Phase 3 Clinical Study of KHK7580

(An Intra-Subject Dose-Adjustment Study of KHK7580 for the Treatment of Hypercalcemia in Patients with Parathyroid Carcinoma or Primary Hyperparathyroidism Who Are Unable to Undergo Parathyroidectomy or Relapse After Parathyroidectomy)

Protocol

Sponsor: Kyowa Hakko Kirin Co., Ltd.

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Handling of this Protocol

The information in this protocol is owned by the sponsor, Kyowa Hakko Kirin Co., Ltd., and is provided only to those directly involved in the study, such as the investigator and subinvestigator (including clinical study collaborators and other staff), the head of the study site, the study drug administrator, the study administration office, and the IRB.

Therefore, the information in this protocol should not be disclosed or leaked to third parties who are not involved in this study.

List of Abbreviations and Definitions of Terms

List of abbreviations

Abbreviation	Unabbreviated term
eCRF	Electronic case report form
EDC	Electronic data capture
PHPT	Primary hyperparathyroidism
PTH	Parathyroid hormone
PTx	Parathyroidectomy
SHPT	Secondary hyperparathyroidism

List of definitions of terms

Term	Definition and explanation of term
Study AMG 073 20000204	A Phase 2 Clinical Study of Cinacalcet Hydrochloride at Doses of 30 to 90 mg/day in Patients with Parathyroid Carcinoma or Refractory PHPT
AUC	Area under the plasma drug concentration-time curve
AUC_{0-t}	Area under the plasma drug concentration-time curve up to t hours after administration
$AUC_{0-\infty}$	Area under the plasma drug concentration-time curve up to infinity
C_{max}	Maximum plasma drug concentration
CYP	Cytochrome P450
EDTA-2K	Dipotassium ethylenediaminetetraacetate
EQ-5D	EuroQol 5 Dimension
EQ-5D-5L	5-level EQ-5D version
F	Bioavailability
FAS	Full analysis set
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
IRB	Institutional review board
Study KRN1493-101	A Phase 3 Clinical Study of Cinacalcet Hydrochloride for the Treatment of Hypercalcemia in Patients with Parathyroid Carcinoma or PHPT Who Are Unable to Undergo PTx or Relapse After PTx
LC/MS/MS	Liquid chromatography / tandem mass spectrometry
M1	KHK7580 metabolite: Taurine conjugate of KHK7580
M2	KHK7580 metabolite: Glycine conjugate of KHK7580
MedDRA/J	Medical Dictionary for Regulatory Activities, Japanese version
mRNA	Messenger RNA
PT	Preferred terms in MedDRA/J
QOL	Quality of life
QT	Time from the start of the Q wave to the end of the T wave on the electrocardiogram
QTc	QT interval corrected for heart rate
RNA	Ribonucleic acid
SOC	System organ class in MedDRA/J
$t_{1/2}$	Plasma elimination half-life
t_{max}	Time to peak plasma drug concentration
Pharmaceuticals and Medical Devices Act	Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices
Study drug	KHK7580
Adverse drug reaction	An adverse event whose causal relationship to the study drug has been judged to be “related” or “possibly related.”

List of items investigated (hematology, blood biochemistry, vital signs, and electrocardiogram)

Item investigated	Abbreviation	Term used in case report forms
Red blood cell count	RBC	Erythrocytes
White blood cell count	WBC	Leukocytes
Hematocrit level	Ht level	Hematocrit
Hemoglobin concentration	Hb concentration	Hemoglobin
Platelet count	PLT	Platelets
Basophil	Baso	Basophils/Leukocytes
Eosinophil	Eosino	Eosinophils/Leukocytes
Neutrophil	Neutro	Neutrophils/Leukocytes
Monocyte	Mono	Monocytes/Leukocytes
Lymphocyte	Lymph	Lymphocytes/Leukocytes
Gamma-glutamyltransferase	γ-GTP	Gamma Glutamyl Transferase
Aspartate aminotransferase	AST	Aspartate Aminotransferase
Alanine aminotransferase	ALT	Alanine Aminotransferase
Alkaline phosphatase	ALP	Alkaline Phosphatase
Albumin	Alb	Albumin
Potassium	K	Potassium
Calcium	Ca	Calcium
Chloride	Cl	Chloride
Creatinine	Cr	Creatinine
Creatine kinase	CK	Creatine Kinase
Corrected serum calcium	Corrected serum Ca	Calcium Corrected
Blood urea nitrogen	BUN	Blood Urea Nitrogen
Total cholesterol	T-Cho	Cholesterol
Total bilirubin	T-Bil	Bilirubin
Total protein	TP	Protein
Triglycerides	TG	Triglycerides
Sodium	Na	Sodium
Lactate dehydrogenase	LDH	Lactate Dehydrogenase
Uric acid	UA	Urate
Magnesium	Mg	Magnesium
Phosphorus	P	Phosphate
intact PTH	Intact PTH	Parathyroid Hormone, Intact
whole PTH	Whole PTH	Parathyroid Hormone, Whole
Urine specific gravity	−	Specific Gravity
Urine pH	−	pH
Urinary glucose	−	Glucose
Urinary protein	−	Protein
Urinary urobilinogen	−	Urobilinogen
Occult blood	−	Occult Blood
Pregnancy test	−	−
Height	−	Height
Body weight	−	Weight
Diastolic blood pressure	−	Diastolic Blood Pressure
Systolic blood pressure	−	Systolic Blood Pressure
Body temperature	−	Temperature
Pulse rate	−	Pulse Rate
Basic waveform	−	−

Time from the start of the Q wave to the end of the T wave on the electrocardiogram	QT interval	QT Duration
QT interval corrected for heart rate	QTc	QTc Correction Method Unspecified

Study participation period

The duration of participation in this study for each subject is from the date of obtaining informed consent to the end of the prespecified final examination or withdrawal extermination. The evaluation period is up to 24 weeks, and the period following the end of the evaluation period is defined as the extended administration period. The total duration of study drug administration is 52 weeks, consisting of the evaluation period and the extended administration period combined.

Timing of study drug administration, observation, and examination

Week 0 is defined as the day on which study drug administration is started (Day 1), and Week X is defined as the examination day X weeks after the start of study drug administration.

Baseline

Baseline values are defined as test values obtained before the start of study drug administration (Week 0).

Protocol Summary

I Study Title

An Intra-Subject Dose-Adjustment Study of KHK7580 for the Treatment of Hypercalcemia in Patients with Parathyroid Carcinoma or Primary Hyperparathyroidism Who Are Unable to Undergo Parathyroidectomy or Relapse After Parathyroidectomy

II Study Objectives

II-I Primary Objective

To evaluate the efficacy of KHK7580 orally administered for up to 24 weeks to patients with hypercalcemia in parathyroid carcinoma or PHPT who are unable to undergo PTx or relapse after PTx

II-II Secondary Objective

To evaluate the long-term safety and efficacy of KHK7580 orally administered to patients with hypercalcemia in parathyroid carcinoma or PHPT who are unable to undergo PTx or relapse after PTx

III Study Phase

Phase 3

IV Endpoints

IV-I Efficacy Evaluation

Primary endpoint

- Number and percentage of subjects whose corrected serum Ca level was maintained at ≤ 10.3 mg/dL for 2 weeks in the evaluation period

Secondary endpoints

- Number and percentage of subjects whose corrected serum Ca level was decreased by ≥ 1.0 mg/dL from baseline and remained decreased for 2 weeks in the evaluation period
- Corrected serum Ca level at each time point
- Intact PTH level at each time point
- Whole PTH level at each time point

IV-II Safety Evaluation

- Presence or absence of adverse events and adverse drug reactions, and the details thereof
- Laboratory values
- Vital sign

IV-III Pharmacokinetic Evaluation

- Plasma KHK7580 concentration
- Pharmacokinetic parameters (t_{max} and C_{max})

IV-IV Other Evaluation

- QOL assessment (EQ-5D-5L)

V Target Disease

Patients with hypercalcemia in parathyroid carcinoma or PHPT who are unable to undergo PTx or relapse after PTx

VI Inclusion Criteria

1) Personally submitted written voluntary informed consent to participate in the study
2) Aged ≥ 20 years at the time of consent
3) A diagnosis of parathyroid carcinoma or PHPT who are unable to undergo PTx or relapse after PTx
4) Corrected serum Ca level > 11.3 mg/dL at screening

VII Exclusion Criteria

1) Treatment with cinacalcet hydrochloride (e.g., Regpara®) within 2 weeks before screening
2) Start of treatment with denosumab (e.g., Ranmark® and Pralia®), bisphosphonates* and calcitonins for the treatment of hypercalcemia, and zoledronic acid hydrate (e.g., Reclast®) for the treatment of osteoporosis; change in dose or dosing regimen of such drugs; or change in type of such drugs within 12 weeks before screening
   *: Alendronate sodium hydrate (e.g., Teiroc®), zoledronic acid hydrate (e.g., Zometa® and zoledronic acid), and pamidronate disodium hydrate (e.g., Aredia®)
3) Start of treatment with an active vitamin D preparation or its derivative, Ca preparation, bisphosphonates* for the treatment of osteoporosis, or calcitonins for purposes other than the treatment of hypercalcemia; change in dose or dosing regimen of such drugs; or change in type of such drugs within 2 weeks before screening
   *: Alendronate sodium hydrate (e.g., Fosamac®), ibandronate sodium hydrate (e.g., Bonviva®), etidronate disodium (e.g., Didronel®), minodronic acid hydrate (e.g., Recalbon®), and sodium risedronate hydrate (e.g., Benet®)
4) Current or history of serious drug allergy. Drug dependence or alcohol dependence and/or their past history
5) Severe heart disease (e.g., Class ≥ III per New York Heart Association classification; see Attachment 5 of the protocol [supplementary volume])
6) Severe hepatic impairment (e.g., treatment with antiviral therapy)
7) Uncontrolled hypertension or diabetes
8) History of diagnosis and treatment of malignant tumor within 5 years before screening (excluding parathyroid carcinoma, basal cell carcinoma, or surgically resected intraepithelial carcinoma of uterine cervix)
9) Treatment with another investigational product (drug or unapproved medical device) in a clinical study or any study equivalent to clinical study within 12 weeks before screening
10) Pregnant, lactating, possibly pregnant female subject (subjects who have been amenorrheic for at least 12 months after the last menstrual period without an alternative medical cause are to be considered to have no childbearing potential) with positive pregnancy test at screening or with

negative pregnancy test at screening who is unwilling to use adequate contraception according to the physician's instructions or wishes to become pregnant during participation in the study

11) Diagnosis of hypercalcemia induced by malignant tumor other than parathyroid carcinoma

12) History of participating in a study of KHK7580 and prior exposure to KHK7580

13) Other subjects unfit for participation in this study in the judgment of the investigator or subinvestigator

VIII Target Number of Subjects

At least 10 subjects receiving study treatment

IX Study Drug

Identification code: KHK7580

Generic name: Evocalcet (JAN), evocalcet (INN)

Chemical nomenclature:

2-{4-[(3*S*)-3-{[(1*R*)-1-(Naphthalen-1-yl)ethyl]amino}pyrrolidin-1-yl]phenyl}acetic acid

Molecular formula: $C_{24}H_{26}N_2O_2$

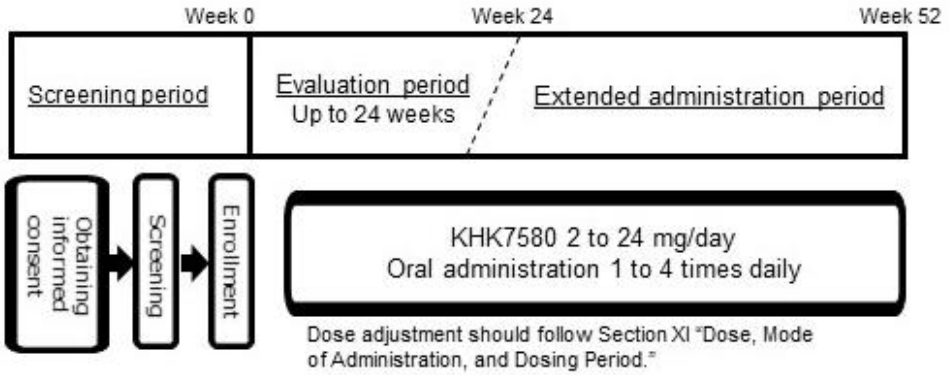
Molecular mass: 374.48

X Study Design

This study is a multicenter, intra-subject dose adjustment study. It consists of the screening period (from the time of consent to the start of study drug administration), the evaluation period (up to 24 weeks from the start of study drug administration), and the extended administration period (until Week 52 after the evaluation period).

