Statistical Analysis Plan

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

Study Number: Cabozantinib-5001

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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.

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

Statistical Analysis Plan

(Final analysis)

Product name	CABOMETYX Tablets
Study title	CABOMETYX Tablets General Drug Use Results Surveillance Study "Renal Cell Carcinoma"
Sponsor	Takeda Pharmaceutical Company Limited.

Takeda Pharmaceutical Company Limited.
Head of Biostatistics Office

Original: Prepared on May 20, 2024

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List of Terms and Abbreviations

- This drug: CABOMETYX Tablets is abbreviated as this drug.
- Adverse event: AE that occurred after receiving Cabometyx.
- Adverse reactions, etc.: Acronym of the term "adverse reactions/infections." Adverse events for which the causal relationship with Cabometyx is other than “Not related ” in the assessment of the investigator. In this statistical analysis plan, the term "adverse drug reactions/infections" is used in the title, and "adverse drug reactions, etc." is used in the text and tables.
- Serious adverse events: Adverse events assessed as “serious ” by the investigator. Events listed in the MedDRA code list (PT code) of the Important Medical Events List will be handled as serious even if the investigator's assessment is “non-serious.”
- Related to Cabometyx: AEs other than ‘ Not Related ’ for Cabometyx will be handled as ‘ Related ’ and AEs assessed as ‘ Not Related ’ for Cabometyx will be handled as ‘ Not Related ’.
- Summary statistics: A general term for the number of subjects, mean, standard deviation, maximum, minimum, and quartiles.
- Patients whose CRFs were not collected: Registered patients whose CRFs were not collected.
- Patients whose CRFs were collected: Registered patients whose CRFs were collected.
- Days after treatment: Day -1 is defined as the day before the first dose of Cabometyx, and Day 1 is defined as the day of the first dose of Cabometyx.
- Duration of Cabometyx treatment (days): Calculated as the end date of Cabometyx treatment - start date of Cabometyx treatment +1. However, if “Continuing after the end of the observation period ” is selected for the administration status of Cabometyx, the date of last observation will be calculated as the end date of administration of Cabometyx.
- Timing of onset of adverse events (or adverse reactions, etc.): Calculated as the date of onset of adverse events (or adverse reactions, etc.) - the start date of the first administration of Cabometyx +1.
- Cabometyx monotherapy patients: patients who received only Cabometyx without concomitant use of nivolumab.
- Patients receiving nivolumab combination therapy: Patients receiving Cabometyx in combination with nivolumab.
- Duration of disease:

- Actual number (unit: year) = (Year of the first administration of Cabometyx - Year of the diagnosis of renal cell carcinoma) + (Month of the first administration of Cabometyx - Month of the diagnosis of renal cell carcinoma)/12 (Rounded off to one decimal place).
  If the month of diagnosis is unknown, it should be calculated as January of the year described.
  If the year of diagnosis is unknown, the data will be considered missing.

- BMI (kg/m ^{2}): Calculated with weight (kg)/height (m) ^{2} (rounded to one decimal place).
- Patients with hepatic impairment: Patients with complication specified as MedDRA SMQ "liver disorder (narrow)" in the column of disease name
- Renal Impairment: patients with complication specified as Takeda MedDRA query (TMQ) (Renal Disease) in the disease term field
- RDI (Relative Dose Intensity): Calculated using the following formula.
  - RDI (%) = (Total dose of Cabometyx (mg)/Total duration of treatment (days))/60 ×100

    However, for patients treated with nivolumab combination therapy, the calculation is performed using the following formula.

    RDI (%) = (Total dose of Cabometyx (mg)/Total duration of treatment (days))/40 ×100

Analysis Sets

In this study, the “safety analysis set ” and“ effectiveness analysis set ” will be established as analysis sets. It is defined as follows:

- Safety analysis set

Defined as "Patients with locked CRFs who have received at least one dose of Cabometyx and are evaluable for the safety." Patients with locked CRFs who meet the following conditions will be excluded from the safety analysis set.

- Cabometyx naïve
- Administration before contract period
- Enrollment outside the enrollment period
- Enrollment after the start date of prescription of Cabometyx (31 days)
- Onset status of adverse event unknown
- Withdrew consent

- Effectiveness analysis set

Defined as "Patients evaluable for effectiveness without major protocol deviation among patients eligible for safety evaluation." Patients eligible for the safety evaluation who meet any of the following conditions will be excluded from the efficacy evaluation.

- Other than target disease
- Exclusion criteria deviation

Number of digits to be displayed

- Percentage (%)

Incidence of AEs or ADRs:
Round off to 2 decimal places.
Other than the above:
Round the second decimal place and display to the first decimal place.

- Summary statistics

Mean, 14 quantiles, median, 34 quantiles:
Round the second digit of the source data to display up to the first digit of the source data.
Standard deviation:
Round the third digit of the source data to display to the second digit of the source data.
Min, Max:
The same number of digits as that of the source data will be displayed.

Safety specification (Important identified risks, important potential risks, and important missing information)

- Important identified risks
  - Hepatic failure, hepatic function disorder: Events falling under MedDRA PT included in any of the following MedDRA SMQs:

    ·Drug related hepatic disorders – severe events only (narrow)

    ·Cholestasis and jaundice of hepatic origin (narrow)

    ·LIVER LABORATORY TESTS, SIGNS AND SYMPTOMS (NARROW)
  - Pancreatitis: Events that fall under MedDRA PT included in MedDRA SMQ "acute pancreatitis (narrow)" or any of the following MedDRA PTs:

    ·Amylase increased, Amylase abnormal, Lipase increased, Lipase abnormal, Pancreatic enzymes increased, Pancreatic enzyme test abnormal, Pancreatic enzyme abnormality, Hyperamylasaemia, Hyperlipasaemia

