CLINICAL STUDY PROTOCOL

A PHASE 2, 12-WEEK, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF DS-1211B IN INDIVIDUALS WITH PSEUDOXANTHOMA ELASTICUM

DS1211-A-U201

IND NUMBER 135092

VERSION 3.0, 16 JAN 2023

VERSION 2.0, 03 OCT 2022

VERSION 1.0, 22 OCT 2021

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INVESTIGATOR AGREEMENT

A Phase 2, 12-Week, Randomized, Double-Blind, Placebo-Controlled Study of DS-1211b in Individuals with Pseudoxanthoma Elasticum

Investigator's Signature:

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representative.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Council for Harmonisation guidelines on Good Clinical Practice (ICH E6), and applicable regional regulatory requirements.

I agree to make available to Sponsor personnel, their representatives and relevant regulatory authorities, my subjects' study records in order to verify the data that I have entered into the case report forms. I am aware of my responsibilities as a Principal Investigator as provided by the Sponsor.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

Print Name	**Signature**
Title	**Date (DD MMM YYYY)**

SUMMARY OF CHANGES

Please refer to the comparison document for Protocol Version 3.0 (dated 16 Jan 2023) versus Protocol Version 2.0 (dated 03 Oct 2022) for actual changes in text. The Summary of Changes below is a top-line summary of major changes in the current DS1211-A-U201 clinical study protocol (Version 3.0) by section.

Amendment Rationale:

CCI [redacted]

CONVENTIONS USED IN THIS SUMMARY OF CHANGES		
All locations (section numbers and/or paragraph/bullet numbers) refer to the current protocol version, which incorporates the items specified in this Summary of Changes document.		
Minor edits, such as update to language that does not alter original meaning, update to version numbering, formatting, change in font color, corrections to typographical errors, use of abbreviations, moving verbiage within a section or table, change in style, or change in case, are not noted in the table below.		
Section # and Title	**Description of Change**	**Brief Rationale**
CCI [redacted]		

CONVENTIONS USED IN THIS SUMMARY OF CHANGES
CCI [redacted]

PROTOCOL SYNOPSIS

Protocol Title
A Phase 2, 12-Week, Randomized, Double-Blind, Placebo-Controlled Study of DS-1211b in Individuals with Pseudoxanthoma Elasticum
Protocol Number
DS1211-A-U201
Sponsor/Collaborators
Daiichi Sankyo, Inc.
Registry Identification(s)
TBD: NCT Number: ###, EudraCT Number: 2022-000676-19, or RCT Number: ### as applicable]
IND Number
IND Number 135092
Study Phase
Phase 2
Study Design
Study DS1211-A-U201 is a 12-week, randomized, double-blind, placebo-controlled, parallel-group study that aims to assess the safety, tolerability, and pharmacokinetic (PK) and pharmacodynamic (PD) dose response of DS 1211b in individuals with pseudoxanthoma elasticum (PXE) by using biomarkers relating to tissue-nonspecific alkaline phosphatase (TNAP) inhibition. Eligible individuals with PXE will be randomized to 1 of 4 arms in a 1:1:1:1 ratio, to receive CCI [redacted] of DS 1211b or placebo in tablet form for once daily dosing for a total of 12-week dosing, followed by a postdose biomarker assessment and a 2-week follow-up safety check. Approximately 12 to 16 individuals with PXE will be enrolled in each group.
Study Completion
The study completion date will occur when all study participants have completed their follow-up safety check or discontinued from the study early.
Planned Geographical Coverage, Study Sites and Location
The study will be conducted at approximately 10 study sites located in the US and possibly in the European region.
Study Population
Adult individuals with an established diagnosis of PXE
Study Objectives/Outcome Measures and Endpoints
The table below lists primary study objectives and endpoints with outcome measures.

Objectives	Outcome Measure	Endpoints	Category
Primary			
To assess the safety and tolerability of DS-1211b compared with placebo in subjects with PXE	**Title:** Safety parameters **Description:** Descriptive statistics of safety endpoints **Time frame:** From the time the subject signs the study informed consent form (ICF) and up to Day 98 (14 days after the last dose of study drugs)	Incidence of adverse events (AEs), including serious adverse events (SAEs), and treatment-emergent AEs, physical examination/assessment findings including vital sign measurements, standard clinical laboratory parameters, and electrocardiograms	Safety
To assess the dose response by assessing the treatment changes in PD endpoints	**Title**: PD endpoints **Description**: Profiles of alkaline phosphatase (ALP) and TNAP substrates **Time frame**: Data are collected at baseline through Day 98.	ALP, inorganic pyrophosphate (PPi), and pyridoxal 5'-phosphate (PLP)	Pharmacodynamic
Secondary			
To characterize the PK of DS-1211a (the free form of DS-1211b in plasma) in subjects with PXE	**Title**: PK endpoints **Description**: Plasma concentration and PK parameters of DS-1211a **Time frame**: Data are collected at baseline through Day 84.	Plasma concentration and PK parameters of DS-1211a Include, but are not limited to, maximum plasma concentration, time to reach maximum plasma concentration, trough plasma concentration, area under the plasma concentration-time curve during dosing interval, area under the plasma concentration-time curve up to the last quantifiable time, and area under the plasma concentration-time curve up to infinity (if possible to calculate)	Pharmacokinetic
Study Duration			
The study start date is the date when the first prospective study participant has signed the ICF. A PXE individual will be considered as eligible for randomization when the Investigator or designee has obtained written consent and confirmed all eligibility criteria have been met during the screening period and when all screening procedures have been completed. Anticipated total duration of the study is expected to be approximately 5 months for individual study participants.			