The investigator or subinvestigator will conduct the screening after obtaining the written consent. Subsequently, eligible subjects will be enrolled before the start of study drug administration.

The design of this study is outlined below.



After enrollment, the date of the start of study treatment (Day 1) will be defined as Week 0, and the subjects will start to receive study drug at the starting dose of 2 mg once daily (daily dose: 2 mg). However, the starting dose may be 2 mg twice daily (daily dose: 4 mg) for subjects with a corrected serum Ca level of > 12.5 mg/dL at screening. Subsequently, the dose level will be adjusted for each subject in accordance

with Section XI “Dose, Mode of Administration, and Dosing Period” so that corrected serum Ca level can be controlled at ≤ 10.3 mg/dL, and the study drug will be orally administered at each dose level 1 to 4 times daily.

Subjects whose corrected serum Ca level have been maintained at ≤ 10.3 mg/dL for 2 weeks will be transferred to the extended administration period at the time even before Week 24. Other subjects will be transferred to the extended administration period at Week 24 if the investigator or subinvestigator has confirmed that there are no problems with their transfer to the extended administration period. The study treatment period will be 52 weeks consisting of the evaluation period and the extended administration period. The time of transition to the extended administration period (starting week of prolongation) will be recorded in the electronic case report form (eCRF). Subjects will be withdrawn from the study at the end of the evaluation period if, at the discretion of the investigator or subinvestigator, they will not be transferred to the extended administration period. If a subject did not enter the extended administration period, the reason will be recorded in the eCRF.

Subjects will visit the hospital once every 2 weeks during the evaluation period. In the extended administration period following the evaluation period, subjects should visit the hospital to undergo scheduled tests at Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52. If the dose is increased or administration is resumed after an interruption, the date 2 weeks after the dose increase or resumption will be designated as the date of post-dose-increase (or post-resumption) visit, on which the subject should visit the hospital to undergo scheduled tests.

XI. Dose, Mode of Administration, and Dosing Period

Dose and mode of administration

Study treatment will start with once-daily administration of KHK7580 2 mg (daily dose: 2 mg). However, the starting dose of KHK7580 may be 2 mg twice daily (daily dose: 4 mg) for subjects with a corrected serum Ca level of > 12.5 mg/dL at screening. Thereafter, the dosage will be adjusted in accordance with Section XII “Dose Adjustment Criteria” until completion or discontinuation of the study. KHK7580 will be administered orally every day at any dosage and administration specified in (1) to (6), and administration at any other dosage and administration will not be allowed.

(1) 2 mg once daily (daily dose: 2 mg)
(2) 2 mg twice daily (daily dose: 4 mg)
(3) 4 mg twice daily (daily dose: 8 mg)
(4) 6 mg twice daily (daily dose: 12 mg)
(5) 6 mg three time daily (daily dose: 18 mg)
(6) 6 mg four times daily (daily dose: 24 mg)

Dosing period

52 weeks (the evaluation period [up to 24 weeks] and the extended administration period combined)

XII Dose Adjustment Criteria

XII-I Criteria for Dose Increase

In principle, dose increase will be performed on the day of scheduled visit. If all of the following criteria are met, the dose will be increased on a step-by-step basis in accordance with the dose and mode of administration specified in (1) to (6), Section XI.

- Corrected serum Ca level > 10.3 mg/dL at the time of hospital visit.
- The current dose has been administered for at least 2 weeks.
- There are no safety problems with dose increase in the subject in the judgment of the investigator or subinvestigator.

XII-II Dose Reduction

The dose will be reduced if the investigator or subinvestigator determines that the dose should be reduced due to the occurrence of an adverse event, etc. In principle, the dose of the study drug will be reduced on a step-by-step basis; however, if the investigator or subinvestigator deems it necessary, the dose may be reduced by two or more levels at a time. In that case, the lowest possible dose is 2 mg once daily (daily dose: 2 mg). If it is judged that the dose should be reduced further while once-daily administration at a dose of 2 mg is performed (daily dose: 2 mg), study treatment will be interrupted.

XII-III Dose Increase After Dose Reduction

In principle, the first dose increase after dose reduction will be performed on the day of scheduled visit. Dose increase may be performed when the investigator or subinvestigator determines that the dose can be increased. In principle, dose increase will be performed on a step-by-step basis; however, if the investigator or subinvestigator deems it necessary, the dose may be increased by two or more levels at a time, provided that the post-increase dose matches the dosage and administration immediately before dose reduction.

XII-IV Criteria for Treatment Interruption

Study drug administration will be interrupted if any of the following criteria is met.

- Corrected serum Ca level ≤ 7.5 mg/dL.
- The investigator or subinvestigator has determined that study drug administration should be interrupted due to the occurrence of an adverse event, etc.
- The investigator or subinvestigator has determined that the dose should be reduced while the study drug is administered at a dose of 2 mg once daily (daily dose: 2 mg).

XII-V Resumption of Study Drug Administration After Interruption

In principle, study drug administration will be resumed on the day of scheduled visit. Administration will be resumed after the corrected serum Ca level has reached or exceeded 8.4 mg/dL and the investigator or subinvestigator has judged that administration can be resumed in consideration of the safety of the subject. The dosage and administration at the time of resumption of administration will be the same as those immediately before interruption or the dosage and administration at a lower level.

The duration of an interruption should not exceed 8 consecutive weeks; if the investigator or subinvestigator has judged that it is impossible to resume administration, the subject will be withdrawn from the study.

XIII Planned Study Period

August 2017 - October 2019

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1 HISTORY AND BACKGROUND OF THE STUDY

1.1 Background

1.2 KHK7580

1.3 Non-Clinical Study Results

1.4 Clinical Study Results

1.5 Background to This Study

2 COMPLIANCE WITH GCP, ETC.

In keeping with the spirit of the Declaration of Helsinki, this study will be conducted in compliance with the Pharmaceuticals and Medical Devices Act, the Ministerial Ordinance on Good Clinical Practice for Drugs (Ordinance of the Ministry of Health and Welfare No. 28 of March 27, 1997), and partial amendments to the Ministerial Ordinance.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

To evaluate the efficacy of KHK7580 orally administered for up to 24 weeks to patients with hypercalcemia in parathyroid carcinoma or PHPT who are unable to undergo PTx or relapse after PTx

3.1.2 Secondary Objective

To evaluate the long-term safety and efficacy of KHK7580 orally administered to patients with hypercalcemia in parathyroid carcinoma or PHPT who are unable to undergo PTx or relapse after PTx

3.2 Endpoints

3.2.1 Efficacy Evaluation

3.2.1.1 Primary Endpoint

- Number and percentage of subjects whose corrected serum Ca level was maintained at ≤ 10.3 mg/dL for 2 weeks in the evaluation period

3.2.1.2 Secondary Endpoints

- Number and percentage of subjects whose corrected serum Ca level was decreased by ≥ 1.0 mg/dL from baseline and remained decreased for 2 weeks in the evaluation period
- Corrected serum Ca level at each time point
- Intact PTH level at each time point
- Whole PTH level at each time point

3.2.2 Safety Evaluation

- Presence or absence of adverse events and adverse drug reactions, and the details thereof
- Laboratory values
- Vital sign

3.2.3 Pharmacokinetic Evaluation

- Plasma KHK7580 concentration
- Pharmacokinetic parameters (t_{max} and C_{max})

3.2.4 Other Evaluation

- QOL assessment (EQ-5D-5L)

4 STUDY DESIGN

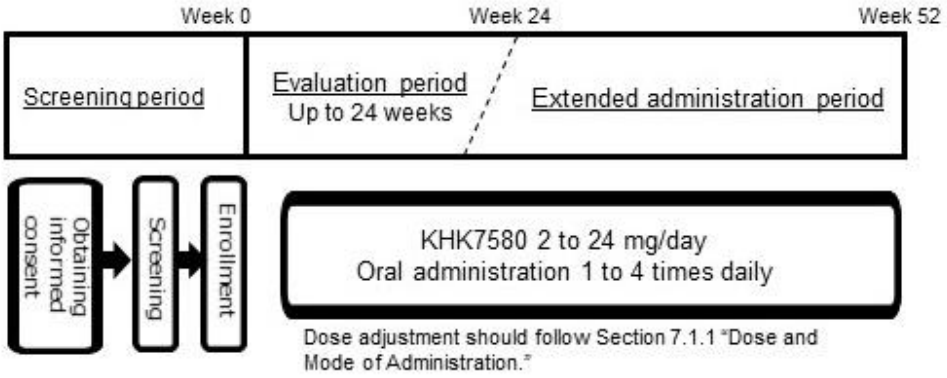
4.1 Study Design

The design of this study is outlined in Table 4.1-1.

This study is a multicenter, intra-subject dose adjustment study. It consists of the screening period (from the time of consent to the start of study drug administration), the evaluation period (up to 24 weeks from the start of study drug administration), and the extended administration period (until Week 52 after the evaluation period).

The investigator or subinvestigator will conduct the screening after obtaining the written consent. Subsequently, eligible subjects will be enrolled before the start of study drug administration.

Table 4.1-1. Outline of the study design



After enrollment, the date of the start of study treatment (Day 1) will be defined as Week 0, and the subjects will start to receive study drug at the starting dose of 2 mg once daily (daily dose: 2 mg). However, the starting dose may be 2 mg twice daily (daily dose: 4 mg) for subjects with a corrected serum Ca level of > 12.5 mg/dL at screening. Subsequently, the dose level will be adjusted for each subject in accordance with Section 7.1.1 "Dose, Mode of Administration, and Dosing Period" so that corrected serum Ca level can be controlled at ≤ 10.3 mg/dL, and the study drug will be orally administered at each dose level 1 to 4 times daily.

Subjects whose corrected serum Ca level have been maintained at ≤ 10.3 mg/dL for 2 weeks will be transferred to the extended administration period at the time even before Week 24. Other subjects will be transferred to the extended administration period at Week 24 if the investigator or subinvestigator has confirmed that there are no problems with their transfer to the extended administration period. See Table 9.1-1 "Schedule of observation, investigation, and examination (evaluation period)" and Table 9.1-2 "Schedule of observation, investigation, and examination (extended administration period)" for visit schedules for subjects transitioning to the extended administration period before Week 24. The study treatment period will be 52 weeks consisting of the evaluation period and the extended administration period. The time of transition to the extended administration period (starting week of prolongation) will be recorded in the electronic case report form (eCRF). Subjects will be withdrawn from the study at the end of the evaluation period if, at the discretion of the investigator or subinvestigator, they will not be transferred

to the extended administration period. If a subject did not enter the extended administration period, the reason will be recorded in the eCRF.