1 Number of medical institutions surveyed, number of patients enrolled, and patient composition

1.1 Disposition of patients

Analyzed:	All registered patients (registered patients)	
Analysis item:	Enrolled patients	
	Study site	
	Patients with no CRF collected	
	CRF collected patients	
	Patients excluded from safety evaluation *	
	Reason for exclusion (multiple counts)	[No administration, administration before the contract period, enrollment outside the enrollment period, enrollment after 31 days from the start date of prescription of Cabometyx, occurrence of adverse events unknown, consent withdrawal]
	Safety analysis set	
	Patients excluded from efficacy evaluation *	
	Reason for exclusion	[Other than target disease, deveation of exclusion criteria]
	Effectiveness analysis set	
Analytical method:	For the above analytical variables, the following analyses will be performed, and a diagram of patient composition will be prepared.	
	The number of study sites will also be shown for patients enrolled. A medical institution with different clinical departments in the study will be counted as one medical institution.	
	If there is no patient meeting the reason for exclusion, 0 patient will be displayed.	
	For patients excluded from the safety evaluation and efficacy evaluation, the number of patients by reason for exclusion will be tabulated and a list will be prepared.	
	*"Patients excluded from safety evaluation" refer to patients excluded from "patients included in safety evaluation" among patients whose case study forms are collected. Similarly, “patients excluded from efficacy evaluation ” refer to patients who are excluded from the“ efficacy evaluation population ” among the “safety evaluation population.”	
	（1） Calculation of frequencies	

2 Patient characteristics

2.1 Patient characteristics

Analyzed:	Safety analysis set	
Analysis item:	Sex	[Male, Female]
	Age (years)	[Min<= - <18, 18<= - <65, 65<= - <75, 75<= - <85, 85<= - <=Max]
		[Min<= - <15, 15<= - <65, 65<= - <75, 75<= - <85, 85<= - <=Max]
	Duration of disease (years)	[Min<= - <1, 1<= - <=Max]
	Histological diagnosis	[Clear cell, non-clear cell, unknown]
	Clinical Stage (At the start of administration)	[I, II, III, IV, unknown]
	Treatment category (At the start of administration)	[Outpatient, Inpatient]
	Karnofsky Performance Status Scale (at the start of treatment)	[10<= - <=40, 50<= - <=70, 80<= - <=100]
	IMDC Risk Categorization (At the start of administration)	[favorable, intermediate, poor, unknown]
	Metastasis (At the start of administration)	[Absent, present, unknown]
	Destination of metastasis (multiple counts)	[Brain, lung, liver, bone, lymph node, others]
	Height (cm)	[Min<= - <140, 140<= - <150, 150<= - <160, 160<= - <170, 170<= - <=Max, not measured]
	Weight (kg)	[Min<= - <50, 50<= - <65, 65<= - <=Max, not measured]
	BMI(kg/m2)	[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <30.0, 30.0<= - <=Max]
	History of radiotherapy prior to the start of Cabometyx	[Absent, present]
	Anatomical Location (Count Multiple)	[Brain, lung, liver, bone, lymph node, others]

Presence/absence of prior systemic drug therapy for renal cell carcinoma before the start of Cabometyx (not including preoperative or postoperative adjuvant drug therapy)	[Absent, present]
History of systemic drug therapy for renal cell carcinoma before the start of Cabometyx (multiple counts)	[Sunitinib, pazopanib, sorafenib, temsirolimus, everolimus, axitinib, interferon alpha, nivolumab, ipilimumab + nivolumab, axitinib + pembrolizumab, avelumab + axitinib, others]
Treatment or surgery for renal cell carcinoma prior to the start of Cabometyx	[Absent, present]
Nephrectomy The status of treatment or surgery for renal cell carcinoma before the start of Cabometyx administration is “Present. ”	[Total nephrectomy, partial nephrectomy, no nephrectomy]
Presence/absence of history of preoperative or postoperative adjuvant drug therapy before the start of administration of Cabometyx When nephrectomy (yes/no) is "total nephrectomy" or "partial nephrectomy"	[Absent, present]
History of preoperative or postoperative adjuvant drug therapy before the start of administration of Cabometyx (duplicate counting)	[Preoperative and postoperative]
Presence or absence of medical history	[Absent, present]
Presence or absence of complications	[Absent, present]
Presence or absence of hepatic impairment	[Absent, present]

	Presence or absence of renal impairment	[Absent, present]
Analytical method:	For the above analytical variables, frequency tabulation of categorical data and summary statistics of continuous data will be calculated. This tabulation will be performed for the overall population and by patients receiving Cabometyx monotherapy and patients receiving nivolumab combination therapy.	

3 Details of treatment

3.1 Administration status of Cabometyx

Analyzed:	Safety analysis set	
Analysis item:	Cabometyx Starting Dose (mg)	[60 mg/day, 40 mg/day, 20 mg/day, 20 mg/day every other day, others]
	Duration of treatment (days)	
	Cabometyx Mean dose (mg/day)	
	RDI(%)	
	Presence or absence of dose reduction	[Absent, present]
	Dose after dose reduction (multiple counts)	[40 mg/day, 20 mg/day, others]
	Cabometyx Monotherapy Cases	[20 mg/day, 20 mg/day every other day, other]
	Patients receiving combination therapy with nivolumab	
	Presence or absence of interruption	[Absent, present]
	Discontinuation of Cabometyx	[Absent, present]
	Reason for discontinuation (multiple counts)	[Treatment goal achieved, adverse event onset, transfer to another hospital, etc., the patient no longer visits the hospital, pregnancy, lack of efficacy (including PD), other]
Analytical method:	For the above analytical variables, frequency tabulation of categorical data and summary statistics of continuous data will be calculated. This tabulation will be performed for the overall population and by patients receiving Cabometyx monotherapy and patients receiving nivolumab combination therapy.	

3.2 Status of Administration of Therapeutic Drugs for Renal Cell Carcinoma Other than Cabometyx

Analyzed:	Safety analysis set	
Analysis item:	Presence/absence of concomitant drugs for the primary disease administered during the observation period	[Absent, present]
	Drug name (duplicate counting)	
Analytical method:	For the above analytical variables, frequency tabulations of categorical data will be calculated. This tabulation will be performed for the overall population and by patients receiving Cabometyx monotherapy and patients receiving nivolumab combination therapy.	

3.3 Status of Administration of Nivolumab

Analyzed:	Patients receiving combination therapy with nivolumab among patients included in safety evaluation	
Analysis item:	Duration of nivolumab treatment (days)	
Analytical method:	For the above analytical variables, summary statistics of continuous data will be calculated.	