Study Population/Eligibility Criteria

Study participants must satisfy all of the following criteria to be included in the study:

- Sign and date the ICF, prior to the start of any study-specific qualification procedures.
- Are male or female participants aged 18 to 75 years at screening.
- Have an established diagnosis of PXE, with typical ocular and dermatological clinical features[1,2]:
  - Ocular findings – angioid streaks or peau d'orange
  - Skin findings – characteristic PXE papules and plaques or diagnostic histopathological changes in lesional skin
- Are fully vaccinated for coronavirus disease 2019 (COVID-19) per current CDC guidelines.
- For women of childbearing potential (not postmenopausal as a result of either natural or postsurgery cessation of menses), must have a negative serum pregnancy test at screening and must be willing to use an effective method of birth control, as detailed in Section 17.2 upon entering study screening, during the treatment period, and up until the time of the follow-up visit.
- Is willing and able to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.

Individuals who meet any of the following criteria at screening will be disqualified from entering the study:

- Have a history of bone fracture in the past 6 months.
- Have a history of active metabolic bone disease that significantly affect the interpretation of study biomarker results, excluding osteopenia or osteoporosis without fragility fracture.
- Have a history of calcium pyrophosphate deposit disease such as chondrocalcinosis, pseudogout, pyrophosphate arthropathy.
- Have a history of hypophosphatasia.
- Have a history of untreated hyperparathyroidism.
- Participated in another interventional research study in the past 60 days.
- Are participating or participated within the last 12 months in PXE trials (eg, trials with PPi, PPi analogues such as bisphosphonate, or ENPP1 and its analogues) or in clinical trials relating to bone mineralization.
- Used bisphosphonate in the preceding 12 months or had plans to use bisphosphonate during the study.
- Used strong inhibitors or inducers of Cytochrome P450 isozymes, 2C19, 3A4, or 3A5.
- CCI [redacted]
- CCI [redacted]
- Have an alkaline phosphatase <lower limit of normal (LLN) range.
- Have alanine aminotransferase or aspartate aminotransferase >2 × upper limit of normal (ULN) range; total bilirubin > 1× ULN.
- Have PLP > ULN.
- Have hemoglobin <10.0 g/dL.

- Have a QTcF interval duration >450 ms at screening.
- Have moderate to severe renal insufficiency (Creatinine clearance <60 mL/min by Cockcroft-Gault method).
- Are pregnant or breast-feeding women.
- Were women of childbearing potential unwilling to use contraceptive methods.
- Have a history of sulfonamide allergy.
- Have any elective surgery planned during the study period.
- Have any other significant condition (medical, psychiatric, social, or medication) that, in the judgment of the Investigator, would prevent full participation or would be inappropriate for the study.

Investigational Medicinal Product, Dose, and Mode of Administration

- DS-1211b CCI [redacted] tablets in CCI [redacted] dose strength will be used for study dose levels of CCI [redacted].
- Matching placebo tablets
- Tablets to be administered orally for once daily dosing.

Planned Sample Size and Key Statistical Analysis

CCI [redacted] Sample size is not based on statistical consideration but is chosen on the basis of feasibility and clinical consideration from biomarker results of the completed Phase 1 healthy volunteer studies.

Safety endpoints, difference in biomarkers between active doses and placebo, plasma concentration of DS-1211a, and PK parameters will be summarized by descriptive statistics. Plasma concentration of DS-1211a will be also analyzed by noncompartmental methods. Observed values at each assessment and the absolute change and percentage change from baseline will be numerically summarized for primary and exploratory biomarkers by treatment group over time. The 95% confidence interval will be presented for percentage change from baseline in PPi and PLP.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ABCC6	ATP-binding cassette subfamily C member 6
AE	adverse event
AESI	adverse events of interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUCinf	area under the plasma concentration-time curve up to infinity
AUClast	area under the plasma concentration-time curve up to the last quantifiable time
AUCtau	area under the plasma concentration-time curve during dosing interval
BSAP	bone-specific alkaline phosphatase
BUN	blood urea nitrogen
Ca	calcium
Cmax	maximum plasma concentration
COVID-19	coronavirus disease 2019
CRF	case report form
eCRF	electronic case report form
CRO	contract research organization
Ctrough	trough plasma concentration
EC	Ethics Committee
ECG	electrocardiogram
EDC	electronic data capture
EIU	exposure in utero
ENPP1	ectonucleotide pyrophosphatase/phosphodiesterase 1
EU	European Union
CCI [redacted]	CCI [redacted]
GCP	Good Clinical Practice
CCI [redacted]	CCI [redacted]
HPP	hypophosphatasia
ICF	informed consent form