Subjects will visit the hospital once every 2 weeks during the evaluation period. In the extended administration period following the evaluation period, subjects should visit the hospital to undergo scheduled tests at Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52. If the dose is increased or administration is resumed after an interruption, the date 2 weeks after the dose increase or resumption will be designated as the date of post-dose-increase (or post-resumption) visit, on which the subject should visit the hospital to undergo scheduled tests.

4.2 Type of Study

Phase 3 clinical study (multicenter, intra-subject, dose adjustment study)

5 STUDY DRUG

5.1 Investigational Drug (Investigational Therapy or Treatment)

Identification code: KHK7580

Generic name: Evocalcet (JAN), evocalcet (INN)

Chemical nomenclature:

2-{4-[(3*S*)-3-{[(1*R*)-1-(Naphthalen-1-yl)ethyl]amino}pyrrolidin-1-yl]phenyl}acetic acid

Molecular formula: $C_{24}H_{26}N_2O_2$

Molecular mass: 374.48

5.2 Contained Amount and Formulation

Light yellow, film-coated tablets each containing 2 mg of KHK7580

5.3 Packaging

Each box contains three PTP sheets, each of which contains 10 tablets of KHK7580 (2 mg). The PTP sheets are packaged in aluminum pillows (with desiccant).

5.4 Labeling

The outer box will be labeled with a statement to the effect that the product is for investigational use, and with the sponsor's name and address, identification code, content, lot number, and storage method.

5.5 Storage Method

Storage at room temperature (1 to 30°C).

5.6 Procedures for Delivery, Storage, Management, and Recovery of Study Drugs

After conclusion of a clinical study agreement, the sponsor will deliver the study drug to the study site via a courier company contracted by . The sponsor will also prepare and deliver to the study site written procedures for the management of the study drug.

The study drug administrator at the study site will appropriately store and manage the study drug in accordance with the written procedures, and will keep records of inventory, use status, returns, disposal, etc. The study drug administrator will check the number of unused study drugs and used study drugs (including PTP sheets and empty boxes), disposal records, etc. as appropriate, and reconcile them with the

study drug accountability record. In principle, PTP sheets and empty boxes should be discarded at the study site after completion of the study, but they may be returned to the sponsor.

When returning or disposing of the study drug, the study drug administrator will provide the sponsor with a copy of the study drug accountability record.

Leftover drugs of subjects who have completed or have been withdrawn from this study will not be reused for any reason whatsoever.

6 CRITERIA FOR SUBJECT ENROLLMENT

6.1 Target Disease (Diagnosis Group)

Patients with hypercalcemia in parathyroid carcinoma or PHPT who are unable to undergo PTx or relapse after PTx

6.2 Inclusion Criteria

Subjects enrolled in this study should satisfy all of the following criteria.

1) Personally submitted written voluntary informed consent to participate in the study
2) Aged ≥ 20 years at the time of consent
3) A diagnosis of parathyroid carcinoma or PHPT who are unable to undergo PTx or relapse after PTx
4) Corrected serum Ca level > 11.3 mg/dL at screening

6.3 Exclusion Criteria

Any individuals falling under any of the following criteria should not be enrolled in this study.

1) Treatment with cinacalcet hydrochloride (e.g., Regpara®) within 2 weeks before screening
2) Start of treatment with denosumab (e.g., Ranmark® and Pralia®), bisphosphonates* and calcitonins for the treatment of hypercalcemia, and zoledronic acid hydrate (e.g., Reclast®) for the treatment of osteoporosis; change in dose or dosing regimen of such drugs; or change in type of such drugs within 12 weeks before screening
   *: Alendronate sodium hydrate (e.g., Teiroc®), zoledronic acid hydrate (e.g., Zometa® and zoledronic acid), and pamidronate disodium hydrate (e.g., Aredia®)
3) Start of treatment with an active vitamin D preparation or its derivative, Ca preparation, bisphosphonates* for the treatment of osteoporosis, or calcitonins for purposes other than the treatment of hypercalcemia; change in dose or dosing regimen of such drugs; or change in type of such drugs within 2 weeks before screening
   *: Alendronate sodium hydrate (e.g., Fosamac®), ibandronate sodium hydrate (e.g., Bonviva®), etidronate disodium (e.g., Didronel®), minodronic acid hydrate (e.g., Recalbon®), and sodium risedronate hydrate (e.g., Benet®)
4) Current or history of serious drug allergy. Drug dependence or alcohol dependence and/or their past history
5) Severe heart disease (e.g., Class ≥ III per New York Heart Association classification; see Attachment 5 of the protocol [supplementary volume])
6) Severe hepatic impairment (e.g., treatment with antiviral therapy)
7) Uncontrolled hypertension or diabetes
8) History of diagnosis and treatment of malignant tumor within 5 years before screening (excluding parathyroid carcinoma, basal cell carcinoma, or surgically resected intraepithelial carcinoma of uterine cervix)
9) Treatment with another investigational product (drug or unapproved medical device) in a clinical study or any study equivalent to clinical study within 12 weeks before screening

10） Pregnant, lactating, possibly pregnant female subject (subjects who have been amenorrheic for at least 12 months after the last menstrual period without an alternative medical cause are to be considered to have no childbearing potential) with positive pregnancy test at screening or with negative pregnancy test at screening who is unwilling to use adequate contraception according to the physician’s instructions or wishes to become pregnant during participation in the study
11） Diagnosis of hypercalcemia induced by malignant tumor other than parathyroid carcinoma
12） History of participating in a study of KHK7580 and prior exposure to KHK7580
13） Other subjects unfit for participation in this study in the judgment of the investigator or subinvestigator

7 REGIMEN AND CONCOMITANT THERAPY

7.1 Dose, Mode of Administration, and Dosing Period

7.1.1 Dose and Mode of Administration

7.1.1.1 Dosage and Administration (Dose per Administration and Dosing Frequency)

Study treatment will start with once-daily administration of KHK7580 2 mg (daily dose: 2 mg). However, the starting dose may be KHK7580 2 mg twice daily (daily dose: 4 mg) for subjects with a corrected serum Ca level of > 12.5 mg/dL at screening. Thereafter, the dosage will be adjusted in accordance with Section 7.1.1.2 “Dose Adjustment Criteria” until completion or discontinuation of the study. KHK7580 will be administered orally every day at any dosage and administration specified in (1) to (6), and administration at any other dosage and administration will not be allowed.

(1) 2 mg once daily (daily dose: 2 mg)
(2) 2 mg twice daily (daily dose: 4 mg)
(3) 4 mg twice daily (daily dose: 8 mg)
(4) 6 mg twice daily (daily dose: 12 mg)
(5) 6 mg three time daily (daily dose: 18 mg)
(6) 6 mg four times daily (daily dose: 24 mg)

7.1.1.2 Dose Adjustment Criteria

7.1.1.2.1 Criteria for Dose Increase

In principle, dose increase will be performed on the day of scheduled visit. If all of the following criteria are met, the dose will be increased on a step-by-step basis in accordance with the dose and mode of administration specified in (1) to (6), Section 7.1.1.1.

- Corrected serum Ca level > 10.3 mg/dL at the time of hospital visit.
- The current dose has been administered for at least 2 weeks.
- There are no safety problems with dose increase in the subject in the judgment of the investigator or subinvestigator.

7.1.1.2.2 Dose Reduction

The dose will be reduced if the investigator or subinvestigator determines that the dose should be reduced due to the occurrence of an adverse event, etc. In principle, the dose of the study drug will be reduced on a step-by-step basis; however, if the investigator or subinvestigator deems it necessary, the dose may be reduced by two or more levels at a time. In that case, the lowest possible dose is 2 mg once daily (daily dose: 2 mg). If it is judged that the dose should be reduced further while once-daily administration at a dose of 2 mg is performed (daily dose: 2 mg), study treatment will be interrupted.

7.1.1.2.3 Dose Increase After Dose Reduction

In principle, the first dose increase after dose reduction will be performed on the day of scheduled visit. Dose increase may be performed when the investigator or subinvestigator determines that the dose can be increased. In principle, dose increase will be performed on a step-by-step basis; however, if the investigator or subinvestigator deems it necessary, the dose may be increased by two or more levels at a time, provided that the post-increase dose matches the dosage and administration immediately before dose reduction.

7.1.1.2.4 Criteria for Treatment Interruption

Study drug administration will be interrupted if any of the following criteria is met.

- Corrected serum Ca level ≤ 7.5 mg/dL.
- The investigator or subinvestigator has determined that study drug administration should be interrupted due to the occurrence of an adverse event, etc.
- The investigator or subinvestigator has determined that the dose should be reduced while the study drug is administered at a dose of 2 mg once daily (daily dose: 2 mg).

7.1.1.2.5 Resumption of Study Drug Administration After Interruption

In principle, study drug administration will be resumed on the day of scheduled visit. Administration will be resumed after the corrected serum Ca level has reached or exceeded 8.4 mg/dL AND the investigator or subinvestigator has judged that administration can be resumed in consideration of the safety of the subject. The dosage and administration at the time of resumption of administration will be the same as those immediately before interruption or the dosage and administration at a lower level.

The duration of an interruption should not exceed 8 consecutive weeks; if the investigator or subinvestigator has judged that it is impossible to resume administration, the subject will be withdrawn from the study.

7.1.2 Dosing Period (Study Length)

52 weeks (the evaluation period [up to 24 weeks] and the extended administration period combined)

7.2 Concomitant Drugs and Therapies (Concomitant Medications)

If a drug or therapy other than the study drug was used between Week 0 and the completion or discontinuation of the study, the following information will be entered into the eCRF. However, concomitant therapy will be entered only if it is used as a treatment for the underlying disease.

- Name of drug/therapy (reported name of drug, med, or therapy)
- Route of administration
- Duration of treatment (start date of medication / end date of medication)
- Reason for use (indication)

With regard to the restricted concomitant medications (Section 7.2.2), however, information about "dosing frequency per interval" and "total daily dose," in addition to the items listed above, will be entered into the eCRF for the following drugs: active vitamin D preparations and their derivatives, Ca preparations, calcitonins not intended for the treatment of hypercalcemia, and bisphosphonates for the treatment of osteoporosis used from 2 weeks before screening until the completion or discontinuation of

the study; zoledronic acid hydrate (e.g., Reclast®) for the treatment of osteoporosis and denosumab (Pralia®) used from 12 weeks before screening until the completion or discontinuation of the study. No entries are necessary for fluid replacement with physiological saline or dissolution media for non-therapeutic purposes, local anesthetics for pain relief at the time of indwelling needle puncture, or contrast media for diagnostic imaging.

7.2.1 Prohibited Concomitant Medication

Cinacalcet hydrochloride (e.g., Regpara®) may not be concomitantly used during the study participation period. This drug should not be used from 2 weeks before screening until the completion or discontinuation of the study.

7.2.2 Restricted Concomitant Medications

If the following restricted concomitant medications are used, changes in the type or dosage and administration thereof will be prohibited from 2 weeks before screening until the completion or discontinuation of the study for 1) to 4), and from 12 weeks before screening until the completion or discontinuation of the study for 5) to 8). Also, in subjects who are not using any of these restricted concomitant medications, administration of a restricted concomitant medication may not be newly started during these time frames.