3.4 Observation period radiotherapy

Analyzed:	Safety analysis set	
Analysis item:	Presence/absence of radiotherapy during the observation period	[Absent, present]
	Anatomical Location (Count Multiple)	[Brain, lung, liver, bone, lymph node, others]
Analytical method:	For the above analytical variables, frequency tabulations of categorical data will be calculated. This tabulation will be performed for the overall population and by patients receiving Cabometyx monotherapy and patients receiving nivolumab combination therapy.	

4 Matters concerning safety

4.1 Occurrence Status of Adverse Events and Adverse Drug Reactions/Infections

4.1.1 Data on adverse events

Analyzed: Safety analysis set

Analysis item: Adverse Events

Analytical method: For the above analytical variable, the following analyses should be performed. This tabulation will be performed for the overall population and by patients receiving Cabometyx monotherapy and patients receiving nivolumab combination therapy.

（1） Number of subjects with adverse events

（2） Number of adverse events

（3） Incidence of adverse events

（4） Type of Adverse Event

The following accounting methods will be used for each analysis.

[Number of patients with adverse events]

- Number of patients with AEs.

[Number of adverse events]

- Number of adverse events experienced. When the same adverse event occurred more than once in the same patient, the total number of events will be tabulated.

[Incidence of adverse events]

- It is calculated as the number of patients with adverse events/the number of patients evaluated for safety ×100.

[Type of adverse event]

- Adverse events will be coded using the MedDRA/J. Data will be broadly classified by SOC, and tabulated by PT within the SOC. If the SOC is "investigations," they will be summarized by HLGT (Sort in ascending order of HLGT code, but not output) and by PT.
- For SOC, the number of patients with adverse events and the incidence of adverse events should be described in SOC internationally agreed order. A subject who experiences the same SOC more than once will be counted as 1 subject in the SOC.
- For PT, the number of patients with adverse events and the incidence will be described in ascending order of PT code. If the same PT occurs more than once in the same subject, the subject will be counted as 1 subject in the PT.

4.1.2 Status of onset of ADRs/infections

Analyzed: Safety analysis set

Analysis item: Adverse Reactions, etc.

Analytical method: For the above analytical variable, the following analyses should be performed. This tabulation will be performed for the overall population and by patients receiving Cabometyx monotherapy and patients receiving nivolumab combination therapy.

（1） Number of patients with adverse drug reactions, etc.

（2） Number of adverse drug reactions

（3） Incidence of adverse drug reactions, etc.

（4） Type of adverse drug reaction, etc.

The following accounting methods will be used for each analysis.

[Number of patients with adverse drug reactions, etc.]

- Number of patients with adverse drug reactions, etc.

[Number of adverse drug reactions]

- Number of adverse drug reactions, etc. that occurred. When the same adverse drug reaction, etc. occurred multiple times in the same patient, the total number of events will be tabulated.

[Incidence of adverse drug reactions, etc.]

- Calculate with the number of patients with adverse reactions, etc./the number of patients evaluated for safety ×100.

[Types of adverse drug reactions, etc.]

- Adverse drug reactions will be coded using MedDRA/J. Data will be broadly classified by SOC, and tabulated by PT within the SOC. If the SOC is "investigations," they will be summarized by HLGT (Sort in ascending order of HLGT code, but not output) and by PT.
- For SOC, the number of patients with adverse drug reactions, etc. and the incidence should be described in the order of SOC international consensus. A subject who experiences the same SOC more than once will be counted as 1 subject in the SOC.
- For PT, the number of patients with adverse drug reactions, etc. and the incidence should be entered in ascending order of PT code. If the same PT occurs more than once in the same subject, the subject will be counted as 1 subject in the PT.

4.1.3 Occurrence Status of Adverse Events and Adverse Drug Reactions/Infections Included in Safety Specifications

4.1.3.1 Incidences of adverse events included in safety specifications (tabulation by risk)

Analyzed: Safety analysis set

Analysis item: Adverse events included in the important identified risks (Hepatic failure, hepatic function disorder, pancreatitis) in the safety specifications

Stratification items: Total

Seriousness [Serious, non-serious]

Analytical method: For the above analytical variables, the following analyses should be performed for each risk and each of the subgroups of the stratification factors. The risks to be covered shall be in accordance with the definitions described in the safety specifications (important identified risks). This tabulation will be performed for the overall population and by patients receiving Cabometyx monotherapy and patients receiving nivolumab combination therapy.

[Number of patients with adverse events]

- Number of patients with AEs.

[Number of adverse events]

- Number of adverse events experienced. When the same adverse event occurred more than once in the same patient, the total number of events will be tabulated.

[Incidence of adverse events]

- It is calculated as the number of patients with adverse events/the number of patients evaluated for safety ×100.

[Type of adverse event]

- Adverse events will be coded using the MedDRA/J. Data will be broadly classified by SOC, and tabulated by PT within the SOC. If the SOC is "investigations," they will be summarized by HLGT (Sort in ascending order of HLGT code, but not output) and by PT.
- For SOC, the number of patients with adverse events and the incidence of adverse events should be described in SOC internationally agreed order. A subject who experiences the same SOC more than once will be counted as 1 subject in the SOC. However, if different in each stratification category, the subject will be counted as 1 subject in each category. For the last stratification item, one item will be adopted in accordance with the order of priority.
- For PT, the number of patients with adverse events and the incidence will be described in ascending order of PT code. If the same PT occurs

more than once in the same subject, the subject will be counted as 1 subject in the PT. However, if different in each stratification category, the subject will be counted as 1 subject in each category. For the following stratification items, 1 case will be adopted in accordance with the order of priority.

Seriousness: Serious → Non-serious

4.1.3.2 Incidences of ADRs/infections included in safety specifications (tabulation by risk)

Analyzed:	Safety analysis set
Analysis item:	Adverse reactions, etc. corresponding to important identified risks (Hepatic failure, hepatic function disorder, pancreatitis) in safety specifications
Stratification items:	Total
	Seriousness [Serious, non-serious]
Analytical method:	For the above analytical variables, the following analyses should be performed for each risk and each of the subgroups of the stratification factors. The risks to be covered shall be in accordance with the definitions described in the safety specifications (important identified risks). This tabulation will be performed for the overall population and by patients receiving Cabometyx monotherapy and patients receiving nivolumab combination therapy.

[Number of patients with ADRs]

- Number of patients with adverse drug reactions, etc.