ABBREVIATION	DEFINITION
ICH	International Council for Harmonisation
ICMJE	International Council of Medical Journal Editors
CCI	CCI
IRB	Institutional Review Board
IRT	interactive response technology
CCI	CCI
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
Mg	magnesium
MOA	mechanism of action
CCI	CCI
CCI	CCI
PD	pharmacodynamic
Pi	inorganic phosphate
PK	pharmacokinetic
PLP	pyridoxal 5'-phosphate
PPi	inorganic pyrophosphate
PXE	pseudoxanthoma elasticum
SAE	serious adverse event
SAP	statistical analysis plan
SAVER	serious adverse event report
CCI	CCI
SoE	schedule of events
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin
TEAE	treatment-emergent adverse event
Tmax	time to reach maximum plasma concentration
TMF	trial master file
TNAP	tissue-nonspecific alkaline phosphatase
ULN	upper limit of normal
CCI	CCI
VEGF	vascular endothelial growth factor

1. INTRODUCTION

1.1. Background

Pseudoxanthoma elasticum (PXE) is a rare, ectopic calcification disease due to autosomal recessive mutation in the ATP-binding cassette subfamily C member 6 (ABCC6) gene. The prevalence of PXE is estimated as approximately 1 in 50,000.[1,2] Clinical manifestations of PXE are usually late onset, slowly progressive, and frequently not recognized until patients are in their 20s to 30s. PXE clinical signs are commonly seen in the skin, the eyes, and the cardiovascular system. Currently, there is no specific treatment for systemic manifestation of PXE except for antivascular endothelial growth factor (VEGF) ocular injection for choroidal neovascularization.

The molecular basis of PXE is the inactivating mutations in the gene encoding ABCC6, an ATP-dependent efflux transporter that is present mainly in the liver.[3] Extracellularly, the excreted nucleoside triphosphate is hydrolyzed by ectonucleotidases to nucleoside monophosphate and inorganic pyrophosphate (PPi), the latter a potent endogenous inhibitor of mineralization. In PXE, the absence of ABCC6-mediated adenosine triphosphate release from the liver results in reduced PPi levels, leading to ectopic calcification.[4]

Pyrophosphate is rapidly degraded to inorganic phosphate by tissue-nonspecific alkaline phosphatase (TNAP), encoded by the ALPL gene. It has been hypothesized that inhibition of TNAP activities would increase endogenous substrate PPi levels, leading to amelioration of the ectopic mineralization phenotype in PXE.[5,6] Indeed, a growing number of in vitro and in vivo pharmacology studies (including animal models of PXE) have confirmed and supported this approach.[7,8,9]

CCI [redacted]

1.2. Study Rationale

DS-1211b is a potent small-molecule inhibitor of TNAP being developed by Daiichi Sankyo for the treatment of ectopic calcification diseases such as PXE. In vitro and in vivo animal studies have shown that it is effective in inhibiting TNAP activities, increasing PPi levels, and reducing ectopic calcification.[12] CCI [redacted]

Therefore, Daiichi Sankyo is proceeding with this study in individuals with an established diagnosis of PXE to continue the development of DS-1211b for the treatment of PXE and potentially other progressive ectopic calcification diseases.

2. OBJECTIVES, OUTCOME MEASURES, AND ENDPOINTS

2.1. Study Objectives

The objectives, definitions of associated endpoints as well as applicable outcome measures are described in Table 2.1. Further requirements for the endpoint analyses and censoring rules, where applicable, can be found in Section 11.4 Section 11.5, and Section 11.6.

Study results, based on the analysis of below endpoints, will be analyzed to assess the dose for future clinical trials.

Table 2.1: Description of Objectives, Outcome Measures, and Endpoints

Objectives	Outcome Measure	Endpoints	Category
Primary			
To assess the safety and tolerability of DS-1211b compared with placebo in subjects with PXE	**Title:** Safety parameters during the study **Description:** Descriptive statistics of safety endpoints **Time frame:** From the time the subject signs the study ICF and up to Day 98 (14 days after the last dose of study drugs)	Incidence of AEs, including SAEs, and treatment-emergent AEs, physical examination/assessment findings including vital sign measurements, standard clinical laboratory parameters, and ECGs	Safety
To assess the dose response by assessing the treatment changes in PD endpoints	**Title**: PD endpoints **Description**: Profiles of ALP and TNAP substrates **Time frame**: Data are collected at baseline through Day 98.	ALP, PPi, and PLP	Pharmacodynamic
Secondary			
To characterize the PK of DS-1211a (the free form of DS-1211b in plasma) in subjects with PXE	**Title**: PK endpoints **Description**: Plasma concentration and PK parameters of DS-1211a **Time frame**: Data are collected at baseline through Day 84.	Plasma concentration and PK parameters of DS-1211a Include, but are not limited to, Cmax, Tmax, Ctrough, AUCtau, AUClast, and AUCinf (if possible to calculate)	Pharmacokinetic

Objectives	Outcome Measure	Endpoints	Category
Exploratory			
CCI [redacted]			
CCI [redacted]			

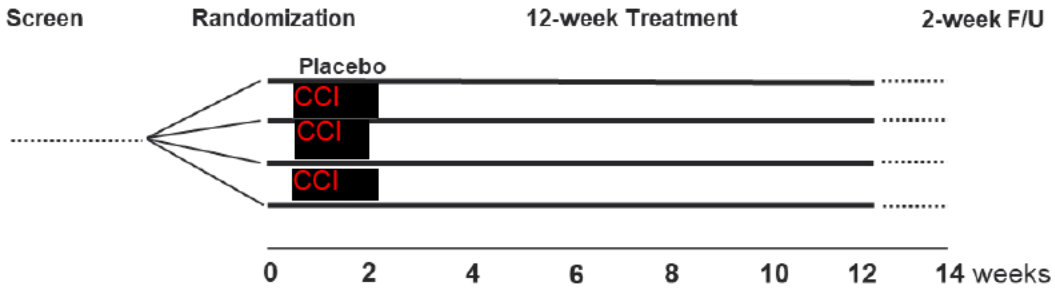
3. STUDY DESIGN

3.1. Overall Design

Study DS1211-A-U201 is a 12-week, randomized, double-blind, placebo-controlled, parallel-group study that aims to assess the safety, tolerability, and pharmacokinetic (PK) and pharmacodynamic (PD) dose response of DS-1211b in individuals with Pseudoxanthoma Elasticum (PXE) by using biomarkers relating to tissue-nonspecific alkaline phosphatase (TNAP) inhibition.