1） Active vitamin D preparations and their derivatives
2） Ca preparations
3） Calcitonins not intended for the treatment of hypercalcemia
4） Bisphosphonates for the treatment of osteoporosis (including those not listed below)
- Alendronate sodium hydrate (e.g., Fosamac®)
- Ibandronate sodium hydrate (e.g., Bonviva®)
- Etidronate disodium (e.g., Didronel®)
- Minodronic acid hydrate (e.g., Recalbon®)
- Sodium risedronate hydrate (e.g., Benet®)

5） Zoledronic acid hydrate for the treatment of osteoporosis. (e.g., Reclast®)
6） Denosumab (e.g., Ranmark® and Pralia®)
7） Calcitonins for the treatment of hypercalcemia
8） Bisphosphonates for the treatment of hypercalcemia (including those not listed below)
- Alendronate sodium hydrate (e.g., Teiroc®)
- Zoledronic acid hydrate (e.g., Zometa® and zoledronic acid)
- Pamidronate disodium hydrate (e.g., Aredia®)

8 REGISTRATION IN THE STUDY

8.1 Method of Subject Registration

The investigator or subinvestigator will provide a thorough explanation about this study to prospective subjects and obtain written informed consent for participation in the study if they are deemed to satisfy the inclusion criteria and not to fall under any of the exclusion criteria. After obtaining written informed consent, the investigator or subinvestigator will send a fax to the contact address indicated in Section 8.4 by means of the Case Registration Form for the KHK7580 Phase 3 Clinical Study (see Attachment 3 of the protocol [supplementary volume]) for subjects whose eligibility has been confirmed through screening. Registration will be carried out in accordance with the provisions of Section 8.2.

8.1.1 Assignment of Subject Identifiers

The investigator or subinvestigator will assign subject identifiers to all subjects who have given their consent at the study site in accordance with the following rules. The same subject identifier will be used for a subject throughout the study participation period. The last four digits of the subject identifier (*XX*-*YY*) will be used as the subject number.

Subject identifier: *7580-101-XX-YY*

XX: Site number (see Attachment 1 of the protocol [supplementary volume])

YY: Serial number of the subject who has given his/her consent at the study site

For example, the subject identifier of a subject who was the first to give his/her consent at a study site (site number: 01) would be *7580-101-01-01*.

When assigning a subject identifier to a subject, the investigator or subinvestigator will record the subject identifier in the screening log.

8.2 Registration Procedure

Subject registration will be carried out in accordance with the following procedures.

1） After obtaining informed consent, the investigator or subinvestigator will perform screening.

2） The investigator or subinvestigator will check subjects against all inclusion and exclusion criteria, prepare the Case Registration Form for the KHK7580 Phase 3 Clinical Study (see Attachment 3 of the protocol [supplementary volume]) for all subjects who have given their consent, whether or not the criteria are met, and notify the Study Registration Center described in Section 8.4 by fax. Registration will be done during the period from the date on which checking results for all inclusion and exclusion criteria are obtained (after screening results are known) until the start of study drug administration. However, if a subject withdraws consent or is found to be ineligible after consent has been obtained, the Case Registration Form for the KHK7580 Phase 3 Clinical Study (see Attachment 3 of the protocol [supplementary volume]) should be prepared promptly and faxed to the Study Registration Center described in Section 8.4.

3） The 7580-101 Study Registration Center will verify the eligibility of subjects. The 7580-101 Study Registration Center may inquire with the investigator or subinvestigator before the scheduled date of study drug administration if any questions arise about the information provided at the time of registration. For subjects who do not satisfy the inclusion criteria and/or fall under

any of the exclusion criteria, the investigator or subinvestigator will enter the reason for ineligibility, subject identifier, date of obtaining written informed consent, and sex in the eCRF.

4) The investigator or subinvestigator will record and maintain a screening log of registered subjects.

8.3 Re-registration

Subjects who were found to be ineligible may be re-registered at the discretion of the investigator or subinvestigator, provided that consent is obtained anew and the subjects undergo screening once again. When a subject who was once found to be ineligible is re-registered, a new subject identifier will be assigned.

8.4 Contact for Registration

7580-101 Study Registration Center

Fax:

Reception hours: 9:00 to 18:00 (except Saturdays, Sundays, national holidays, and the period from December 29 through January 3)

9 OBSERVATION, INVESTIGATION, AND EXAMINATION ITEMS AND SCHEDULE

9.1 Schedule

Screening will be performed in subjects who have given their written informed consent. Afterwards, the study drug will be administered to subjects whose eligibility has been confirmed and for whom registration has been completed, and observation, investigation, and examination will be performed according to the schedule described in Table 9.1-1 and Table 9.1-2. Details are given in Section 9.3 “Observation and Investigation Items and the Timing Thereof” and Section 9.4 “Examination Items and the Timing Thereof.” Visits and examinations will be carried out on the scheduled visit dates with an allowable window of ± 4 days during the period between Week 2 and Week 24, and on the scheduled visit dates with an allowable window of ± 7 days thereafter. If a decision is made to discontinue study drug administration on a day of scheduled visit, the results of the examination on that scheduled visit date may be handled as the results of withdrawal examination.

Table 9.1-1. Observation, investigation, and examination schedule (evaluation period)

	Obtaining informed consent	Screening	Registration	Evaluation period																	At discontinuation[l]
				Time after administration of the study drug (Weeks)																	
				0					2	4[e]	6[e]	8[f]	10[f]	12[g]	14[g]	16[h]	18[h]	20[i]	22[i]	24[j]	
Time after administration (h)				Before administration	0.5	1	2	3													
Obtaining informed consent	X																				
Study drug administration				←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	→
Subject demographics		X[a]																			
Registration			X																		
Height		X[a]																			
Body weight				X																X	X
QOL assessment				X																X	X
Vital sign				X					X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology				X					X	X	X	X	X	X	X	X	X	X	X	X	X
Blood biochemistry 1		X[b]		X					X	X	X	X	X	X	X	X	X	X	X	X	X
Blood biochemistry 2				X					X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis				X					X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma drug concentration[c]				X	X	X	X	X	X	X[k]		X[k]		X[k]		X[k]		X[k]		X[k]	
Pregnancy test[d]		X																			X
Electrocardiogram (12-lead)				X					X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events				←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	→
Confirmation of the use status of concomitant medications	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	→
Investigation of administration status				←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	→

The allowable window period is ± 4 days of the scheduled visit dates (except for Week 0).

a) Performed after informed consent is obtained and before the start of study drug administration (Week 0).

b) Corrected serum Ca, Ca, and Alb levels will be measured. In the event that the test result does not meet inclusion criteria 4), re-testing may be performed. If performed in Week 0, it will be handled as a test result in Week 0.

c) From Week 2 onwards, if a subject is not taking the study drug as of the day before his/her visit to the hospital, it is permissible not to perform blood collection on the day of hospital visit. It is also permissible not to perform post-dose blood collection in a subject for whom a decision to interrupt study drug administration has been made on the day of hospital visit.

d) Female subjects only. However, no pregnancy test is required if at least 12 months have passed since the last menstrual period without any other medical reason.

e) Subjects whose corrected serum Ca level has been maintained at ≤ 10.3 mg/dL for 2 weeks will immediately transition to the extended administration period, with the next visit being Week 8.

f) Subjects whose corrected serum Ca level has been maintained at ≤ 10.3 mg/dL for 2 weeks will immediately transition to the extended administration period, with the next visit being Week 12.

g) Subjects whose corrected serum Ca level has been maintained at ≤ 10.3 mg/dL for 2 weeks will immediately transition to the extended administration period, with the next visit being Week 16.

h) Subjects whose corrected serum Ca level has been maintained at ≤ 10.3 mg/dL for 2 weeks will immediately transition to the extended administration period, with the next visit being Week 20.

i) Subjects whose corrected serum Ca level has been maintained at ≤ 10.3 mg/dL for 2 weeks will immediately transition to the extended administration period, with the next visit being Week 24.
j) Subjects whose corrected serum Ca level has been maintained at ≤ 10.3 mg/dL for 2 weeks will immediately transition to the extended administration period, with the next visit being Week 28.
k) If the subject transitions to the extended administration period, plasma drug concentrations may be measured at the end of the evaluation period (0.5, 1, 2, and 3 hours) (see Table 9.1-2 "Observation, investigation, and examination schedule (extended administration period)").
l) If a decision is made to discontinue study drug administration on a day of scheduled visit, the results of the examination on that scheduled visit date may be handled as the results of withdrawal examination.

Table 9.1-2. Observation, investigation, and examination schedule (extended administration period)

	Extended administration period																	
	Time after the start of study drug administration (Weeks)																[h] At the first visit following dose increase or resumption after interruption	[l] At discontinuation
	8[a]	12[b]	16[c]	20[d]	24[e]	After the end of the evaluation period[j]				28[f]	32	36	40	44	48	52		
Time after administration (h)						0.5	1	2	3									
Study drug administration (h)	←	—	—	—	—	—	—	—	—	—	—	—	—	—	→		X	
Body weight					X											X		X
QOL assessment					X											X		X
Vital sign	X	X	X	X	X					X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X					X	X	X	X	X	X	X	X	X
Blood biochemistry 1	X	X	X	X	X					X	X	X	X	X	X	X	X	X
Blood biochemistry 2	X	X	X	X	X					X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X					X	X	X	X	X	X	X	X	X
Plasma drug concentration[g]	X[i]	X[i]	X[i]	X[i]	X[i]	X	X	X	X									
Pregnancy test[k]																X		X
Electrocardiogram (12-lead)	X	X	X	X	X					X	X	X	X	X	X	X	X	X
Adverse events	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Confirmation of the use status of concomitant medications	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Investigation of administration status	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→

The allowable window for the scheduled visit dates is ± 4 days until Week 24 and ± 7 days thereafter.
a) For subjects who completed the evaluation period in Week 4 or 6, hospital visits in the extended administration period will start in Week 8.
b) For subjects who completed the evaluation period in Week 8 or 10, hospital visits in the extended administration period will start in Week 12.
c) For subjects who completed the evaluation period in Week 12 or 14, hospital visits in the extended administration period will start in Week 16.
d) For subjects who completed the evaluation period in Week 16 or 18, hospital visits in the extended administration period will start in Week 20.

e) For subjects who completed the evaluation period in Week 20 or 22, hospital visits in the extended administration period will start in Week 24.
f) For subjects who completed the evaluation period in Week 24, hospital visits in the extended administration period will start in Week 28.
g) If a subject is not receiving the study drug as of the day before his/her visit to the hospital, it is permissible not to perform blood collection on the day of hospital visit. It is also permissible not to perform post-dose blood collection in a subject for whom a decision to interrupt study drug administration has been made on the day of hospital visit.
h) If the dose of the study drug is increased (with or without prior dose reduction) or administration is resumed after an interruption on a scheduled visit date, the date 2 weeks after the dose increase or resumption will be designated as the date of post-dose-increase (or post-resumption) visit, and scheduled tests will be performed on that date.
i) If measurement of plasma drug concentrations was not performed after the end of the evaluation period (0.5, 1, 2, and 3 hours), it should be performed by Week 24.
j) On this date, subjects should not take the study drug before hospital visit.
k) Female subjects only. However, no pregnancy test is required if at least 12 months have passed since the last menstrual period without any other medical reason.
l) If a decision is made to discontinue study drug administration on a day of scheduled visit, the results of the examination on that scheduled visit date may be handled as the results of withdrawal examination.