[Number of adverse drug reactions]

- Number of adverse drug reactions, etc. If the same adverse drug reaction, etc. occurred multiple times in the same patient, the total number of events will be tabulated.

[Incidence of ADRs]

- Calculate with the number of patients with adverse reactions, etc./the number of patients evaluated for safety ×100.

[Type of adverse drug reaction, etc.]

- Adverse drug reactions will be coded using MedDRA/J. Data will be broadly classified by SOC, and tabulated by PT within the SOC. If the SOC is "investigations," they will be summarized by HLGT (Sort in ascending order of HLGT code, but not output) and by PT.
- For SOC, the number of patients with adverse drug reactions, etc. and the incidence should be described in the order of SOC international consensus. A subject who experiences the same SOC more than once will be counted as 1 subject in the SOC. However, if different in each

stratification category, the subject will be counted as 1 subject in each category. For the last stratification item, one item will be adopted in accordance with the order of priority.

- For PT, the number of patients with adverse drug reactions, etc. and the incidence should be entered in ascending order of PT code. If the same PT occurs more than once in the same subject, the subject will be counted as 1 subject in the PT. However, if different in each stratification category, the subject will be counted as 1 subject in each category. For the following stratification items, 1 case will be adopted in accordance with the order of priority.
  Seriousness: Serious → Non-serious

4.2 Incidences of adverse events and adverse drug reactions/infections in patients excluded from safety evaluation

4.2.1 Incidences of adverse events in patients excluded from safety evaluation

Analyzed:	Patients excluded from safety evaluation
Analysis item:	Adverse Events
Analytical method:	For the above analytical variable, analyses should be performed in the same manners as in Section 4.1.1. This tabulation is for all subjects only.

4.2.2 Occurrence of ADRs/infections in patients excluded from safety evaluation

Analyzed:	Patients excluded from safety evaluation
Analysis item:	Adverse Reactions, etc.
Analytical method:	For the above analytical variable, analyses should be performed in the same manners as in Section 4.1.2. This tabulation is for all subjects only.

4.3 Status of adverse events and onset of adverse reactions/infections by seriousness, CTCAE Grade (worst value), timing of onset, outcome, and causal relationship with Cabometyx

4.3.1 Occurrence status of adverse events by seriousness, CTCAE Grade (worst value), time to onset, outcome, and causal relationship to Cabometyx

Analyzed:	Safety analysis set	
Analysis item:	Adverse Events	
Stratification items:	Total	
	Seriousness	[Serious, non-serious]
	CTCAE Grade (worst)	[Grade1, Grade2, Grade3, Grade4, Grade5]
		[Grade ≥ 3]

	Time of onset (Day)	[1<= - <=21, 22<= - <=84, 85<= - <=168, 169<= - <=Max]
	Outcome	[Recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, death (due to the event), unknown]
	Relationship to Cabometyx	[Related, Not Related]

Analytical method: For the above analysis set, the following analyses will be performed in each stratum of the stratification factor. This tabulation will be performed for the overall population and by patients receiving Cabometyx monotherapy and patients receiving nivolumab combination therapy.

（1） Number of subjects with adverse events

（2） Number of adverse events

（3） Incidence of adverse events

（4） Type of Adverse Event

The following accounting methods will be used for each analysis.

[Number of patients with adverse events]

- Number of patients with AEs.

[Number of adverse events]

- Number of adverse events experienced. When the same adverse event occurred more than once in the same patient, the total number of events will be tabulated.

[Incidence of adverse events]

- It is calculated as the number of patients with adverse events/the number of patients evaluated for safety ×100.

[Type of adverse event]

- Adverse events will be coded using the MedDRA/J. Data will be broadly classified by SOC, and tabulated by PT within the SOC. If the SOC is "investigations," they will be summarized by HLGT (Sort in ascending order of HLGT code, but not output) and by PT.
- For SOC, the number of patients with adverse events and the incidence of adverse events should be described in SOC internationally agreed order. A subject who experiences the same SOC more than once will be counted as 1 subject in the SOC. However, one case of the same SOC will be adopted in accordance with the last priority.
- In PT, the number of patients with adverse events and the incidence of them will be entered in ascending order of PT code. If the same PT

occurs more than once in the same subject, the subject will be counted as 1 subject in the PT. However, 1 case of the same PT will be adopted in the following order of priority.

Seriousness: Serious → Non-serious

CTCAE Grade (worst value):

Grade5→Grade4→Grade3→Grade2→Grade1

Timing of onset (days): 1-21 days →22 to 84 days →85 to 168 days → ≥ 169 days

Outcome: Fatal (due to the event) → recovered with sequelae → not recovered → recovering → recovered → unknown

Causal relationship with Cabometyx: Related → Not related

4.3.2 Occurrence status of ADRs/infections by seriousness, CTCAE Grade (worst value), time to onset, and outcome

Analyzed:	Safety analysis set	
Analysis item:	Adverse Reactions, etc.	
Stratification items:	Total	
	Seriousness	[Serious, non-serious]
	CTCAE Grade (worst)	[Grade1, Grade2, Grade3, Grade4, Grade5] [Grade ≥ 3]
	Time of onset (Day)	[1<= - <=21, 22<= - <=84, 85<= - <=168, 169<= - <=Max]
	Outcome	[Recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, death (due to the event), unknown]

Analytical method: For the above analysis set, the following analyses will be performed in each stratum of the stratification factor. This tabulation will be performed for the overall population and by patients receiving Cabometyx monotherapy and patients receiving nivolumab combination therapy.

（1） Number of patients with adverse drug reactions, etc.

（2） Number of adverse drug reactions

（3） Incidence of adverse drug reactions, etc.

（4） Type of adverse drug reaction, etc.

The following accounting methods will be used for each analysis.

[Number of patients with ADRs]

- Number of patients with adverse drug reactions, etc.

[Number of adverse drug reactions]

- Number of adverse drug reactions, etc. If the same adverse drug reaction, etc. occurred multiple times in the same patient, the total number of events will be tabulated.

[Incidence of ADRs]

- Calculate with the number of patients with adverse reactions, etc./the number of patients evaluated for safety ×100.

[Type of adverse drug reaction, etc.]

