis will be based on the immunogenicity-evaluable set. Summaries will be provided by dose and overall. The incidence of immunogenicity (ADA positive) will be calculated. The impact of anti–TAK-164 antibodies ADA on the PK profile, pharmacodynamic profile, and clinical safety may be evaluated.

7.11 Safety Analysis

The safety analyses will be performed based on the safety analysis set.

7.11.1 Adverse Events

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary for the purpose of summarization.

All treatment-emergent AEs (TEAEs) will be tabulated. A TEAE for tabulation is defined as: any AE that occurs after administration of the first dose of study drug and up through 30 days after the last dose of study drug. AEs will be tabulated according to the MedDRA by system organ class (SOC) and preferred term (PT), and will include the following categories:

- TEAEs.
- Drug-related TEAEs.
- Grade 3 or higher TEAEs
- Drug-related, Grade 3 or higher TEAEs.
- Treatment-emergent SAEs.
- Drug-related Treatment-emergent SAEs.
- TEAEs resulting in study drug discontinuation.
- The most commonly reported TEAEs (ie, those events reported by ≥ 10% of all patients).
- Nonserious TEAEs (more than 5% in any dose level).

Patients with the same AE more than once will have the maximum intensity of that event counted within each system organ class, and once within each preferred term.

An overall summary of AE will include numbers and percentages of patients who had any TEAE, drug-related TEAE, grade 3 or higher TEAE, grade 3 or higher drug-related TEAE, SAE, drug-related SAE, TEAE resulting in discontinuation, and on-study deaths.

7.11.1.1 Serious Adverse Events

The number and percentage of subjects experiencing at least 1 treatment emergent serious AE (SAE) will be summarized by MedDRA primary system organ class and preferred term. Drug-related SAEs will be summarized similarly.

A by-subject listing of the SAEs will be presented (the subject listing will contain all SAEs regardless of treatment emergent AE status).

7.11.1.2 Deaths

A by-subject listing of the deaths will be presented. All deaths occurring on-study and during follow-up will be displayed (regardless of treatment emergent AE status). An on-study death is defined as a death that occurs between the first dose of study drug and 30 days of the last dose of study drug.

7.11.1.3 Adverse Events Resulting in Discontinuation of Study Drug

Treatment-emergent AEs that resulted in discontinuation of study drugs will be summarized by preferred terms. Numbers and percentages of patients in which each of the AEs resulted in study drug discontinuation will be also be summarized.

7.11.1.4 Dose Limiting Toxicities (DLTs)

A by-patient listing of DLTs in Cycle 1 will be presented by dose level for patients in the DLT-evaluable population. Numbers and percentages of patients who had a DLT will be also be summarized by dose level and overall based on the DLT analysis set.

7.11.2 Clinical Laboratory Evaluations

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units. If a lab value is reported using a non-numeric qualifier (e.g., less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier.

If a patient has repeated laboratory values for a given time point, the value from the last evaluation will be used.

In each case, the laboratory test results will be summarized by Baseline, Post-Baseline Minimum and Post-Baseline Maximum. Change from Baseline to Post-Baseline Minimum and Change from Baseline to Post-Baseline Maximum will also be summarized.

Mean laboratory values over time will be plotted for key laboratory parameters, including Hb, leukocytes, ANC, platelets, and liver function tests [ALT, AST, ALP, total bilirubin], phosphate, creatinine). Laboratory data will also be presented in listings. Unscheduled laboratory test results will be listed and included in laboratory shift tables.

Shift tables will be constructed for laboratory parameters to tabulate changes in NCI CTCAE for toxicity from baseline to post baseline worst on study CTC grade, if available. Parameters to be tabulated will include:

- Hematology: Hemoglobin, hematocrit, platelet (count), leukocytes with differential, neutrophils (ANC)
- Serum chemistry: Creatinine, Bilirubin (total), BUN, Phosphate, Alkaline phosphatase (ALP), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT)

7.11.3 Vital Signs

The actual values of vital sign parameters including temperature, heart rate, systolic and diastolic blood pressure, and weight, will be summarized over time for each dose level and overall. Change of vital signs from baseline values will also be summarized over time.

7.11.4 12-Lead ECGs

A summary of ECG abnormalities will be presented by visit. ECG intervals (QT and QTcF, PR interval, QRS duration, and heart rate) will be summarized in a similar fashion to laboratory test results, along with mean change from baseline to each post treatment time point.

7.11.5 Pregnancy Test

7.11.6 Other Observations Related to Safety

Not applicable.

7.12 Interim Analysis

Not applicable.

7.13 Changes in the Statistical Analysis Plan

Parts B and C of the protocol will not be conducted (Figure 4.a); therefore, the endpoints and relevant analyses have been removed from the SAP.

8.0 REFERENCES

1. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eu J Cancer 2009;45:228-247.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	08-May-2020 15:17 UTC