9.2 Subject Demographics

The following items will be investigated and entered into the eCRF.

- Date of informed consent
- Sex
- Date of birth
- Medical history – Complication
- Medical history – Past medical history
- Medical history – Primary disease
- Date of diagnosis for primary disease
- Occurrence of pharmacotherapy for primary disease/PTx/parathyroid intervention therapy and start date of procedure
- Use status of cinacalcet hydrochloride (cinacalcet hydrochloride before screening)
  - Total daily dose
  - Dosage (dosing frequency per interval)
  - Dosing period (start date of medication and end date of medication)
  - Reason of medication stopped
  - UGI tract disturbance due to cinacalcet hydrochloride
- Other items related to the inclusion and exclusion criteria

Visit [allowable window]: At the time of screening [from the time of obtaining consent until before the start of study drug administration (Week 0)]

9.3 Observation and Investigation Items and the Timing Thereof

9.3.1 Exposure

The following items will be entered into the eCRF for each scheduled visit date.

- Start date of treatment
- End date of treatment
- Dosage and administration[*1] (planned dosing frequency and dose)
- Status of study drug administration (number of tablets taken [actual dose] and compliance[*2])
- Date and time when the study drug was taken[*3]

*1: If the dose was reduced or study drug administration was interrupted, the reason will be investigated and entered into the eCRF. For dose reduction or interruption due to an adverse event, the details of the adverse event will be entered into the eCRF.

*2: Only for 1 week prior to plasma drug concentration measurement. The date on which the subject took the study drug in accordance with the dosage and administration specified by his/her doctor will be designated as the study drug compliance date, and the status of study drug compliance for 1 week prior to plasma drug concentration measurement will be recorded in the eCRF on a daily basis.

*3: Only on the scheduled visit dates on which the plasma drug concentration is measured. The date and time of study drug administration immediately before plasma drug concentration measurement (latest date/time of administration before specimen collection), and, for Week 0 and the date of

plasma drug concentration measurement after the end of the evaluation period, the time of study drug administration on that day (latest time of administration before specimen collection of 0.5h/1h/2h/3h on the specimen collection day) will be entered into the eCRF.

Visit: [Evaluation period] Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24, and at the time of discontinuation
[Extended administration period] Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52, at the first visit following dose increase or resumption after interruption, and at the time of discontinuation

Allowable window: Within 4 days before and after the scheduled visit dates during the period from Week 2 to Week 24, and within 7 days before and after the scheduled visit dates thereafter

9.3.2 QOL Assessment (EQ-5D-5L)

A five-item questionnaire survey on health condition will be conducted, and the results will be entered into the eCRF. In the questionnaire, the answer best representing the health condition on the day of the survey will be selected from among five options.

The health condition on the day of the survey will also be assessed using a visual analogue scale, and the results will be entered into the eCRF.

Visit: Weeks 0, 24, and 52, and at the time of discontinuation

Allowable window: Within 4 days before and after the scheduled visit date in Week 24, and within 7 days before and after the scheduled visit date in Week 52

9.4 Examination Items and the Timing Thereof

9.4.1 Laboratory Tests

In order to determine whether there are any changes in laboratory values after study drug administration, tests will be performed according to the prespecified testing schedule, and the date of testing (date of sample collection) and test results (except for screening tests) will be entered into the eCRF. The tests in Week 0 will be performed before the first administration of the study drug. All laboratory tests, except for intact PTH and whole PTH levels, will be performed at the study site. Intact PTH and whole PTH levels will be measured at a central laboratory, and the results will be reported to the study site and sponsor. The allowable window for the timing of measurement of test items will be within 4 days before and after the scheduled visit dates during the period from Week 2 to Week 24, and within 7 days before and after the scheduled visit dates thereafter.

9.4.1.1 Hematology

Test items: WBC, WBC fraction (Baso, Eosino, Neutro, Mono, and Lymph), RBC, Ht level, Hb concentration, and PLT

Visit: [Evaluation period] Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24, and at the time of discontinuation

[Extended administration period] Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52, at the first visit following dose increase or resumption after interruption, and at the time of discontinuation

9.4.1.2 Blood Biochemistry 1

Test items (in-hospital measurement): T-Cho, TG, TP, BUN, UA, Cr, T-Bil, AST, ALT, γ-GTP, LDH, ALP, CK, Na, K, Cl, Mg, corrected serum Ca[*1], Ca, Alb, and P

Visit: At the time of screening[*2]

[Evaluation period] Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24, and at the time of discontinuation

[Extended administration period] Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52, at the first visit following dose increase or resumption after interruption, and at the time of discontinuation

*1: If the serum Alb value is less than 4.0 g/dL, the serum Ca level will be corrected according to the following formula. If the serum Alb level is 4.0 g/dL or higher, the actual serum Ca level will be handled as the corrected serum Ca level.

Corrected serum Ca level (mg/dL) = actual serum Ca level (mg/dL) + 4 - serum Alb value (g/dL)

*2: Ca, corrected serum Ca level, and Alb will be measured. In the event that the test result does not meet inclusion criteria 4), re-testing may be performed. If performed in Week 0, it will be handled as a test result in Week 0.

9.4.1.3 Blood Biochemistry 2

Test items (central measurement): Intact PTH and whole PTH levels

Visit: [Evaluation period] Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24, and at the time of discontinuation

[Extended administration period] Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52, at the first visit following dose increase or resumption after interruption, and at the time of discontinuation

9.4.1.4 Urinalysis

Test items: Specific gravity, pH, and qualitative measurements (glucose, protein, urobilinogen, and occult blood)

Visit: [Evaluation period] Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24, and at the time of discontinuation

[Extended administration period] Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52, at the first visit following dose increase or resumption after interruption, and at the time of discontinuation

9.4.2 Vital Signs and Other Tests

The following tests will be performed, and the date of measurement and test results will be entered into the eCRF. The tests in Week 0 will be performed before the first administration of the study drug. The

allowable window for the timing of measurement of test items will be within 4 days before and after the scheduled visit dates during the period from Week 2 to Week 24, and within 7 days before and after the scheduled visit dates thereafter.

9.4.2.1 Height

Test item: Height

Visit [allowable window]: At the time of screening [from the time of obtaining consent until before the start of study drug administration (Week 0)]

9.4.2.2 Weight

Test item: Weight

Visit: Weeks 0, 24, and 52, and at the time of discontinuation

9.4.2.3 Vital Signs

Test items: Blood pressure, pulse rate, and body temperature (axillary)

Visit: [Evaluation period] Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24, and at the time of discontinuation

[Extended administration period] Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52, at the first visit following dose increase or resumption after interruption, and at the time of discontinuation

9.4.3 Standard 12-Lead Electrocardiogram (ECG)

A standard 12-lead ECG will be performed and the following items will be entered into the eCRF.

- Date of ECG
- Result or finding of ECG

If there are any findings, it will be determined whether or not the findings are clinically problematic (interpretation: normal or abnormal, not clinically significant/abnormal, clinically significant), and will be entered into the eCRF.

Test items: Basic waveform, QT interval, and QTc

However, if the above items are not measurable due to atrial fibrillation or the like, such a measurement failure will not be handled as a deviation.

Visit: [Evaluation period] Weeks 0*, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24, and at the time of discontinuation

[Extended administration period] Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52, at the first visit following dose increase or resumption after interruption, and at the time of discontinuation

*: Performed before the first administration of the study drug.

Allowable window: Within 4 days before and after the scheduled visit dates during the period from Week 2 to Week 24, and within 7 days before and after the scheduled visit dates thereafter

9.4.4 Pregnancy Test

Test item: Pregnancy status*

Visit: At the time of screening, Week 52, and at the time of discontinuation

*: Female subjects only. However, no pregnancy test is required if at least 12 months have passed since the last menstrual period without any other medical reason.

9.4.5 Drug Concentration Measurement

9.4.5.1 Plasma KHK7580 Concentrations

Plasma KHK7580 concentrations will be measured. Residual samples after measurement of plasma drug concentrations may be used for the analysis of KHK7580 metabolites that is not planned in this study. Drug concentration data from this study may also be combined with data from other studies for population pharmacokinetic analysis.

9.4.5.2 Blood Collection Method and Sample Processing Method

Venous blood (2 mL) will be collected in a vacuum blood collection tube containing EDTA-2K, and mixed promptly by inverting the tube. The plasma obtained by centrifugation will be divided into two equal portions and dispensed into two sample tubes. The plasma samples will be frozen immediately after dispensing, and cryopreserved at -20°C or below until the start of measurement.

The date and time of blood collection (date/time of specimen collection) and the date and time when the study drug was taken (see Section 9.3.1) will be entered into the eCRF.

9.4.5.3 Blood Collection Time Points

Visit of blood collection [allowable window]:

Weeks 0 (before the first administration of the study drug, and 0.5 hours [± 10 minutes], 1 hour [± 10 minutes], 2 hours [± 15 minutes], and 3 hours [± 15 minutes] after the first administration of the study drug), 2, 4, 8, 12, 16, 20, and 24, after the end of the evaluation period* (0.5 hours [± 10 minutes], 1 hour [± 10 minutes], 2 hours [± 15 minutes], and 3 hours [± 15 minutes] after administration of the study drug)

*: If a subject transitions to the extended administration period before Week 24, blood collection will be performed in any one of Week 4, 8, 12, 16, 20, or 24. Subjects should come to the hospital without taking the study drug on the day when plasma drug concentration measurement after the end of the evaluation period is performed.

Blood collection may be omitted if a subject was not taking the study drug as of the day before the day of blood collection. It is also permissible not to perform post-dose blood collection in a subject for whom a decision to interrupt study drug administration has been made on the day of blood collection.

9.4.5.4 Measurement Method and Test Plan

Plasma drug concentration measurement will be performed at the Technical Solution Headquarters, using its own established LC/MS/MS method. Prior to the measurement, the study director at the company's headquarters will prepare a test plan for concentration measurement.

9.4.5.5 Method for Transportation of Plasma Samples

will take charge of collecting samples taken at study sites for drug concentration measurement. The company will forward frozen samples to .

Study sites, , and will store records of sample transfer and related information.

9.4.5.6 Reporting of Measurement Results

The final report on measured plasma drug concentrations will be prepared by and submitted to the sponsor.

9.5 Adverse Events

9.5.1 Definition of Adverse Events

An adverse event is defined as any undesirable medical incident that occurs in a subject receiving the study drug. This refers to any unwanted or unintended signs (including abnormal changes in clinical laboratory values), symptoms, or diseases that occur when the study drug is administered, whether or not they are causally related to the study drug. Adverse drug reactions are defined as adverse events that are judged to be either "related" or "possibly related" in terms of their causal relationship to the study drug. In patients with parathyroid carcinoma, exacerbation of the primary disease and accessory symptoms are not considered adverse events.

For laboratory test items (hematology and blood biochemistry), the presence or absence of deviation (abnormal value) will be checked based on the reference values at each study site; if an abnormal value is observed, it will be judged whether the change is clinically problematic (abnormal change) as compared with the value before the start of study drug administration. However, changes in intact PTH levels, Ca levels, and corrected serum Ca levels will be handled as abnormal changes if such changes cannot be explained from the pharmacological perspective as judged by the investigator or subinvestigator in view of the pharmacological action of KHK7580.

For signs, symptoms, and abnormal changes in clinical laboratory values associated with a specific disease (diagnostic name), the diagnostic name will be adopted as the adverse event term. However, in cases where signs or symptoms that are atypical for a specific disease, or extremely severe signs and symptoms develop, each of these signs and symptoms, as well as the diagnostic name, will be handled as adverse events.