- Adverse drug reactions will be coded using MedDRA/J. Data will be broadly classified by SOC, and tabulated by PT within the SOC. If the SOC is "investigations," they will be summarized by HLGT (Sort in ascending order of HLGT code, but not output) and by PT.
- For SOC, the number of patients with adverse drug reactions, etc. and the incidence should be described in the order of SOC international consensus. A subject who experiences the same SOC more than once will be counted as 1 subject in the SOC. However, one case of the same SOC will be adopted in accordance with the last priority.
- In PT, the number of patients with adverse drug reactions, etc. and the incidence thereof should be entered in ascending order of PT code. If the same PT occurs more than once in the same subject, the subject will be counted as 1 subject in the PT. However, 1 case of the same PT will be adopted in the following order of priority.

  Seriousness: Serious → Non-serious

  CTCAE Grade (worst value):

  Grade5→Grade4→Grade3→Grade2→Grade1

  Timing of onset (days): 1-21 days →22 to 84 days →85 to 168 days → ≥ 169 days

  Outcome: Fatal (due to the event) → recovered with sequelae → not recovered → recovering → recovered → unknown

4.3.3 Status of occurrence of adverse events and adverse reactions/infections specified in the safety specification by seriousness, CTCAE Grade (worst value), time to onset, outcome, and causal relationship with Cabometyx

4.3.3.1 Occurrence status of adverse events specified in the safety specification by seriousness, CTCAE Grade (worst value), time to onset, outcome, and causal relationship to Cabometyx

Analyzed: Safety analysis set

Analysis item: Adverse events included in the important identified risks (Hepatic failure, hepatic function disorder, pancreatitis) in the safety specifications

Analytical method: For the above analytical variable, analyses should be performed in the same manners as in Section 4.3.1.

4.3.3.2 Occurrence status of ADRs/infections specified in safety specifications by seriousness, CTCAE Grade (worst value), time to onset, and outcome

Analyzed: Safety analysis set

Analysis item: Adverse reactions, etc. corresponding to important identified risks (Hepatic failure, hepatic function disorder, pancreatitis) in safety specifications

Analytical method: For the above analytical variable, analyses should be performed in the same manners as in Section 4.3.2.

4.3.4 Status of occurrence of adverse events and adverse reactions/infections by CTCAE Grade (worst value) and by administration status of Cabometyx

4.3.4.1 Occurrence status of adverse events by CTCAE Grade (worst value) and Cabometyx administration status

Analyzed: Safety analysis set

Analysis item: AEs with (Discontinuation (except interruption), interruption, dose reduction) if Cabometyxdose changed

Stratification items: Total

CTCAE Grade (worst) [Grade1, Grade2, Grade3, Grade4, Grade5]

[Grade ≥ 3]

Analytical method: For the above analysis set, the following analyses should be performed by stratum of the stratification factor and by administration status of Cabometyx (Discontinuation (except interruption), interruption, dose reduction). This tabulation will be performed for the overall population and by patients receiving Cabometyx monotherapy and patients receiving nivolumab combination therapy.

（1） Number of subjects with adverse events

（2） Number of adverse events

（3） Incidence of adverse events

（4） Type of Adverse Event

The following accounting methods will be used for each analysis.

[Number of patients with adverse events]

- Number of patients with AEs.

[Number of adverse events]

- Number of adverse events experienced. When the same adverse event occurred more than once in the same patient, the total number of events will be tabulated.

[Incidence of adverse events]

- It is calculated as the number of patients with adverse events/the number of patients evaluated for safety ×100.

[Type of adverse event]

- Adverse events will be coded using the MedDRA/J. Data will be broadly classified by SOC, and tabulated by PT within the SOC. If the SOC is "investigations," they will be summarized by HLGT (Sort in ascending order of HLGT code, but not output) and by PT.
- For SOC, the number of patients with adverse events and the incidence of adverse events should be described in SOC internationally agreed order. A subject who experiences the same SOC more than once will be counted as 1 subject in the SOC. However, one case of the same SOC will be adopted in accordance with the last priority.
- In PT, the number of patients with adverse events and the incidence of them will be entered in ascending order of PT code. If the same PT occurs more than once in the same subject, the subject will be counted as 1 subject in the PT. However, 1 case of the same PT will be adopted in the following order of priority.

  CTCAE Grade (worst value):

  Grade5→Grade4→Grade3→Grade2→Grade1

4.3.4.2 CTCAE Grade (worst value), occurrence status of adverse reactions/infections by administration status of Cabometyx

Analyzed:	Safety analysis set
Analysis item:	Adverse reactions, etc. of (Discontinuation (except interruption), interruption, dose reduction) because there was presence or absence of dose change for Cabometyx
Stratification items:	Total
	CTCAE Grade (worst) [Grade1, Grade2, Grade3, Grade4, Grade5]
	[Grade ≥ 3]
Analytical method:	For the above analysis set, the following analyses should be performed by stratum of the stratification factor and by administration status of Cabometyx (Discontinuation (except interruption), interruption, dose reduction). This tabulation will be performed for the overall population and by patients

receiving Cabometyx monotherapy and patients receiving nivolumab combination therapy.

（1） Number of patients with adverse drug reactions, etc.

（2） Number of adverse drug reactions

（3） Incidence of adverse drug reactions, etc.

（4） Types of adverse drug reactions, etc.

The following accounting methods will be used for each analysis.

[Number of patients with adverse reactions, etc.]

- Number of patients with adverse drug reactions, etc.

[Number of adverse drug reactions]

- Number of adverse drug reactions, etc. If the same adverse drug reaction, etc. occurred multiple times in the same patient, the total number of events will be tabulated.

[Incidence of adverse drug reactions, etc.]

- Calculate with the number of patients with adverse reactions, etc./the number of patients evaluated for safety ×100.

[Types of adverse drug reactions, etc.]

- Adverse drug reactions will be coded using MedDRA/J. Data will be broadly classified by SOC, and tabulated by PT within the SOC. If the SOC is "investigations," they will be summarized by HLGT (Sort in ascending order of HLGT code, but not output) and by PT.
- For SOC, the number of patients with adverse drug reactions, etc. and the incidence should be described in the order of SOC international consensus. A subject who experiences the same SOC more than once will be counted as 1 subject in the SOC. However, one case of the same SOC will be adopted in accordance with the last priority.
- For PT, the number of patients with adverse drug reactions, etc. and the incidence should be entered in ascending order of PT code. If the same PT occurs more than once in the same subject, the subject will be counted as 1 subject in the PT. However, 1 case of the same PT will be adopted in the following order of priority.