Eligible individuals with established diagnosis of PXE will be randomized to 1 of 4 arms in a 1:1:1:1 ratio, to receive CCI DS-1211b or placebo in tablet form for once daily dosing (Figure 3.1), for a total of 12-week dosing, CCI CCI

Figure 3.1: Study Schema



F/U = follow-up

The study will be conducted at approximately 10 study sites located in the US and possibly in the European region.

The study start date is the date when the first study subject has signed the informed consent. A PXE individual will be considered as eligible for randomization when the Investigator or designee has obtained written consent and has confirmed all eligibility criteria have been met during the screening period and when all screening procedures have been completed.

Study safety assessments include physical examinations/assessments, adverse events (AEs), electrocardiogram, and safety laboratory tests.

The Schedule of Events (SoE) is presented in Table 3.1. An intraday schedule for Visit 2 to Visit 5 is presented in Table 3.2.

3.2. Discussion of Study Design

This safety, tolerability, and dose-ranging study will evaluate DS-1211b doses that will inhibit TNAP sufficiently CCI

Safety, tolerability, PK, and mechanism of action (MOA)-related PD biomarkers (ALP, PPi, and PLP) will be assessed from the CCI doses, CCI , of DS-1211b versus placebo. TNAP inhibition increases PPi levels, the MOA by which DS-1211b is proposed to reduce ectopic calcification. However, excessive TNAP inhibition increases the risk of recapitulating clinical manifestations of hypophosphatasia (HPP), a genetic mineralization disorder of TNAP deficiency accompanied by abnormally and persistently elevated PPi and PLP levels. Therefore, a careful benefit-to-risk characterization of the extent of TNAP inhibition that achieves a balance between increases in PPi versus increases in PLP is critical for selecting a target DS-1211b dose for later studies.

The 3 doses proposed for this study cover the likely range of a clinically safe and effective dose, based on results from nonclinical pharmacology studies, completed studies in healthy volunteers (safety, TNAP inhibition, PPi and PLP), published literature in HPP (PLP and PPi), and literature in PXE (PPi), as discussed in Section 1. CCI

doses in this study will provide a test range covering the possible target dose.

These results will be used for modeling and simulation at the end of the study to further evaluate the eventual recommended clinical dose for future clinical trials.

3.3. Schedule of Events

Table 3.1: Schedule of Events

Period	Screening	Baseline	Treatment Period			Postdose	Follow-up	Notes
Visit Number	**1**	**2**	**3**	**4**	**5 (EOT)**	**6**	**7**	
Study Day	**- 30 to -1**	**1**	**15**	**43**	**84[a]**	**Last dose+3[b,c]**	**98[c]**	[a] Or day of early discontinuation. [b] To be scheduled at 2 to 4 days after last dose (eg, Visit 5 or early discontinuation). [c] In-home visit unless otherwise specified by Investigator.
Window (days)			**±3**	**±3**	**±3**	**±1**	**±5**	
Eligibility Assessments								
Informed consent	X							Obtain prior to performing any study procedures
Inclusion/Exclusion	X							
Randomization		X						
Demographics	X							
History								
Medical/Surgical	X							
Safety Assessments								
Vital signs	X	X	X	X	X	X	X	Measurements include pulse, respiratory rate, body temperature, and systolic and diastolic blood pressure. Blood pressure to be recorded while subject is in recumbent position, having rested in this position for at least 5 minutes. Vital signs to be collected after ECGs and prior to blood draws
Height/Weight	X							
Physical examination	X	X	X	X	X		X[d]	[d] Physical assessment to be performed by visiting nurse for the in-home visit.

Period	Screening	Baseline	Treatment Period			Postdose	Follow-up	Notes
Visit Number	**1**	**2**	**3**	**4**	**5 (EOT)**	**6**	**7**	
Study Day	**- 30 to -1**	**1**	**15**	**43**	**84[a]**	**Last dose+3[b,c]**	**98[c]**	[a] Or day of early discontinuation. [b] To be scheduled at 2 to 4 days after last dose (eg, Visit 5 or early discontinuation). [c] In-home visit unless otherwise specified by Investigator.
Window (days)			**±3**	**±3**	**±3**	**±1**	**±5**	
Triplicate 12-lead ECG	X	X	X	X	X		X	• See Table 3.2 for detailed information on Visits 2 to 5. • ECGs to be collected prior to vital signs and blood draws • Triplicates at each collection • Screening and follow-up visits (V1 and V7): 1 triplicate collection
AEs	X	X						All AEs occurring after the subject signs the ICF and up to Day 98 (14 days after last dose) should be collected.
SAEs	X	X						All SAEs occurring after the subject signs the ICF and up to Day 98 (14 days after last dose) should be collected.
Medications and Nondrug Therapies								
Prior medications	X							Medications used within 30 days prior to screening will be recorded. COVID-19 vaccination to be recorded regardless of time frame relative to screening.
Concomitant medications	X	X	X	X	X		X	
Laboratory Assessments								
Hematology	X	X	X	X	X		X	Fasting required. Blood collection should follow ECG and vital signs if indicated at same time point. See Section 9.8 for details
Coagulation	X	X	X	X	X		X	PT, aPTT and INR; predose (V2 to V5). Blood collection should follow ECG and vital signs if indicated at the same timepoint.
Chemistry	X	X	X	X	X	X[e]	X	Fasting required at all visits[e] except the postdose visit (Visit 6). Blood collection should follow ECG and vital signs if indicated at same timepoint. See Section 9.8 for details
Urine analysis	X	X			X			Fasted, use spot urine

