Clinical Study Protocol

NCT Number: NCT04804813

Title: CABOMETYX Tablets General Drug Use Results Surveillance Study “Renal Cell Carcinoma"

Study Number: Cabozantinib-5001

Document Version and Date: Version 4 / 12-DEC-2022

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

A summary of changes to previous protocol versions is appended to the end of the document.

Note; This document was translated into English as the language on original version was Japanese.

General use-results surveillance study protocol
CABOMETYX Tablets general drug-use surveillance
"Renal cell carcinoma"

Sponsor	**Takeda Pharmaceutical Company Limited.**
Protocol Number	**Cabozantinib-5001**
Version Number	**Version 4**
Date of preparation	**December 12, 2022**

TABLE OF CONTENTS

1.0 BACKGROUND OF IMPLEMENTATION

In the Japanese and overseas clinical studies of CABOMETYX Tablets (Hereinafter referred to as Cabometyx in patients with renal cell carcinoma, hepatic function disorder applicable to Hy's Law [Note] was not reported, but hepatic enzyme increased such as alanine aminotransferase (Hereinafter referred to as ALT) increased and aspartate aminotransferase (Hereinafter referred to as AST) increased was frequently observed. In addition, amylase increased and lipase increased have occurred at a certain incidence, and serious pancreatic enzyme increased, pancreatitis, and acute pancreatitis for which a causal relationship with Cabometyx could not be ruled out have also been reported.

When using Cabometyx, early detection by appropriate monitoring, appropriate management through dose reduction/interruption, and supportive care before an event becomes severe is important to avoid the progression to serious hepatic dysfunction or pancreatitis. Therefore, additional pharmacovigilance activities are necessary to confirm the occurrence (frequency and severity), clinical course, therapeutic measures, and progression to severe diseases of hepatic dysfunction, pancreatitis, and increased laboratory value (ALT, AST, amylase, lipase) in clinical practice, and to collect information on the appropriateness of the safety measures taken in clinical practice for Cabometyx.

For the combination therapy with nivolumab (genetical recombination) (Hereinafter referred to as nivolumab), since the incidence of hepatic enzyme increased was higher than that with Cabometyx monotherapy in the global phase 3 study (Study CA2099 ER), it was concluded that the same information as the above should be collected.

Therefore, a general drug use-results surveillance study in patients with unresectable or metastatic renal cell carcinoma in routine clinical practice (Hereinafter referred to as this investigation) was planned. This study will be conducted in compliance with GPSP Ordinance and all applicable regulatory requirements.

Note)ALT or AST > 3 × ULN and total bilirubin > 2 × ULN, plus alkaline phosphatase (Hereinafter referred to as ALP) < 2 × ULN

2.0 OBJECTIVES

To investigate the occurrence status of adverse reactions (adverse events), especially hepatic failure, hepatic function disorder, and pancreatitis (Information on incidence, severity, treatment, course, outcome, etc.) in patients with unresectable or metastatic renal cell carcinoma under actual use status of Cabometyx.

3.0 SAFETY SPECIFICATION

Hepatic failure, hepatic function disorder, pancreatitis

4.0 PLANNED SAMPLE SIZE AND RATIONALE

4.1 PLANNED SAMPLE SIZE

Cabometyx monotherapy: 300 patients (as registered patients)

Patients treated with nivolumab combination therapy: 50 patients (as the number of enrolled patients)

4.2 RATIONALE

Cabometyx Monotherapy Cases: In Study Cabozantinib-2001, 7/35 (20.0%) patients had ALT or AST elevations > 3 × ULN. Since it was considered possible to evaluate the event at a certain level by collecting at least 50 patients, the planned sample size was set at 300 patients to collect 50 patients, assuming the incidence of hepatic dysfunction to be 20.0% and taking withdrawals/dropouts into account.

The incidence of pancreatitis or acute pancreatitis AEs was 4/331 (1.2%) and 1/35 (2.9%) patients in Study XL184-308 and Study Cabozantinib-2001, respectively. Increases in pancreatic enzymes such as amylase and lipase were amylase increased in 5/35 subjects (14.3%), lipase increased in 3/35 subjects (8.6%), and pancreatic enzymes increased in 1/35 subjects (2.9%) in Study Cabozantinib-2001. Therefore, it is considered possible to confirm adverse events corresponding to “pancreatitis” or“ acute pancreatitis ” in at least 1 subject with a probability of 95% or higher and evaluate a certain number of adverse events related to “pancreatitis (including pancreatic enzyme increased) ” by collecting 300 cases.