9.5.2 Definition of Serious Adverse Events

"Serious adverse event" refers to an adverse event that falls under any of the following conditions. However, hospitalization for examination and hospitalization planned in advance are exceptions.

1) Results in death
2) Is life-threatening
3) Requires inpatient hospitalization or causes prolongation of existing hospitalization
4) Results in persistent or significant disability/incapacity (in the opinion of the reporter)
5) Is a congenital anomaly
6) Other medically significant conditions

9.5.3 Definition of Other Significant Adverse Events

"Other significant adverse events" are defined as all events, except serious adverse events, that result in discontinuation or interruption of study drug administration or in dose reduction.

9.5.4 Items to Be Investigated

Information from the start of study drug administration to Week 52 (or at the time of discontinuation) will be entered into the eCRF for the following items.

Adverse events will be followed until they have been reversed to their state before study drug administration, or until the investigator or subinvestigator determines that follow-up is no longer necessary based on the subject's condition, including symptoms, findings, and laboratory values.

1) Reported term for the adverse event
2) Start date of adverse event
3) Severity/intensity
   - Mild: Signs or symptoms are present but do not interfere with daily activities.
   - Moderate: Discomfort interferes with daily activities or there is an impact on the clinical condition
   - Severe: Daily activities are impossible or there is a significant impact on the clinical condition
4) Seriousness (serious event)
   - Serious (Yes): Events that correspond to the definition in Section 9.5.2
   - Non-serious (No): Events that do not correspond to the definition in Section 9.5.2
5) Action taken with study treatment
   - Dose not changed
   - Dose reduced
   - Drug interrupted
   - Drug withdrawn
   - Not applicable
6) Other actions: Action other than that taken with study treatment (other action taken)
   - None
   - Other drugs
   - Other
7) Outcome of adverse event
   - Recovered/resolved
   - Recovering/resolving
   - Not recovered/not resolved
   - Recovered/resolved with sequelae
   - Fatal
   - Unknown
8) End date of adverse event
9) Causal relationship with the study drug (causality)

   The causal relationship with the study drug will be classified into the following three categories. For "not related," the reason for the judgment will be entered into the eCRF.
   - Not related
   - Possibly related
   - Related

9.6 Number of Blood Collections and the Volume of Blood Collected

Total number of blood collections: 29 times

Total volume of blood collected: 234 mL

As a guide, the prespecified number of blood collections and the volume of blood collected during the study participation period are shown in Table 9.6-1 and Table 9.6-2. The total number of blood collections and the total volume of blood collected have been calculated on the assumption that subjects will complete the evaluation period in Week 24 and go through the extended administration period until Week 52. However, the total number of blood collections and the total volume of blood collected may increase in cases where screening is carried out more than once and where a post-dose-increase (or post-resumption) visit occurs during the extended administration period. The total number of blood collections and the total volume of blood collected may also increase if additional/follow-up examination is performed in consideration of the safety of a subject.

Table 9.6-1. Breakdown of the volume of blood collected (informed consent - evaluation period)

	Screening	Time after the start of administration (Weeks)																	At the time of discontinuation
		0					2	4	6	8	10	12	14	16	18	20	22	24	
Time after administration (h)		Before administration	0.5	1	2	3													
Hematology	-	2	-	-	-	-	2	2	2	2	2	2	2	2	2	2	2	2	2
Blood biochemistry 1	2	4	-	-	-	-	4	4	4	4	4	4	4	4	4	4	4	4	4
Blood biochemistry 2	-	4	-	-	-	-	4	4	4	4	4	4	4	4	4	4	4	4	4
Plasma drug concentration	-	2	2	2	2	2	2	2	-	2	-	2	-	2	-	2	-	2	-
Total volume of blood collected	2	12	2	2	2	2	12	12	10	12	10	12	10	12	10	12	10	12	10

Table 9.6-2. Breakdown of the volume of blood collected (extended administration period)

	Time after the start of administration (Weeks)															At the first visit following dose increase or resumption after interruption	At discontinuation
	8	12	16	20	24	After the end of the evaluation period				28	32	36	40	44	48	52		
Time after administration (h)						0.5	1	2	3									
Hematology	2	2	2	2	2	-	-	-	-	2	2	2	2	2	2	2	2	2
Blood biochemistry 1	4	4	4	4	4	-	-	-	-	4	4	4	4	4	4	4	4	4
Blood biochemistry 2	4	4	4	4	4	-	-	-	-	4	4	4	4	4	4	4	4	4
Plasma drug concentration	2	2	2	2	2	2	2	2	2	-	-	-	-	-	-	-	-	-
Total volume of blood collected	12	12	12	12	12	2	2	2	2	10	10	10	10	10	10	10	10	10

10 MANAGEMENT OF SUBJECTS

10.1 Notification to Other Departments and Hospitals

Prior to the start of study drug administration, the investigator or subinvestigator will check whether the subject is visiting other departments or hospitals. If the subject has been visiting another department or hospital, the investigator or subinvestigator will inform the attending physician of the subject's participation in the study. If subjects used a drug other than those prescribed by the investigator or subinvestigator, the name and use status of the drug will be investigated.

The investigator or subinvestigator will take a similar action if a subject has newly visited another department or hospital during the study period.

10.2 Subject Compliance Instruction and Investigation of Compliance Status

The investigator or subinvestigator will prescribe the study drug to the subject at each visit. When prescribing the study drug, each subject will be explained and instructed on the dosage and administration and how to take the drug. As a guide, subjects will be instructed to take the drug once daily at 24-hour intervals, twice daily at 12-hour intervals, three times daily at 8-hour intervals, or four times daily at 6-hour intervals. Subjects will be instructed to bring at the next visit the study drugs that were not taken and empty PTP sheets for study drugs that were taken. If non-compliance with the study drug is noted, thorough instructions will be given once again. In particular, if an overdose is observed, the investigator or subinvestigator will take adequate measures while giving due consideration to the safety of the subject and determine whether or not the subject may continue the study.

10.3 Instructions to Subjects

The investigator, subinvestigator, or clinical study collaborator will instruct subjects on the following.

10.3.1 Visits to the Hospital

After giving their written informed consent, subjects will undergo screening. Afterwards, subjects will visit the hospital in accordance with Section 9.1 "Schedule." Subjects who have been withdrawn from the study will undergo withdrawal examination as soon as possible.

10.3.2 Medication Diary

The investigator or subinvestigator will explain and instruct subjects to describe in the medication diary the status of study drug compliance on a daily basis and the time when the study drug was last taken before the scheduled visit, after the start of study drug administration. Subjects will also be instructed to bring their medication diary with them on scheduled visit dates. The medication diary will be checked on each scheduled visit date as to whether the medication diary is kept as specified in Section 10.2 "Subject Compliance Instruction and Investigation of Compliance Status." If any inappropriate description is found, instructions will be given once again.

10.3.3 Contraception

The investigator or subinvestigator will instruct the subject to use appropriate contraceptive methods from the date of informed consent until 12 weeks after the end of the study drug administration in females

of childbearing potential or from the date of the start of the study drug administration until 12 weeks after the end of the study drug administration in men of reproductive potential. The appropriate contraceptive methods are either a combination of two types from among condoms, oral contraceptives, intrauterine contraceptive devices, and diaphragms, or abstinence. The investigator or subinvestigator will adequately inform subjects about the risk of pregnancy and the appropriate contraceptive methods.

10.3.4 Measures Taken in the Event of Pregnancy

Female subjects will be instructed to promptly report to the investigator or subinvestigator if it is found that they are pregnant after informed consent, and male subjects will also be instructed to promptly report to the investigator or subinvestigator if their partner becomes pregnant after the start of study drug administration. In the event that a female subject becomes pregnant, the investigator or subinvestigator will take appropriate measures for safety assurance, such as immediately withdrawing the subject from the study, and will follow up the subject until follow-up is deemed no longer necessary. In the event that a partner of a male subject becomes pregnant, the necessary follow-up and other measures will be performed after obtaining voluntary written consent of the partner.

11 ADVERSE EVENT REPORTING

11.1 Adverse Events for Mandatory Reporting

11.1.1 Definition of Serious Adverse Events

See Section 9.5.2 “Definition of Serious Adverse Events.”

11.1.2 Treatment and Follow-Up of Adverse Events

11.1.2.1 Treatment of the Subject

If an adverse event occurs, the investigator or subinvestigator will take appropriate measures to ensure the safety of the subject, such as providing appropriate medical care or withdrawing the subject from the study as necessary.

11.1.2.2 Reporting to the Parties Concerned

11.1.2.2.1 Reporting of Serious Adverse Events

1) If a serious adverse event occurs, the investigator or subinvestigator will immediately (within 24 hours of learning of the event’s occurrence) report the event to the Emergency Safety Information Reception Center or the sponsor, either orally, by telephone, email, or fax (using Attachment 4 “Serious Adverse Event Report (First Report)” of the protocol (supplementary volume) or in the form specified by the study site), regardless of whether the event is causally related to the administration of the study drug.
2) Afterwards, the investigator will also submit a Serious Adverse Event Report (Detailed Report) to the sponsor and the head of the study site within 7 days after he/she becomes aware the event’s occurrence. In doing so, the investigator will report to the head of the study site by identifying any serious unexpected adverse drug reaction.
3) The investigator will also provide additional information as requested by the sponsor, the head of the study site, and the IRB.
4) The head of the study site will consult the IRB as to whether the study may be continued at the study site.

Emergency contact

Emergency Safety Information Reception Center

Tel.: (pronounced as “*shikyu fukusayo*” in Japanese, meaning urgency and adverse drug reaction); fax:
Reception hours: 24 hours (seven days a week)

11.1.2.2.2 Reporting of Non-Serious Adverse Events

If any adverse event of special concern occurs, the investigator or subinvestigator will promptly report to the sponsor about the event and the measures taken. Any other adverse events will also be reported to the sponsor as appropriate.

11.1.2.3 Follow-Up of Adverse Events

Adverse events will be followed until they have been reversed to their state before study drug administration, or until the investigator or subinvestigator determines that follow-up is no longer necessary based on the subject's condition, including symptoms, findings, and laboratory values. The eCRF should include information from study drug administration to the end of the study.

12 CRITERIA FOR SUBJECT WITHDRAWAL AND DISCONTINUATION OF THE STUDY, AND PROCEDURES THEREFOR

12.1 Withdrawal of a Subject from the Study

12.1.1 Subject Withdrawal Criteria

A subject will be withdrawn from the study if any of the following conditions apply.

1) The subject is found to be ineligible for participation in this study after the start of the study.
2) The subject wishes to withdraw the consent for the study.
3) It is found not feasible to conduct the necessary observations and examinations due to the subject's private reasons.
4) The subject experiences an adverse event, and the investigator or subinvestigator determines that the subject should be withdrawn from the study.
5) The subject applied PTx or parathyroid intervention therapy.
6) The subject has not taken investigational therapy over 8 weeks.
7) The investigator or subinvestigator determines that the subject should be withdrawn from the study.

12.1.2 Procedure for Withdrawing Subjects

The investigator or subinvestigator will take appropriate measures for a subject who has been withdrawn from the study due to a safety problem such as the occurrence of an adverse event. All subjects who have been withdrawn from the study will undergo withdrawal examination as soon as possible after safety is confirmed.