  CTCAE Grade (worst value):

  Grade5→Grade4→Grade3→Grade2→Grade1

4.3.5 Time to initial onset of adverse events and adverse drug reactions/infections included in the safety specifications

Analyzed:	Patients with adverse events or adverse drug reactions included in the safety specifications among the patients included in the safety evaluation
Analysis item:	Time to initial onset of adverse events included in the important identified risk (Hepatic failure, hepatic function disorder, pancreatitis) in the safety specifications (days) Time to initial onset of ADRs, etc. corresponding to the important identified risks (Hepatic failure, hepatic function disorder, pancreatitis) in the safety specifications (days)
Analytical method:	For the above analytical variables, summary statistics will be calculated for the time of the first onset (Day). This tabulation will be performed for the overall population and by patients receiving Cabometyx monotherapy and patients receiving nivolumab combination therapy.

4.4 Status of administration of Cabometyx due to adverse events and adverse reactions/infections

4.4.1 Administration status of Cabometyx due to adverse events

Analyzed:	Safety analysis set	
Analysis item:	Adverse Events	
Stratification items:	Presence or absence of dose change for Cabometyx	[Absent, present]
	Breakdown of changes (duplicate counting)	[Discontinued (except for interruption), interrupted, dose reduced, unknown]
Analytical method:	For the above analysis set, frequencies of the number of adverse events will be tabulated for each CTCAE Grade (worst value) of adverse events and stratification by the stratification factor. Similar frequency tabulation will be performed for total and CTCAE Grade ≥ 3. For the incidence of events by stratification factor, the denominator will be the number of events by CTCAE Grade (worst value). This tabulation will be performed for the overall population and patients treated with Cabometyx monotherapy and patients treated with nivolumab combination therapy separately.	

4.4.2 Administration status of Cabometyx due to adverse reactions/infections

Analyzed:	Safety analysis set
Analysis item:	Adverse Reactions, etc.

Stratification items:	Presence or absence of dose change for Cabometyx	[Absent, present]
	Breakdown of changes (duplicate counting)	[Discontinued (except for interruption), interrupted, dose reduced, unknown]
Analytical method:	For the above analysis set, frequencies of the number of adverse drug reactions, etc. will be tabulated for each CTCAE Grade (worst value) of adverse drug reactions, etc. and stratified by stratification items. Similar frequency tabulation will be performed for total and CTCAE Grade ≥ 3. For the incidence of events by stratification factor, the denominator will be the number of events by CTCAE Grade (worst value). This tabulation will be performed for the overall population and patients treated with Cabometyx monotherapy and patients treated with nivolumab combination therapy separately.	

4.4.3 Administration status of Cabometyx due to adverse events and adverse reactions/infections specified in the safety specifications

4.4.3.1 Administration status of Cabometyx due to adverse events included in safety specifications

Analyzed:	Safety analysis set	
Analysis item:	Adverse events included in the important identified risks (Hepatic failure, hepatic function disorder, pancreatitis) in the safety specifications	
Stratification items:	Presence or absence of dose change for Cabometyx	[Absent, present]
	Breakdown of changes (duplicate counting)	[Discontinued (except for interruption), interrupted, dose reduced, unknown]
Analytical method:	For the above analysis set, frequencies of the number of adverse events will be tabulated for each CTCAE Grade (worst value) of adverse events corresponding to each risk and stratification by the stratification factor. Similar frequency tabulation will be performed for total and CTCAE Grade ≥ 3. For the incidence of events by stratification factor, the denominator will be the number of events by CTCAE Grade (worst value). This tabulation will be performed for the overall population and patients treated with Cabometyx monotherapy and patients treated with nivolumab combination therapy separately.	

4.4.3.2 Administration status of Cabometyx due to adverse reactions/infections included in safety specifications

Analyzed:	Safety analysis set	
Analysis item:	Adverse reactions, etc. corresponding to important identified risks (Hepatic failure, hepatic function disorder, pancreatitis) in safety specifications	
Stratification items:	Presence or absence of dose change for Cabometyx	[Absent, present]
	Breakdown of changes (duplicate counting)	[Discontinued (except for interruption), interrupted, dose reduced, unknown]
Analytical method:	For the above analysis set, frequencies of the number of adverse drug reactions, etc. will be tabulated for each CTCAE Grade (worst value) of adverse drug reactions, etc. corresponding to each risk and after stratification by the stratification item. Similar frequency tabulation will be performed for total and CTCAE Grade ≥ 3. For the incidence of events by stratification factor, the denominator will be the number of events by CTCAE Grade (worst value). This tabulation will be performed for the overall population and patients treated with Cabometyx monotherapy and patients treated with nivolumab combination therapy separately.	

4.5 Factors that may affect safety

4.5.1 Status of occurrence of adverse events and adverse drug reactions/infections by patient background and treatment characteristics

Analyzed:	Safety analysis set	
Analysis item:	Adverse Events	
	Adverse events included in the important identified risks (Hepatic failure, hepatic function disorder, pancreatitis) in the safety specifications	
	Adverse Reactions, etc.	
	Adverse reactions, etc. corresponding to important identified risks (Hepatic failure, hepatic function disorder, pancreatitis) in safety specifications	
Stratification items:	Sex	[Male, Female]
	Age (years)	[Min<= - <18, 18<= - <65, 65<= - <75, 75<= - <85, 85<= - <=Max] [Min<= - <15, 15<= - <65, 65<= - <75, 75<= - <85, 85<= - <=Max]
	Duration of disease (years)	[Min<= - <1, 1<= - <=Max]
	Histological diagnosis	[Clear cell, non-clear cell, unknown]