Patients receiving nivolumab combination therapy: In Study CA2099ER, increases in ALT or AST to more than 3 times the upper limit of normal were observed in 7/22 patients (31.8%) in the Japanese population. Since it was considered possible to evaluate the event at a certain level by collecting at least 15 patients with the event, the planned sample size was set to be 50 patients to collect 15 patients assuming that the incidence of hepatic dysfunction in this survey is 30.0%. Acute pancreatitis occurred in 1/320 subjects (0.3%) in Study CA2099ER. In the Japanese population, lipase increased was observed in 7/22 patients (31.8%) and amylase increased in 2/22 patients (9.1%). Therefore, adverse events related to "pancreatitis (including pancreatic enzyme increased)" can be evaluated to a certain extent by collecting data from 50 patients.

5.0 STUDY POPULATION

To be conducted in patients with unresectable or metastatic renal cell carcinoma. However, patients who meet any of the following exclusion criteria will not be included in the study. Refer to the package insert.

Exclusion Criteria

The subject has a history of hypersensitivity to any ingredients of Cabometyx.

6.0 DOSAGE AND ADMINISTRATION

The usual adult dosage is 60 mg of cabozantinib administered orally once daily in the fasted state. The dose may be reduced according to the patient's condition.

When administering in combination with nivolumab (genetical recombination), the usual adult dosage is 40 mg of cabozantinib administered orally once daily in the fasted state. The dose may be reduced according to the patient's condition.

7.0 PLANNED NUMBER OF MEDICAL INSTITUTIONS BY DEPARTMENT

Department of Nephrology and Urology, etc. Approximately 150 sites

8.0 METHODS

8.1 OBSERVATION PERIOD

26 weeks

If administration of Cabometyx is discontinued for any reason, patients will be monitored until 30 days after discontinuation of administration of Cabometyx or the start of subsequent systemic anticancer therapy, whichever comes first. If a patient is lost to follow-up (dropout), the observation period will end at the time point when the patient is determined to be lost to follow-up.

*Rationale for the observation period

The median (minimum-maximum) time to onset of adverse events related to hepatic function disorder was 28 days (1 to 1119 days) and 15 days (4 to 114 days) in Studies XL184-308 and Cabozantinib-2001, respectively. The respective 34 quantile (Q3) was 56 and 25 days.

The median (minimum-maximum) time to onset of adverse events related to "pancreatitis (including pancreatic enzyme increased)" was 29 days (1 to 757 days) in Study XL184-308 and 29 days (2 to 255 days) in Study Cabozantinib-2001. The corresponding 34 quantile (Q3) was 83 and 53 days, respectively.

Based on the above, most of the events observed can be identified if the observation period is set at 26 weeks after the start of treatment.

Regarding the time to onset of adverse events related to the safety specification "Hepatic failure, hepatic function disorder" and "pancreatitis," a certain number of events can be identified within 26 weeks of nivolumab combination therapy based on the results of Study CA2099ER, as with Cabometyx monotherapy.

8.2 REQUEST TO STUDY SITES AND CONTRACT

Takeda Pharmaceutical Company Limited. will conclude a written contract with each study site prior to the conduct of this observational study.

8.3 PATIENT CONSENT

Prior to patient enrollment, the investigator will explain the contents of the informed consent form to the patient (or his/her legally acceptable representative) and obtain oral or written consent from the patient (or his/her legally acceptable representative) to provide information for this study.

When written informed consent is obtained, the patient (or legally acceptable representative) must sign and date the informed consent form. The investigator shall retain the original signed consent form.

The informed consent form will describe the outline of the study, the handling of the patient's personal and personal health information in the study, and the fact that the patient is free to withdraw from the study at any time without giving a reason and without prejudice to his/her further medical care.

An identification number is assigned to each patient who signs the informed consent form.

8.4 PATIENT ENROLLMENT METHOD

The study will be conducted by a “central registration method ” using an electronic data capture system (Hereinafter referred to as EDC) via Web.