For subjects who stopped visiting the hospital after study drug administration, follow-up and prespecified assessments will be carried out as much as possible while taking into account the human rights of the subject.

The investigator or subinvestigator will investigate the date of withdrawn and the reason for withdrawal, and enter this information into the eCRF.

12.2 Site-Specific Study Discontinuation or Interruption

In the event of discontinuation or interruption of the study at a given study site due to reasons such as doubts about the safety of the study drug, the investigator must promptly notify the head of the study site in writing and provide a detailed written explanation of the discontinuation or interruption. The head of the study site will promptly report to the sponsor and IRB in writing to that effect and the reasons therefor.

This study will also be discontinued at the study site if any of the following conditions apply. In that case, appropriate measures will be taken in the same manner as above.

1） The head of the study site proposes the revision of the protocol based on the opinions from the IRB that the head of the study site consulted, but the sponsor cannot accept the proposal.
2） The IRB consulted by the head of the study site states that the study should not be continued, and the head of the study site directs that the study be discontinued.
3） The study site has committed a serious or continuing violation of GCP, this protocol, or the clinical study agreement.

12.3 Discontinuation or Suspension of the Entire Study

In the event of discontinuation or suspension of the entire study during the course of the study, the sponsor will promptly notify the head of all study sites and the regulatory authorities, providing them with the details of the reasons for the discontinuation or suspension. Upon receiving the notification, the head of the study site will promptly notify the investigator and the IRB of the discontinuation or suspension and the reasons therefor in writing. If the entire study is discontinued or suspended, the investigator will promptly notify subjects of the discontinuation or suspension, provide appropriate medical care, and take other necessary measures.

13 STATISTICAL ANALYSIS

13.1 Statistical Analysis Methods

The main analytical items for evaluation of efficacy, safety, and pharmacokinetics, as well as the analytical methods, are as follows.

Unless otherwise noted, categorical data will be summarized by frequency and percentage, and continuous data by summary statistics. The summary statistics will involve calculation of the number of subjects, mean, standard deviation, minimum, median, and maximum.

13.1.1 Efficacy Evaluation

13.1.1.1 Primary Evaluation

- The number and percentage of subjects whose corrected serum Ca level was maintained at ≤10.3 mg/dL for 2 weeks in the evaluation period will be calculated, along with the exact 95% confidence interval. Whether or not the lower limit of the exact 95% confidence interval exceeds the threshold ratio of 11% will be used as a criterion for judging the efficacy.

13.1.1.2 Secondary Evaluations

- The number and percentage of subjects whose corrected serum Ca level was decreased by ≥ 1.0 mg/dL from baseline and remained decreased for 2 weeks in the evaluation period will be calculated, along with the accurate two-sided 95% confidence interval.
- The summary statistics of the actual measured values of corrected serum Ca level and changes from baseline will be calculated for each measurement time point.
- The summary statistics of the actual measured values of intact PTH level and changes from baseline will be calculated for each measurement time point.
- The summary statistics of the actual measured values of whole PTH level and changes from baseline will be calculated for each measurement time point.

13.1.2 Safety Evaluation

The incidence of each adverse event and adverse drug reaction that occurred or worsened after the start of study drug administration will be calculated. Calculation of the incidence of each adverse event and adverse drug reaction will be performed based on the MedDRA PT and SOC.

With regard to laboratory parameters and vital sign values, summary statistics will be calculated for each evaluation time point.

13.1.3 Pharmacokinetic Evaluation

With regard to plasma KHK7580 concentrations, descriptive statistics will be shown for each blood collection time point. Pharmacokinetic parameters (t_{max} and C_{max}) will also be calculated for each subject and descriptive statistics will be provided. In this study, C_{max} is defined as the maximum plasma concentrations at 0.5, 1, 2, and 3 hours after administration, and t_{max} is defined as the time to reach the maximum plasma concentration.

13.1.4 Other Evaluation

The results of the EQ-5D-5L will be tabulated.

13.2 Target Number of Subjects

At least 10 subjects receiving study treatment

For the rationale, see Section 24.10 “Rationale for the Target Number of Subjects.”

13.3 Significance Level Used

A two-sided *p*-value of 5% will be used as a guide when a test is performed on an exploratory.

13.4 Criteria for Discontinuation of the Study

No study discontinuation criteria based on statistical evidence are provided.

13.5 Procedures for Handling Missing, Rejected, and Abnormal Data

For the analyses specified in Section 13.1, failure to obtain evaluable data for two consecutive weeks regarding the binary response variables for the percentage of subjects in the primary and secondary endpoints will be handled as an “unachieved” subject. Any missing value in continuous data will be handled as missing data, and no special complementary processing by a statistical method will be performed. If any specific handling of the data becomes necessary due to unforeseen events that were not expected at the start of the study, the handling method will be determined before database lock and described in the analysis plan.

13.6 Procedures for Preparing the Analysis Plan and Reporting Deviations from the Original Plan

The details of the final analysis plan, including the analyses shown in Section 13.1, will be finalized as the analysis plan by the time of database lock. Major changes to the analysis plan will be described in the clinical study report.

13.7 Selection of Subjects for Analysis

The following populations will be subject to analysis. Whether or not to include individual subjects in each of the analysis populations will be determined prior to database lock if necessary.

13.7.1 FAS

The FAS is defined as the population of the eligible subjects enrolled, excluding those falling under either or both of the following conditions. The FAS will be subject to efficacy evaluation.

- Subjects who have not received any study drug
- Subjects from whom no data of corrected serum Ca levels after the start of study drug administration have been obtained

13.7.2 Safety Analysis Set

The safety analysis set is defined as the population of the eligible subjects enrolled, excluding those falling under the following condition.

- Subjects who have not received any study drug

13.7.3 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set is defined as the population of the eligible subjects enrolled, excluding those falling under either or both of the following conditions.

- Subjects who have not received the study drug as prescribed
- Subjects in whom no blood collection for pharmacokinetic analysis has been performed after study drug administration

14 ETHICAL CONSIDERATIONS

14.1 IRB

14.1.1 Review of the Appropriateness of Study Conduct

Prior to the conduct of the study, the protocol, the content of the informed consent form for subjects, and the appropriateness of study conduct will be reviewed from the perspective of ethical, scientific, and medical appropriateness, and approved by the IRB consulted by the head of the study site.

14.1.2 Continued Review

The investigator will submit a written summary of the current status of the study to the head of the study site at least one a year or upon request by the IRB for continued review by the IRB.

14.2 Selection of Subjects and Safety Assurance

In selecting subjects, the investigator or subinvestigator will carefully examine the appropriateness of study participation from the viewpoint of protecting human rights, by, for example, excluding those who may suffer undue disadvantage from not participating in the study (socially vulnerable persons).

The investigator or subinvestigator will determine the eligibility of subjects for registration based on the enrollment criteria and thereby avoid registration of subjects whose safety cannot be ensured.

During the study participation period, the investigator and subinvestigator will constantly monitor the health condition of subjects, such as by securing methods for emergency contact with the subjects, and collect and communicate safety information that may be relevant to the study drug. In the event of an adverse event, the investigator and subinvestigator will provide appropriate medical care, etc. to the subject, and, if necessary, discontinue study drug administration to ensure the safety of the subject.

14.3 Protection of Subjects' Personal Information and Privacy

In preparing eCRF, the investigator or subinvestigator will use subject identifiers to identify individual subjects, and protect subjects' personal information.

Persons belonging to the sponsor's organization involved in clinical studies should not divulge any subject secret learned in the course of duties in connection with the study without justifiable reason.

14.4 Time and Method of Obtaining Consent

14.4.1 Informed Consent

14.4.1.1 Informed Consent of Subjects

The investigator or subinvestigator will fully explain the details of this study to persons deemed appropriate as study subjects based on the informed consent form prescribed separately, prior to their participation in the study. In this process, a clinical study collaborator may also provide a supplementary explanation about the study. After giving the subject sufficient time to think about whether or not to participate in the study, the investigator or subinvestigator will obtain the subject's voluntary consent to participate in the study in writing (consent document defined separately) before screening.

The investigator or subinvestigator who provided the explanation and the subject will affix their names and seals or signatures onto the consent form, and the consent form will be dated by each person. If a clinical study collaborator has provided a supplementary explanation, he/she will also affix his/her name and seal or signature onto the consent form, and date it.

14.4.2 Storage of the Consent Form

The consent form will be made in triplicate unless otherwise stipulated by the study site. The investigator or subinvestigator will provide the subject with a copy of the consent form for storage and a written explanation. The investigator or subinvestigator will submit the consent form for storage at the study site to the department designated by the study site, such as the study administration office of each study site, and also store the consent form for storage by the investigator together with the medical records, etc.

14.5 Contents of the Informed Consent Form

The following items must be included in the informed consent form.

1) Experimental nature of the study
2) Study objectives
3) Name, title, and contact information of the investigator
4) Method of the study
5) Potential advantages to the subject's mental and physical health as a result of the use of the study drug (or, if no such advantages are expected, a statement to that effect), and potential disadvantages to the subject
6) Matters related to other treatment methods
7) Duration of participation in the study
8) That the subject may withdraw from the study at any point in time
9) That the subject will not be treated disadvantageously by not participating in or withdrawing from the study
10) That the source documents may be viewed by clinical research associates, auditors, IRB, etc. on condition that the subject's confidentiality is protected
11) That the confidentiality of the subject will be protected
12) Contact information of the study site in the event of health damage
13) That necessary treatment will be provided in the event of health damage
14) Matters related to compensation for health damage
15) The type of IRB that will investigate and deliberate on the appropriateness of the study, matters to be investigated and deliberated at each IRB, and other IRB-related matters pertaining to this study
16) Matters related to costs to be borne by the subject, if any
17) Necessary matters related to the study

The following items should not be included in the informed consent form.

1) A statement to the effect that a prospective subject should waive his/her rights, or any matter that makes him/her suspect such waiver

2) A statement to the effect that the sponsor, the study site, the investigator, or the subinvestigator is exempt from liability or their liability is reduced, or any matter that implies such exemption or reduction

14.6 Providing Information to Subjects, Revising the Informed Consent Form, and Obtaining Re-Consent

If the investigator or subinvestigator obtains new information that may influence the subject's intention to continue participating in the study, the investigator or subinvestigator will promptly explain the contents of the new information to subjects during the study, and confirm whether or not the subject intends to continue participating in the study. Then, the investigator or subinvestigator will record in the medical record the contents of the explanation, the date of the explanation, the person with whom the intention was confirmed, and the intention.

If the investigator deems it necessary to revise the informed consent form based on the explanation provided, he/she will promptly revise the informed consent form and obtain IRB approval. Then, the investigator or subinvestigator will provide an explanation once again by using the revised informed consent form, and obtain the subject's written re-consent to continue participating in the study in the same manner as when obtaining the initial consent.

15 MONETARY PAYMENT AND COMPENSATION FOR HEALTH DAMAGE

15.1 Costs Related to the Study

The cost of all tests performed during the period of KHK7580 administration should be borne by the sponsor under the system for healthcare services provided combining insurance-covered and non-covered services pertaining to the clinical study.

15.2 Expenses for Reducing the Burden of Subjects' Participation in the Study

In order to reduce the burden of costs associated with subjects' participation in study subjects, the sponsor should pay expenses for reducing the burden to the subjects through the study site concerned in accordance with the provisions of the study site.