Clinical Stage (At the start of administration)	[I, II, III, IV, unknown]
Treatment category (At the start of administration)	[Outpatient, Inpatient]
Karnofsky Performance Status Scale (at the start of treatment)	[10<= - <=40, 50<= - <=70, 80<= - <=100]
IMDC Risk Categorization (At the start of administration)	[favorable, intermediate, poor, unknown]
Metastasis (At the start of administration)	[Absent, present, unknown]
Destination of metastasis (multiple counts)	[Brain, lung, liver, bone, lymph node, others]
BMI(kg/m2)	[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <30.0, 30.0<= - <=Max]
History of radiotherapy prior to the start of Cabometyx	[Absent, present]
Anatomical Location (duplicate counting)	[Brain, lung, liver, bone, lymph node, others]
Presence/absence of prior systemic drug therapy for renal cell carcinoma before the start of Cabometyx (not including preoperative or postoperative adjuvant drug therapy)	[Absent, present]
History of systemic drug therapy for renal cell carcinoma before the start of Cabometyx (multiple counts)	[Sunitinib, pazopanib, sorafenib, temsirolimus, everolimus, axitinib, interferon alpha, nivolumab, ipilimumab + nivolumab, axitinib + pembrolizumab, avelumab + axitinib, others]
Treatment or surgery for renal cell carcinoma prior to the start of Cabometyx	[Absent, present]
Nephrectomy The status of treatment or surgery for renal cell carcinoma before the start of Cabometyx administration is "Present. "	[Total nephrectomy, partial nephrectomy, no nephrectomy]

Presence/absence of history of preoperative or postoperative adjuvant drug therapy before the start of administration of Cabometyx When nephrectomy (yes/no) is "total nephrectomy" or "partial nephrectomy"	[Absent, present]
History of preoperative or postoperative adjuvant drug therapy before the start of administration of Cabometyx (duplicate counting)	[Preoperative and postoperative]
Presence or absence of medical history	[Absent, present]
Presence or absence of complications	[Absent, present]
Presence or absence of hepatic impairment	[Absent, present]
Presence or absence of renal impairment	[Absent, present]
Cabometyx Starting Dose (mg)	[60 mg/day, 40 mg/day, 20 mg/day, 20 mg/day every other day, others]

Analytical method: For the above analysis set, the following analyses should be performed for each stratum of the stratification factor. This tabulation will be performed for the overall population and by patients receiving Cabometyx monotherapy and patients receiving nivolumab combination therapy.

（1） Number of subjects with adverse events
（2） Incidence of adverse events
（3） Number of patients with adverse events included in the safety specifications
（4） Incidence of Adverse Events Included in Safety Specifications
（5） Number of patients with adverse drug reactions, etc.
（6） Incidence of adverse drug reactions, etc.
（7） Number of patients with adverse drug reactions, etc. included in safety specifications
（8） Incidence of adverse drug reactions included in safety specifications

The following accounting methods will be used for each analysis.
[Number of patients with adverse events included in adverse events/safety specifications]

- Number of patients with AEs/AEs included in the safety specification.

[Incidence of adverse events/adverse events included in safety specifications]

It is calculated as the number of patients with adverse events/adverse events included in the safety specification/the number of patients evaluated for safety ×100.

[Number of patients with adverse drug reactions/adverse drug reactions included in the safety specifications]

- Number of patients with adverse drug reactions/adverse drug reactions specified in the safety specification.

[Incidence of adverse drug reactions/adverse drug reactions included in the safety specifications]

Calculate as the number of patients with adverse reactions, etc./adverse reactions, etc. corresponding to the safety specifications/the number of patients evaluated for safety ×100.

4.5.2 Incidences of ADRs/infections by gender

Analyzed:	Safety analysis set	
Analysis item:	Adverse Reactions, etc.	
Stratification items:	Sex	[Male, Female]
Analytical method:	For the above analytical variable, the analysis of should be performed in the same manner as in Section 4.1.2 for each of the subgroups of the stratification factors. This tabulation will be performed for the overall population and by patients receiving Cabometyx monotherapy and patients receiving nivolumab combination therapy.	

4.5.3 Incidences of ADRs and infections by age group

Analyzed:	Safety analysis set	
Analysis item:	Adverse Reactions, etc.	
Stratification items:	Age	[Min<= - <18, 18<= - <65, 65<= - <75, 75<= - <85, 85<= - <=Max] [Min<= - <15, 15<= - <65, 65<= - <75, 75<= - <85, 85<= - <=Max]
Analytical method:	For the above analytical variable, the analysis of should be performed in the same manner as in Section 4.1.2 for each of the subgroups of the stratification factors. This tabulation will be performed for the overall population and by patients receiving Cabometyx monotherapy and patients receiving nivolumab combination therapy.	

4.5.4 Status of occurrence of ADRs/infections by presence/absence of hepatic impairment

Analyzed:	Safety analysis set	
Analysis item:	Adverse Reactions, etc.	
Stratification items:	Presence or absence of hepatic impairment	[Absent, present]
Analytical method:	For the above analytical variable, the analysis of should be performed in the same manner as in Section 4.1.2 for each of the subgroups of the stratification factors. This tabulation will be performed for the overall population and by patients receiving Cabometyx monotherapy and patients receiving nivolumab combination therapy.	

4.5.5 Status of occurrence of ADRs/infections by presence/absence of renal impairment

Analyzed:	Safety analysis set	
Analysis item:	Adverse Reactions, etc.	
Stratification items:	Presence or absence of renal impairment	[Absent, present]
Analytical method:	For the above analytical variable, the analysis of should be performed in the same manner as in Section 4.1.2 for each of the subgroups of the stratification factors. This tabulation will be performed for the overall population and by patients receiving Cabometyx monotherapy and patients receiving nivolumab combination therapy.	

5 Matters concerning efficacy

5.1 Antitumor effect

Analyzed:	Effectiveness analysis set
Analysis item:	Antitumor effect
Analytical method:	For each of the above analysis items, frequency tabulation of the assessment results will be performed in the effectiveness analysis set, and the response rate and 95% confidence interval of the response rate will be calculated. Furthermore, band graphs will be prepared for the above analysis results. This tabulation is performed separately for patients receiving Cabometyx monotherapy and patients receiving nivolumab combination therapy.