Period	Screening	Baseline	Treatment Period			Postdose	Follow-up	Notes
Visit Number	**1**	**2**	**3**	**4**	**5 (EOT)**	**6**	**7**	
Study Day	**- 30 to -1**	**1**	**15**	**43**	**84[a]**	**Last dose+3[b,c]**	**98[c]**	[a] Or day of early discontinuation. [b] To be scheduled at 2 to 4 days after last dose (eg, Visit 5 or early discontinuation). [c] In-home visit unless otherwise specified by Investigator.
Window (days)			**±3**	**±3**	**±3**	**±1**	**±5**	
Pregnancy test	X	X	X	X	X		X	Serum pregnancy tests to be performed at V1 Screening Visit. Urine pregnancy test to be performed at V2, V3, V4, V5, and V7. If positive, a serum pregnancy test should be performed.
Pharmacokinetic Assessments								
PK Sampling		X[f]	X[g]	X[g]	X[f]			[f] Full collection/ [g] Sparse collection (See Table 3.2) Central laboratory testing. Blood collection should follow ECG and vital signs if indicated at same timepoint. Sampling will be obtained under nonfasted condition except for the predose samples, which will be collected after an overnight fast (≥ 8 hours). The windows for blood sample collection are as follows: 120 minutes at the predose timepoint and by ±10% of the nominal sampling time thereafter.
Pharmacodynamic Assessments								
ALP, PPi, and PLP	X[h]	X[f]	X[g]	X[g]	X[f]	X[h,i]	X[h,i]	[f] Full collection/[g] Sparse collection (See Table 3.2) [h] Single timepoint sample collection [i] ALP and PLP only Central laboratory testing. Blood collection should follow ECG and vital signs if indicated at same timepoint. All samples will be obtained under nonfasted condition except for the predose samples (Visits 2 to 5), which will be collected after an overnight fast (≥8 hours). The windows for blood sample collection are as follows: 120 minutes at the predose timepoint and by ±10% of the nominal sampling time thereafter.

Period	Screening	Baseline	Treatment Period			Postdose	Follow-up	Notes
Visit Number	**1**	**2**	**3**	**4**	**5 (EOT)**	**6**	**7**	
Study Day	**- 30 to -1**	**1**	**15**	**43**	**84[a]**	**Last dose+3[b,c]**	**98[c]**	[a] Or day of early discontinuation. [b] To be scheduled at 2 to 4 days after last dose (eg, Visit 5 or early discontinuation). [c] In-home visit unless otherwise specified by Investigator.
Window (days)			**±3**	**±3**	**±3**	**±1**	**±5**	
								Study participants should withhold the intake of vitamin B6 or vitamin B6-containing supplements on the day of the study visits (Visit 1 to Visit 7) until the completion of the study procedures. See Section 6.3 for additional details.
CCI [redacted]								

Period	Screening	Baseline	Treatment Period			Postdose	Follow-up	Notes
Visit Number	**1**	**2**	**3**	**4**	**5 (EOT)**	**6**	**7**	
Study Day	**- 30 to -1**	**1**	**15**	**43**	**84[a]**	**Last dose+3[b,c]**	**98[c]**	[a] Or day of early discontinuation. [b] To be scheduled at 2 to 4 days after last dose (eg, Visit 5 or early discontinuation). [c] In-home visit unless otherwise specified by Investigator.
Window (days)			**±3**	**±3**	**±3**	**±1**	**±5**	
CCI [redacted]								
Study Drug (DS-1211b/placebo)								
Dispense		X		X				
Assess treatment compliance			X	X	X			
CCI [redacted]								

CCI

[redacted]

4. STUDY POPULATION

4.1. Inclusion Criteria

Study participants must satisfy all of the following criteria to be included in the study:

1. Sign and date the ICF prior to the start of any study-specific qualification procedures.
2. Are male or female participants aged 18 to 75 years at screening.
3. Have an established diagnosis of PXE, with typical ocular and dermatological clinical features[1,2]:
    a. Ocular findings – angioid streaks or peau d'orange
    b. Skin findings – characteristic PXE papules and plaques or diagnostic histopathological changes in lesional skin
4. Are fully vaccinated for coronavirus disease 2019 (COVID-19) per current Center for Disease Control and Prevention guidelines
5. For women of childbearing potential (not postmenopausal as a result of either natural or postsurgery cessation of menses), must have a negative serum pregnancy test at screening and must be willing to use an effective method of birth control, as detailed in Section 17.2 upon entering study screening, during the treatment period, and up until the time of the follow-up visit.
6. Are willing and able to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.