For patients to whom Cabometyx is prescribed after the first day of the contract period with the medical

institution, the investigator or a person designated by the investigator will enter information related to patient registration in EDC by 30 days after the start date of prescription of Cabometyx (The start date of prescription is defined as "Day 0, " and the day after the start date of prescription is defined as" Day 1. "), and the investigator will put an electronic signature.

8.5 PREPARATION AND SUBMISSION OF SURVEY FORMS

Information will be collected using EDC.

The investigator or a person designated by the investigator will enter data in EDC for all registered patients promptly after performing necessary observations, and the investigator will put an electronic signature. If the administration of Cabometyx cannot be confirmed, enter this fact (no need to enter other items).

If administration of Cabometyx is discontinued during the observation period due to the onset of an adverse event, observation will be continued after discontinuation of administration until the adverse event resolves or is resolving as much as possible, and the event will be entered in EDC.

9.0 PLANNED STUDY PERIOD

Studyperiod: March 2021 to March 2024

Patient registration period: March 2021 to 2023 August [Note)]

Note)Even patients for whom Cabometyx is prescribed by August 31, 2023, patient registration (entry in EDC) will not be accepted on and after September 1, 2023.

If the number of registered patients for the entire study reaches the planned number before August 31, 2023, the registration will be closed before the end of the patient registration period. If the patient registration period is shortened, the study period will also be changed according to the shortened period.

10.0 INVESTIGATION ITEMS

The investigator or a person designated by the investigator will enter the following items in EDC.

10.1 PATIENT REGISTRATION

1) Investigation items

Date of prescription of Cabometyx, patient identification number, sex, age (at the time of prescription of Cabometyx), presence or absence of consent (verbal or written), assessment of exclusion criteria, presence or absence of prior systemic drug therapy for renal cell carcinoma, presence or absence of concomitant use of nivolumab

2) Timing of study

At patient enrollment

10.2 PATIENT CHARACTERISTICS

1) Investigation items

Timing of diagnosis of renal cell carcinoma, diagnosis of histological type, clinical stage (stage), treatment category (at the start of treatment with Cabometyx), Karnofsky Performance Status, IMDC

risk classification, complications (presence/absence and details), medical history (presence/absence and details), height, weight, treatment history before the start of treatment with Cabometyx (presence/absence and details), metastases (presence/absence and details)

2) Timing of study

At the start of administration of Cabometyx

10.3 DETAILS OF TREATMENT

1) Investigation items

Administration status of Cabometyx (Start date, date of interruption, date of dose change, date of completion, daily dose, reason for discontinuation), administration status of concomitant medication * (Presence/absence, drug name, and treatment period), radiotherapy (presence/absence and details)

*In this study, only therapeutic drugs for the primary disease are to be investigated.

2) Timing of study

Period from the start of administration of Cabometyx to Week 26 (or discontinuation of administration)

10.4 TEST/OBSERVATION ITEMS

When each examination/observation is performed at each time point under the actual use status in daily medical practice, it should be entered in EDC.

10.4.1 Antitumor effect

1) Parameter

Best overall response referring to the RECIST 1.1 extract and the date of the assessment

2) Timing of study

Period from initiation of Cabometyx treatment to Week 26 (or 30 days after discontinuation of treatment or start of subsequent systemic anticancer therapy, whichever comes first)

10.4.2 Other Observations

1) Observation Items

Presence/absence of pregnancy [only for female patients], withdrawal of consent [only for patients who withdrew consent]

2) Timing of sstudy

Period from the start of administration of Cabometyx to Week 26 (or discontinuation of administration)

10.5 ADVERSE EVENTS

1) Adverse events

Adverse events (see Table 1) that meet any of the following criteria will be collected:

・Safety specification: hepatic failure, hepatic impairment, pancreatitis

- Fulminant hepatitis, hepatic failure, hepatic function abnormal (a condition in which there is abnormality in liver function such as metabolic or synthetic capacity), laboratory abnormalities in liver function (ALT increased *, AST increased *, bilirubin increased, etc.), etc. (These AE terms are examples only, the most medically relevant AE term will be entered in EDC)

- Acute pancreatitis, pancreatic enzyme laboratory abnormalities (Lipase increased **, amylase increased **, etc.)