5.2 Tumor response by patient background factors and treatment factors

Analyzed:	Effectiveness analysis set	
Analysis item:	Antitumor effect	
Stratification items:	Sex	[Male, Female]
	Age (years)	[Min<= - <18, 18<= - <65, 65<= - <75, 75<= - <85, 85<= - <=Max] [Min<= - <15, 15<= - <65, 65<= - <75, 75<= - <85, 85<= - <=Max]
	Duration of disease (years)	[Min<= - <1, 1<= - <=Max]
	Histological diagnosis	[Clear cell, non-clear cell, unknown]
	Clinical Stage (At the start of administration)	[I, II, III, IV, unknown]
	Karnofsky Performance Status Scale (at the start of treatment)	[10<= - <=40, 50<= - <=70, 80<= - <=100]
	IMDC Risk Categorization (At the start of administration)	[favorable, intermediate, poor, unknown]
	Metastasis (At the start of administration)	[Absent, present, unknown]
	Destination of metastasis (multiple counts)	[Brain, lung, liver, bone, lymph node, others]
	BMI(kg/m2)	[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <30.0, 30.0<= - <=Max]
	History of radiotherapy prior to the start of Cabometyx	[Absent, present]
	Presence/absence of prior systemic drug therapy for renal cell carcinoma	[Absent, present]

before the start of Cabometyx (not including preoperative or postoperative adjuvant drug therapy)	
History of systemic drug therapy for renal cell carcinoma before the start of Cabometyx (multiple counts)	[Sunitinib, pazopanib, sorafenib, temsirolimus, everolimus, axitinib, interferon alpha, nivolumab, ipilimumab + nivolumab, axitinib + pembrolizumab, avelumab + axitinib, others]
Treatment or surgery for renal cell carcinoma prior to the start of Cabometyx	[Absent, present]
Nephrectomy	[Total nephrectomy, partial nephrectomy, no nephrectomy]
The status of treatment or surgery for renal cell carcinoma before the start of Cabometyx administration is "Present. "	
Presence/absence of history of preoperative or postoperative adjuvant drug therapy before the start of administration of Cabometyx	[Absent, present]
When nephrectomy (yes/no) is "total nephrectomy" or "partial nephrectomy"	
History of preoperative or postoperative adjuvant drug therapy before the start of administration of Cabometyx (duplicate counting)	[Preoperative and postoperative]
Presence or absence of medical history	[Absent, present]
Presence or absence of complications	[Absent, present]
Presence or absence of hepatic impairment	[Absent, present]
Presence or absence of renal impairment	[Absent, present]
Cabometyx	[60 mg/day, 40 mg/day, 20 mg/day, 20 mg/day every other day, others]

Analytical method:	For each of the above analysis items, frequency tabulation of assessment results will be performed for each stratum of the stratification factor in the efficacy evaluation population, and the response rate and 95% confidence interval of the response rate will be calculated. This tabulation is performed separately for patients receiving Cabometyx monotherapy and patients receiving nivolumab combination therapy.

6 Incidences of adverse reactions/infections in the additional pharmacovigilance plan

6.1 Incidences of adverse reactions and infections in the additional pharmacovigilance plan (Attached Form 12)

Analyzed:	Safety analysis set
Analysis item:	Adverse reactions, etc. included in safety specifications (Important identified risks, important potential risks, and important missing information)
Stratification items:	Seriousness [Serious, non-serious]
Analytical method:	For the above analytical variable, the following analyses should be performed for each stratum of the stratification factor in accordance with Attached Form 12, (Note) 1~4 of PSEHB/PED Notification No. 0325/10 dated March 25, 2020. （1） Number of patients with events and incidence Risk names and the order of risk names shall be in accordance with the definitions described in the safety specification (Important identified risks, important potential risks, and important missing information).

7 Incidence of adverse reactions/infections in post-marketing surveillance, etc.

7.1 Incidence of adverse reactions/infections in post-marketing surveillance, etc. (Attached Form 15)

Analyzed: Safety analysis set

Analysis item: Adverse Reactions, etc.

Analytical method: For the above analytical variable, the following analyses should be performed.

（1） Status of post-marketing surveillance, etc.

1） Number of patients included in safety analysis

2） Number of patients with adverse drug reactions, etc.

3） Incidence of adverse drug reactions, etc.

（2） Types of adverse drug reactions, etc.

1） Number of patients with adverse drug reactions, etc. and incidence (by SOC)

2） Number of patients with adverse drug reactions, etc. and incidence of them (by PT)

The following accounting methods will be used for each analysis.

[Number of patients with adverse drug reactions, etc.]

- Number of patients with adverse drug reactions, etc.

[Incidence of adverse drug reactions, etc.]

- Calculate with the number of patients with adverse reactions, etc./the number of patients in the safety analysis set ×100.

[Types of adverse drug reactions, etc.]

- Adverse drug reactions will be coded using MedDRA/J. Data will be broadly classified by SOC, and tabulated by PT within the SOC. If the SOC is "investigations," they will be summarized by HLGT (Sort in ascending order of HLGT code, but not output) and by PT.
- For SOC, the number of patients with adverse drug reactions, etc. and the incidence should be described in the order of SOC international consensus. A subject who experiences the same SOC more than once will be counted as 1 subject in the SOC.
- For PT, the number of patients with adverse drug reactions, etc. and the incidence should be entered in ascending order of PT code. If the same PT occurs more than once in the same subject, the subject will be counted as 1 subject in the PT.

*The "number of patients in the safety analysis set" refers to the "analysis set" (described above) for this analysis.

8 Case summary in post-marketing surveillance, etc.

8.1 Case summaries from post-marketing surveillance, etc. (Attached Form 16)

Analyzed:	Safety analysis set
Analysis item:	Case Number
	Name of medical institution
	Sex
	Age
	Reason for use (Disease code and name)
	Comorbidity (Disease code and name)
	Route of Administration
	Maximum Dose
	Mean dose
	Unit
	Duration of use (Cabometyx treatment period)
	Concomitant medications (Drug code and name)
	Degree of efficacy
	Reactions (Disease code, name of disease, outcome)
	Case Study form No.
	Dropout
	Reason for Dropout
Analytical method:	For the above analytical items, a list will be prepared in accordance with the guidelines for preparation of reexamination data entry file specified in PSEHB/PED Notification No. 1119 No. 3 dated November 19, 2020.

Preparation history (version control)

Version	Date	Prepared/changed by	Comments
Original Version	2024.5.20	[redacted]	Preparation of the first version

[Appendix 1] Comparison Table of Changes

Page	Before change	After amendment	Reason for change