4.2. Exclusion Criteria

Individuals who meet any of the following criteria at screening will be disqualified from entering the study:

1. Have a history of bone fracture in the past 6 months.
2. Have a history of active metabolic bone disease that significantly affect the interpretation of study biomarker results, excluding osteopenia or osteoporosis without fragility fracture.
3. Have a history of calcium pyrophosphate deposit disease such as chondrocalcinosis, pseudogout, and pyrophosphate arthropathy.
4. Have a history of hypophosphatasia.
5. Have a history of untreated hyperparathyroidism.
6. Participated in another interventional research study in the past 60 days.
7. Are participating or have participated within the last 12 months in PXE trials (eg, trials with PPi, PPi analogues such as bisphosphonate, or ENPP1 and its analogues) or in clinical trials relating to bone mineralization.

8. Used bisphosphonate in the preceding 12 months or had plans to use bisphosphonate during the study.
9. Used strong inhibitors or inducers of Cytochrome P450 isozymes, 2C19, 3A4, or 3A5 (Table 17.1 and Table 17.2)
10. CCI [redacted]
11. CCI [redacted]
12. Have an alkaline phosphatase <lower limit of normal (LLN) range
13. Have alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 × upper limit of normal (ULN) range; total bilirubin >1 × ULN
14. Have PLP >ULN
15. Have hemoglobin <10.0 g/dL.
16. Have a QTcF interval duration >450 ms at screening.
17. Have moderate to severe renal insufficiency (Creatinine clearance <60 mL/min by Cockcroft-Gault method).
18. Are pregnant or breast-feeding women.
19. Are female participants unwilling to use contraceptive methods.
20. Have a history of sulfonamide allergy.
21. Have any elective surgery planned during the study period.
22. Have any other significant condition (medical, psychiatric, social, or medication) that, in the judgment of the Investigator, would prevent full participation or would be inappropriate for the study.

5. STUDY TREATMENT(S)

5.1. Assigning Subjects to Treatments and Blinding

5.1.1. Treatment Group(s)/Sequences

The study will consist of 4 treatment groups in which study drug will be administered in a double-blind, placebo-controlled parallel-group study design (see Figure 3.1).

5.1.2. Method of Treatment Allocation

Eligible subjects will be randomized in a 1:1:1:1 ratio into the 4 treatment groups (DS-1211b [redacted] or placebo). The randomization schedule will be generated by an independent biostatistician. Prior to treatment, a randomization number will be assigned to each eligible subject. The randomization assignment will be implemented by an automatic voice or web response system.

5.1.3. Blinding

This study will be a double-blind study. Blinding will be applied to all personnel related to the study (subjects, Investigators, and the Sponsor), with the exception of the independent biostatistician and other staff involved in the preparation, release, and shipment of investigational medicinal products.

The independent biostatistician will generate the randomization schedule in accordance with the operating procedure for allocating study drug. Until the study is unblinded, the study drug randomization schedule will be kept securely.

5.1.4. Emergency Unblinding Procedure

In the case of an emergency where, in the opinion of the Investigator, discontinuation of study drug is not sufficient and the study treatment must be unblinded in order to evaluate further a course of medical treatment, the Investigator can perform the unblinding, after discussion with the Medical Monitor, if possible. Entry of the Adverse Event case report form (CRF) page should be completed before unblinding except in cases where immediate treatment of the subject is required. If immediate treatment is required, the Adverse Event CRF page is to be completed within 24 hours of the unblinding.

In the event of an emergency unblinding, the subject will be informed about his/her treatment assigned. Information about the treatment assignment **must be** restricted to designated study site staff/personnel who are providing immediate care to the subject. Any documentation of the treatment assignment **must be** maintained separately (ie, a secured file). The information **must not be** included in the subject's source files to ensure the treatment assignment will remain blinded to the Contract Research Organization (CRO) monitor and other study personnel not involved with the subject's immediate care.

When an emergency unblinding has occurred, an automatic notification (via e-mail) will be sent to the Investigator and selected Daiichi Sankyo study personnel from the interactive response technology (IRT) vendor. The notification will not contain any unblinding information. This will trigger the follow-up process to document the unblinding by completing the Emergency

Unblinding by Investigator Form (to be provided by study personnel upon receipt of IRT notification) and submission to Daiichi Sankyo Clinical Safety and Pharmacovigilance; please refer to the form for completion instructions.

Once the study treatment has been unblinded for a specific subject, the study treatment should be discontinued for the subject, and the subject should leave the study treatment phase. The end of treatment and follow-up assessments for the subjects will be performed as defined in Section 6.4.

5.2. Study Drug(s)

5.2.1. Description

The study drugs for this study are:

- DS-1211b CCI [redacted] tablet CCI [redacted]
- Matching placebo tablets

5.2.2. Labeling and Packaging

DS-1211b CCI [redacted] tablets and matching placebo tablets will be supplied by the Sponsor. The study drug will be labeled in compliance with regulatory requirements and packaged in double-blinded wallets. The packaging will be clearly labeled "For Clinical Study Use Only," and will display the lot number, storage condition, protocol number, and other required information in accordance with local regulations. Study drug will be assigned via an IRT.

5.2.3. Preparation

All study drugs will be supplied as tablets that need no further preparation at the study sites.