・Serious Adverse Events

・Adverse Events Leading to Discontinuation of Cabometyx

・Adverse events of CTCAE Grade *** 3 or higher

*In this study, patients with elevations of ALT or AST > 3 times the upper limit of normal will be included in the study. Patients with ALT or AST > 3 times the upper limit of normal before the start of treatment will be included in the investigation if clinically significant elevations are observed.

** In this study, any increase in amylase or lipase > 1.5 times the upper limit of normal will be included in the study. Patients with amylase or lipase > 1.5 times the upper limit of normal before the start of treatment will be included in the investigation if a clinically significant increase is observed.

*** Evaluate according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 5.0).

2) Investigation items

Presence or absence of adverse events, name of adverse event, date of onset, CTCAE Grade (worst value), seriousness and reason for seriousness (see Table 2), change in dosage and administration of Cabometyx (presence or absence and details), other action taken for the event (presence or absence and details), date of outcome assessment, outcome, causal relationship with Cabometyx * (see Table 3), changes over time in liver function laboratory values (AST, ALT, ALP, total bilirubin, and PT-INR) **, liver virus tests (HAV (HA-IgM Ab), HBV (HBsAg, HBcAb, HBsAb, HBV-DNA), HCV (HCVAb, HCV-RNA), and HEV (HEV-IgA Ab)) **, changes over time in pancreatic enzyme laboratory values (amylase and lipase) ***, status of drug administration at the onset of events related to the safety specifications, and course of adverse events related to the safety specifications [only serious adverse events]

If the outcome is assessed as “not recovered ” or“ unknown, ” follow-up should be performed as much as possible.

*If the causality with Cabometyx is Not Related, collect the rationale for the determination.

** To be collected only for events related to safety specifications (Hepatic failure, hepatic function disorder).

To be collected only for events related to *** Safety Specification (pancreatitis).

3) Timing of study

Period from initiation of Cabometyx treatment to Week 26 (or 30 days after discontinuation of treatment or start of subsequent systemic anticancer therapy, whichever comes first)

Table 1 Definition of Adverse Events

An Adverse Event (AE) is any untoward medical occurrence in a patient administered a medicinal product. An adverse event does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

※ It is not necessary to regard disease progression as an adverse event simply by meeting the criteria for progressive disease (PD) in the efficacy evaluation of antitumor effect. However, if the progression of the disease is beyond that expected from the natural course of the disease and the drug may have progressed the disease or the progression resulted in death, the event should be handled as an adverse event.

Table 2 Seriousness criteria

1. Results in death (Death) 2. Is life-threatening (life-threatening) The term "life threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. 3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolongation of hospitalization). 4. Results in persistent or significant DISABILITY/INCAPACITY (DISABILITY). 5. Is a congenital anomaly/birth defect (congenital anomaly) 6. May require intervention to prevent one of the outcomes listed in 1~5 above, even though the event is not immediately life-threatening or fatal or does not result in hospitalization, or may expose the patient to danger.

※ Takeda Pharmaceutical Company Limited. shall be handled as a serious adverse event even if it has been reported as non-serious by the reporter but Takeda Pharmaceutical Company Limited. determines it to be serious.

Table 3 Assessment Criteria for Causal Relationship between Adverse Events and Cabometyx

Judgment	Acceptance criteria
Related	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug is at least a reasonable possibility, ie, the relationship cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
Not Related	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as

	underlying diseases, complications, concomitant drugs and concurrent treatments.

11.0 ANALYSIS ITEMS AND METHODS

11.1 MATTERS RELATED TO PATIENT COMPOSITION

The number of patients enrolled, the number of patients whose case study forms are collected, the number of patients evaluated for safety and effectiveness, the number of patients excluded from the evaluation, reasons for exclusion, etc. will be tabulated.

11.2 PATIENT CHARACTERISTICS

Patient characteristics such as gender, age, disease duration, clinical stage, prior treatment history, and presence or absence of hepatic impairment will be tabulated.

11.3 DETAILS OF TREATMENT

The administration status of Cabometyx and therapeutic drugs for renal cell carcinoma other than Cabometyxwill be tabulated.

11.4 MATTERS CONCERNING SAFETY

The following analyses will be performed in the safety analysis set. Adverse events were coded using MedDRA/J and classified by preferred term (PT).; preferred term (PT) and system organ class (System Organ Class); Summarized in SOC).