15.3 Compensation for Health Damage

1) In the event of health damage to a subject as a result of this study, the investigator and subinvestigator should take necessary measures, such as providing medical treatment, and the sponsor should, in accordance with the subject's request, bear the subject's own medical expenses incurred for treatment, excluding benefits from health insurance, etc.
2) If any health damage occurs to a subject as a result of this study and a dispute occurs or is likely to occur later with the subject, etc., the study site should immediately report to the sponsor, and the study site and the sponsor should cooperate to resolve the dispute.
3) If any health damage occurs to a subject as a result of this study and liability for compensation arises afterwards, the compensation paid by the study site and the costs incurred for resolution should be borne by the sponsor, except where the damage is attributable to the study site.

4） If any health damage occurs to a subject as a result of this study and liability for compensation arises afterwards, the sponsor should accept the liability and bear the cost of compensation.

5） The payment of expenses based on the liability for compensation set forth in the preceding paragraph should be made in accordance with the compensation rules established by the sponsor.

16 PROTOCOL COMPLIANCE, DEVIATION, CHANGE, AND AMENDMENT

16.1 Compliance with the Protocol

The investigator and the subinvestigator will comply with the protocol agreed to by the investigator and the sponsor and approved in writing by the IRB consulted by the head of the study site.

16.2 Protocol Deviation or Change

The investigator or subinvestigator should not deviate from or make a change to the protocol unless the investigator reaches a prior written agreement with the sponsor and obtains written approval from the IRB based on the IRB's prior review. In the event of a deviation from or change to the protocol, the investigator or subinvestigator should document all of the deviation, regardless of the reason.

The investigator or subinvestigator may deviate from or make a change to the protocol without prior written agreement with the sponsor and prior approval of the IRB if it is medically unavoidable, such as to eliminate an immediate hazard to the subject. In this case, the investigator should prepare a document describing the deviation or change and the reasons therefor and promptly submit it to the sponsor and the head of the study site. The investigator should also submit the document to the IRB via the head of the study site for approval, and should obtain approval from the head of the study site and the sponsor's agreement in writing.

If a protocol amendment is deemed appropriate in light of the nature of the deviation or change and the reasons therefor, the investigator should submit a protocol amendment draft to the sponsor, the head of the study site, and the IRB via the head of the study site for approval as soon as possible, and should obtain approval from the head of the study site and the sponsor's agreement in writing.

16.3 Protocol Amendment

If the sponsor amends the protocol, the sponsor should provide the investigator with sufficient explanation along with the protocol amendment or a written document describing the amendment, and obtain agreement on the amendment. The investigator should conduct the study in accordance with the amended protocol after obtaining written approval based on the IRB's prior review. However, this should not apply if the change is only related to administrative matters of the study (change of affiliation, job title, address, telephone number, etc.).

17 PRECAUTIONS FOR ELECTRONIC CASE REPORT FORM PREPARATION

For subjects who completed examination and evaluation up to Week 24 (including those who withdrew from the study earlier), the evaluation up to Week 24 (or withdrawal) will be summarized as cut-off data.

17.1 Preparation and Reporting of Electronic Case Report Forms

In this study, an electronic data capture (EDC) system will be employed for data collection. The EDC system provides the study site with the function to enter data into the eCRF, to check the data entered, to respond to queries from the sponsor about input data, and to use electronic signatures. The data entered will be transmitted in encrypted form to the EDC server over the Internet. The sponsor has confirmed in advance that the EDC system complies with the requirements set forth in the Ministerial Ordinance on Good Clinical Practice for Drugs (Ordinance of the Ministry of Health and Welfare No. 28 of March 27, 1997), partial amendments to the Ministerial Ordinance, and the "Use of Electromagnetic Records and Electronic Signatures in Applications for Approvals and Licenses of Pharmaceuticals, etc." (PFSB Notification No. 0401022, dated April 1, 2005).

The investigator will create an eCRF for each subject, verify that all data are accurate and complete, and then provide an electronic signature in the EDC system. If an eCRF was prepared by a subinvestigator or a clinical study collaborator, the investigator will inspect the eCRF to ensure that there are no problems prior to providing his/her electronic signature. The preparation of eCRFs should be in accordance with the "Guidelines on Modification or Correction of the eCRF" provided by the sponsor.

In this study, subject data stored on the EDC server will be handled as the original eCRF. However, if the eCRF is moved from the EDC server to a non-rewritable medium (DVD, etc.), the eCRF in the medium will be handled as the original, and if the eCRF is moved to the electronic document management system, the eCRF in the electronic document management system will be handled as the original. When the eCRF is moved to the electronic document management system, the prespecified written procedures will be followed.

The sponsor will provide a copy of the eCRF and the history of modifications or corrections to the study site.

17.2 Modification or Correction of the eCRF

The investigator, subinvestigator, or clinical study collaborator will follow the "Guidelines on Modification or Correction of the eCRF" provided by the sponsor when modifying or correcting the entry in the eCRF. The history of modifications or corrections of the eCRF will be automatically captured by the EDC system.

17.3 Items for Which the Entry in the eCRF Can Be Handled as the Source Document (Source Data)

The following items will be entered directly into the eCRF, and the entry in the eCRF may be handled as the source document (source data). If a similar entry is present in the medical record, it should be handled as the source document (source data).

1) Adverse event name, severity, seriousness, action taken, outcome date, causal relationship with the study drug, and comments

2） Reasons for the use of concomitant drugs and concomitant therapies
3） Date of discontinuation, reason for discontinuation, action taken, and subsequent course
4） Other special remarks and comments from the investigator or subinvestigator

18 DIRECT ACCESS TO SOURCE DOCUMENTS, ETC.

The investigator, subinvestigator, and the study site conducting this study should make all study-related records such as source documents available for direct access during monitoring and audits by the sponsor and inspection by the IRB and regulatory authorities.

19 QUALITY CONTROL AND QUALITY ASSURANCE OF THE STUDY

The sponsor will confirm through monitoring and auditing whether the study is conducted and the preparation, recording, and reporting of data are carried out in compliance with the protocol and the Ministerial Ordinance on Good Clinical Practice for Drugs ("GCP Ordinance"; Ordinance of the Ministry of Health and Welfare No. 28 of March 27, 1997).

Data management and assurance will be performed in accordance with the sponsor's standard operating procedures for the conduct of clinical studies and auditing procedures.

Clinical research associates will ensure that the study is conducted in compliance with the GCP Ordinance, this protocol, and the written procedures for management of the study drug, and that eCRF entries are consistent with the source documents. Details of specific procedures will be provided in a separate monitoring plan or alternative written procedures.

20 PLANNED STUDY PERIOD

August 2017 - October 2019

21 COMPLETION OF THE STUDY

Upon completion of the administration and observation of all subjects at the study site as stipulated in the protocol, the investigator will report in writing to the head of the study site the fact that the study has been completed and a summary of the study results.

The head of the study site will promptly notify the IRB and the sponsor of the completion of the study in writing, and report the summary of the study results based on the report submitted by the investigator.

22 RETENTION OF RECORDS, ETC.

22.1 Retention at the IRB

1) Materials to be retained

The founder of the IRB will retain the standard operating procedures, a list of the board members (including the qualifications of each board member), a list of the occupations (job titles) and affiliations of the board members, documents submitted, records of meetings and summaries thereof, and other records such as letters.

2) Retention period

The founder of the IRB will retain study-related documents and records until the later of the following dates. However, if the sponsor requires the retention of records for a longer period of time, the founder of

the IRB will discuss the retention period and method with the sponsor. If retention becomes no longer necessary, the sponsor will notify the founder of the IRB via the head of the study site.

- The day of marketing approval for the study drug (or, if the development is discontinued, the day on which three years have elapsed from the day on which the notification of discontinuation of development was received.)
- The day on which three years have elapsed since discontinuation or completion of the study.

22.2 Retention at the Study Site

1) Materials to be retained

The head of the study site will retain the study-related documents or records to be retained at the study site by appointing a person responsible for the retention of each record.

2) Retention period

The head of the study site will retain study-related documents and records until the later of the following dates. However, if the sponsor requires the retention of records for a longer period of time, the head of the study site will discuss the retention period and method with the sponsor. If retention becomes no longer necessary, the sponsor will notify the head of the study site.

- The day of marketing approval for the study drug (or, if the development is discontinued, the day on which three years have elapsed from the day on which the notification of discontinuation of development was received)
- The day on which three years have elapsed since discontinuation or completion of the study

22.3 Retention by the Investigator

The investigator will retain study-related documents or records in accordance with the guidance of the head of the study site.

22.4 Retention by the Sponsor

1) Materials to be retained

The sponsor will retain the study-related documents or records to be retained.

2) Retention period

The sponsor will retain study-related documents and records until the later of the following dates.

- The day on which five years have elapsed from the day of marketing approval for the study drug (or, if the development is discontinued, the day on which three years have elapsed from the day on which the decision to discontinue development was made); or, the day on which reexamination is completed if the drug must undergo reexamination after approval pursuant to the provisions of the Pharmaceuticals and Medical Devices Act and the period until completion of reexamination is more than five years
- The day on which three years have elapsed since discontinuation or completion of the study

22.5 Retention of Source Documents Concerning KHK7580 Concentration Measurements

Source documents concerning measurement of plasma KHK7580 concentrations will be retained at the laboratory where the measurement is performed. The retention period will be until the later of the following dates. Handling of source documents after the retention period will be discussed separately between the investigator and the sponsor.

- The day on which five years have elapsed from the day of marketing approval for the study drug (or, if the development is discontinued, the day on which three years have elapsed from the day on which the notification was received that a decision to discontinue development had been made); or, the day on which reexamination is completed if the drug must undergo reexamination after approval pursuant to the provisions of the Pharmaceuticals and Medical Devices Act and the period until completion of reexamination is more than five years
- The day on which three years have elapsed since discontinuation or completion of the study

22.6 Retention of Source Documents Concerning Clinical Laboratory Tests, etc.

Source documents concerning clinical laboratory tests, etc. will be retained at the study site or the laboratory undertaking measurements. The retention period will be until the later of the following dates. Handling of source documents after the retention period will be discussed separately between the investigator and the sponsor.

- The day on which five years have elapsed from the day of marketing approval for the study drug (or, if the development is discontinued, the day on which three years have elapsed from the day on which the notification was received that a decision to discontinue development had been made); or, the day on which reexamination is completed if the drug must undergo reexamination after approval pursuant to the provisions of the Pharmaceuticals and Medical Devices Act and the period until completion of reexamination is more than five years
- The day on which three years have elapsed since discontinuation or completion of the study

22.7 Retention of Biological Samples

1） Samples collected for hematological examination will be retained and discarded in accordance with the standard operating procedures of after completion of measurements. Samples collected for blood biochemistry and for diagnosis of diseases will be retained in accordance with the standard operating procedures of , and kept for one year thereafter.

2） Blood plasma for pharmacokinetic analysis will be retained at until the final report is completed.

After the retention period specified above, the sponsor will retain the samples on its own responsibility for up to 15 years after completion of the study, and will use them for future research related to KHK7580 (research that does not involve acquisition of genetic information).

23 PUBLICATION OF STUDY RESULTS

The investigator and subinvestigator should obtain prior approval from the sponsor if they publish the results of this study in academic conferences, journals, and the like.

24 RATIONALE FOR THE SETTINGS

25 STUDY ADMINISTRATIVE STRUCTURE

See Attachment 1 of the protocol (supplementary volume).

26 PRIMARY RESPONSIBILITIES OF THE INVESTIGATOR

See Attachment 2 of the protocol (supplementary volume).

27 REFERENCES

Signature Page for

Approval	

Signature Page for