5.2.4. Administration

Study drug is to be administered once daily dosing in the morning either in the fasted state or with a meal.

5.2.5. Storage

Drug supplies must be stored in a secure, limited-access storage area under the recommended storage conditions.

If storage conditions are not maintained per specified requirements, the Sponsor or CRO should be contacted.

5.2.6. Drug Accountability

When a drug shipment is received, the pharmacist or designee will check the amount and condition of the drug against the shipping documentation. The pharmacist or designee shall contact the Sponsor as soon as possible if there is a problem with the shipment.

The Receipt of Shipment Form should be emailed as instructed on the form unless receipt is controlled by an IRT. The original will be retained at the study site.

In addition, the Investigator or designee shall contact Sponsor as soon as possible if there is a problem with the shipment.

Drug Accountability will be conducted via the IRT or local site procedures for study drug, placebo, and commercial product as appropriate. The record must be kept current and should contain the dates and quantities of study drug received, subject's identification number (with or without initials) and supply number as applicable, the person for whom the study drug was dispensed, the date and quantity of study drug dispensed and remaining, and the initials of the dispenser.

The pharmacist (or qualified designee) is responsible for study drug accountability, reconciliation, and record maintenance (ie, Receipt of Shipment Form, dispensation/return record, and certificate of destruction/return receipt).

At the end of the study (or as directed), all unused or partially used study drug will be returned or destroyed as per local laws or site policy and only after the CRO monitor has completed a final inventory. If applicable, the return of study drug must be documented, and the documentation must be included in the return shipment.

Please see the Pharmacy Manual for more details.

5.3. Control Treatment

See Section 5.2.1.

5.4. Dose Interruptions and Reductions

Study subjects should adhere to the protocol-prescribed daily morning dosing schedule throughout the entire study. In case the subject misses the morning dose CCI he/she is allowed to take the dose later the same day.

No subject is allowed to take more than one dose per day, regardless of the number of days of missed doses.

Dose modifications are not allowed in this study. Dose interruptions need to be documented. After any dose interruption, the subject should resume the assigned once daily study drug as soon as possible.

5.5. Method of Assessing Treatment Compliance

Compliance will be assessed by tablet count (returned versus dispensed). Administration of study drug will be recorded in the CRF/Drug Accountability Record. Subjects to be asked whether all tablets were taken orally or if any tablets were disposed/thrown away.

5.6. Prior and Concomitant Medications

Medications used within 30 days prior to screening will be recorded. COVID-19 vaccine doses received prior to the study will be documented as prior medication, regardless of date of administration. COVID-19 vaccine dose administered during the study will be recorded as a concomitant medication.

The following medications are prohibited (See Section 4.2):

- Use of bisphosphonate in the preceding 12 months, or planned use of bisphosphonate during the study.
- Use of medications that are strong inhibitors or inducers of Cytochrome P450 isozymes, 2C19, 3A4, or 3A5 (See Table 17.1 and Table 17.2)
- Use of prescription or over-the-counter medications that, in the judgment of the Investigator, may significantly confound the interpretation of study results
- CCI

CCI

Any medication (other than study drugs) taken by subjects during the course of the study will be recorded and coded by using the World Health Organization drug dictionary.

5.7. Subject Withdrawal/Discontinuation

5.7.1. Reasons for Withdrawal

All subjects are encouraged to adhere to study visit schedule and study treatment.

Any subject who is withdrawn from the study for any reason will have their reasons for withdrawal recorded.

Reasons for withdrawal from study will be categorized into:

- Adverse Event
- Withdrawal by Subject
- Physician Decision
- Death
- Pregnancy
- Protocol Deviation
- Study Termination by Sponsor
- Loss to Follow-up
- Other

5.7.2. Withdrawal Procedures

If a subject is withdrawn from the study, the Investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal including the date of last treatment and the reason for withdrawal.

If the subject is withdrawn because of an adverse event, the Investigator will follow the subject until the adverse event has resolved or stabilized.

All subjects who are withdrawn from the study should complete protocol-specified early discontinuation/end of treatment procedures (Visit 5, and Visits 6 and 7: See Table 3.1).

5.7.3. Subject Replacement

Subject replacement is not planned in this study.

5.7.4. Subject Rescreening Procedures

Rescreening is permitted for any subject who fails to meet eligibility criteria upon initial screening and later has changes in his/her medical condition or other circumstances that in the opinion of the Investigator (in consultation with the Sponsor) warrant reconsideration of study eligibility. The subject identification number must be new at the time of rescreening. The initial screening information and the reason why the subject is ineligible for the initial evaluation will be recorded on the screening log. Data from the initial evaluation will be entered into the clinical database for a subject who is rescreened.

6. STUDY PROCEDURES

See SoE (Table 3.1, Table 3.2), for screening, treatment, end of treatment, and follow-up study procedures.

6.1. Screening

Individuals with an established diagnosis of PXE will be screened between Day -30 through Day -1. Rescreening will be allowed.

6.2. Randomization

This will be a double-blind (subject and Investigator) randomized study.

Individuals who complete the screening process and meet the eligibility requirements will be randomized on Study Day 1.

More information on the method of assigning subjects is found in Section 5.1.2.

6.3. Treatment Period

Approximate visit durations are expected to be:

- Visits 1, 6, and 7: a few hours
- Visit 3 and 4: more than 6 hours
- Visits 2 and 5: more than 10 hours

Visits 1 through 5 are fasting visits (overnight fast [≥8 hours]). Study participants will be allowed to eat after the first blood collection.