11.4.1 Incidence of adverse events

The frequencies of adverse events to be investigated that occur during the observation period will be tabulated by type, time of onset, severity (CTCAE Grade), seriousness, action taken for administration of Cabometyx, causal relationship to Cabometyx, etc.

11.4.2 Factors that may affect safety

Frequencies of target adverse reactions that occur during the observation period will be tabulated by patient background factor (Gender, age, presence or absence of concurrent renal/hepatic impairment, etc.) and Cabometyx monotherapy or nivolumab combination therapy.

11.5 MATTERS CONCERNING EFFICACY

Antitumor effects during the observation period will be tabulated for Cabometyx monotherapy and nivolumab combination therapy in the effectiveness analysis set.

12.0 REGISTRATION OF SURVEY INFORMATION

Information on this study will be registered on the following public website before the start of this study.

- Clinical research protocol/research summary disclosure system: Japan Registry of Clinical Trials
- National Institutes of Health ClinicalTrials Registry: ClinicalTrials.gov

13.0 ORGANIZATIONAL STRUCTURE

13.1 ORGANIZATIONAL STRUCTURE FOR POST-MARKETING SURVEILLANCE, ETC.

See Attachment

14.0 MEDICAL ADVISOR

[redacted]

Activity:

- To give advice on the preparation and revision of the study protocol, etc.
- To give advice on the preparation and revision of the clinical study report
- Other advice requiring various medical judgments for the conduct of this investigation

15.0 CONTRACT RESEARCH ORGANIZATION

(1) [redacted]

Details of operations: Data management operations, EDC construction operations, storage operations of records, etc., support operations related to post-marketing surveillance

(2) [redacted]

Activity: EDC setting management

(3) [redacted]

Activity: Monitoring, statistical analysis

16.0 SCHEDULED TIMING OF MILESTONES FOR EVALUATION OF THE IMPLEMENTATION STATUS OF THE STUDY AND OBTAINED RESULTS, OR REPORTING TO THE PHARMACEUTICALS AND MEDICAL DEVICES AGENCY, AND ITS RATIONALE

At the time of periodic safety reporting: To comprehensively examine safety information.

9 months after study completion (at the time of preparation of the final report):

Final tabulation will be performed after data lock of all registered patients, and the final report will be prepared and submitted.

17.0 ADDITIONAL MEASURES THAT MAY BE IMPLEMENTED BASED ON THE STUDY RESULTS AND CRITERIA FOR DETERMINING THE INITIATION

The Risk Management Plan including the following contents will be reviewed at milestones.

- The necessity for changing the contents of the plan of this study, including the presence or absence of new safety specifications, will be examined.

・Review the necessity of formulating a risk minimization plan for new safety specifications.

18.0 OTHER NECESSARY MATTERS

18.1 REVISION OF THE PROTOCOL

During the study period, the progress status, occurrence of adverse reactions/serious adverse reactions unexpected from Precautions, presence or absence of increased incidence of specific adverse reactions, appropriateness of study items, etc. will be monitored, and if necessary, this protocol will be reviewed and revised. If the approval for partial changes in the dosage and administration or indications is obtained during the implementation period, the necessity of revision of this protocol will be examined as necessary, and the protocol will be revised as necessary.

18.2 ACTIONS TO BE TAKEN IF ANY PROBLEM OR QUESTION IS OBSERVED

If any safety or effectiveness issue is found, actions will be considered after close examination of the data.

Document History

Version	Date	Comments
original version	2021/2/8	New document
2nd version	2021/9/1	1.0 BACKGROUND OF IMPLEMENTATION 4.1 PLANNED SAMPLE SIZE 4.2 RATIONALE 6.0 DOSAGE AND ADMINISTRATION 8.1 OBSERVATION PERIOD 10.1 PATIENT REGISTRATION 11.4.2 FACTORS THAT MAY AFFECT SAFETY 11.5 MATTERS CONCERNING EFFICACY 14.0 MEDICAL ADVISOR
3rd version	2022/5/9	13.0 ORGANIZATIONAL STRUCTURE
4th version	2022/12/12	9.0 PLANNED STUDY PERIOD