Visits 6 and 7 will be conducted as in-home visits unless requested by the study participant or Investigator.

Study participants should withhold the intake of vitamin B6 or vitamin B6-containing supplements on the day of the study visits (Visits 1 to 7). Vitamin B6 or vitamin B6-containing supplements can be resumed after all study-related procedures are completed.

6.4. End of Treatment

Visit 5 (Day 84) is the end of treatment visit. Any study participant who discontinues early will complete early discontinuation assessment using the procedures outlined in the end of treatment visit and the follow-up assessments (Visits 6 and 7).

7. EFFICACY ASSESSMENTS

Not applicable as the study evaluation is based on MOA-related biomarker assessments.

7.1. Assessments for Efficacy Endpoint(s)

Not applicable.

7.2. Appropriateness of Selected Efficacy Assessment(s)

Not applicable.

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

8.1. Pharmacokinetic (PK) Assessment(s)

Venous blood samples will be collected for PK analysis of DS-1211a at the timepoints detailed in Table 3.1 and Table 3.2.

Fasting is not required except for the predose samples, which will be collected after an overnight fast (≥ 8 hours). Whenever electrocardiograms (ECGs) are performed, ECGs should be performed prior to blood collections. The windows for PK blood sample collection are as follows: 120 minutes at the predose timepoint and by ±10% of the nominal sampling time thereafter. The actual dosing time and sampling times will be captured on the electronic Case Report Form (eCRF).

Plasma will be harvested and analyzed for the quantification of DS-1211a using a validated liquid chromatography-tandem mass spectrometry method.

8.2. Pharmacodynamic Assessment(s)

Venous blood samples will be collected for the measurement of ALP, PPi, and PLP following the sampling schedule in Table 3.1 and Table 3.2.

The windows for PD blood sample collection and details on assessment times and deviations are as follows: 120 minutes at the predose timepoint, and by ± 10% of the nominal sampling time thereafter. Changes of biomarker levels from baseline will be calculated on the basis of plasma concentration-time data.

Biomarker samples will be analyzed by using a qualified analytical method for each marker.

8.3. Biomarker Assessment(s)

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The estimated creatinine clearance (in millimeters per minute) will be calculated by using the Cockcroft-Gault equation.

8.4. Immunogenicity

Not applicable.

8.5. Pharmacogenetic (Inherited Genetic) Analysis

A whole blood sample for genomic DNA analysis will be collected from study participants who provide consent (genotyping consent). CCI [redacted] Study participants who do not provide consent for genomic DNA analysis may still participate in the study. CCI [redacted]

CCI [redacted]

9. SAFETY EVALUATION AND REPORTING

9.1. Assessment of Safety Endpoint(s)

The safety endpoints include the following:

- AEs
- ECG findings
- Clinical laboratory test results
- Physical examination/assessment findings
- Hypophosphatasia (HPP) monitoring:
  - Plasma ALP, PLP, PPi, Pi, and Mg
  - Ca (serum and urinary)
  - CCI [redacted]
- Nephrotoxicity monitoring: Serum and urine creatinine, BUN, urine total protein, urine albumin, urine KIM-1, and urine NGAL

9.2. Adverse Event Collection and Reporting

All AEs (see Section 9.4.1 and Section 9.4.2 for definitions) occurring after the subject signs the Informed Consent Form and up to 14 (± 5) days after the last dose of study medication (ie, the follow-up period), whether observed by the Investigator or reported by the subject, will be recorded on the Adverse Event CRF page. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

Medical conditions (including clinically significant laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to the consent date will be recorded as medical history, and not an Adverse Event. Exacerbation of a pre-existing medical occurrence and symptom including increase in severity of the symptom will be recorded as an AE on the Adverse Event section.

All AEs and serious adverse events (SAEs) are to be reported according to the procedures in Section 9.5.

All clinical laboratory results, vital signs, and ECG results or findings should be appraised by the Investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or ECG findings (i.e., not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, dose reduction, require corrective treatment, or constitute an AE in the Investigator's clinical judgment.

At each visit, the Investigator or designee will determine whether any AEs have occurred by evaluating the subject. Adverse events may be directly observed, reported spontaneously by the subject or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality in accordance with the

definitions in Section 9.4. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the serious adverse event (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the Informed Consent Form) procedures or treatments requiring hospitalization for pre-existing conditions that do not worsen in severity should not be reported as SAEs (see Section 9.4.2 for Definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any serious, untoward event that may occur subsequent to the reporting period that the Investigator assesses as related to study drug should also be reported and managed as an SAE.

COVID-19 assessments are detailed in Section 10.1.

9.3. Combined Elevations of Aminotransferases and Bilirubin and Adverse Events of Special Interest

Combined elevations of aminotransferases and bilirubin, either serious or nonserious and whether or not causally related, meeting the laboratory criteria of a potential Hy's Law case (ALT or AST ≥3 × ULN with simultaneous total bilirubin [TBL] ≥ 2 × ULN) should always be reported to the Sponsor by using a special collection eCRF with the Investigator's assessment of seriousness, causality, and a detailed narrative.[14] These events should be reported within 24 hours of Investigator's awareness of the event.

If the subject discontinues study drug because of liver enzyme abnormalities, the subject should have additional clinical and laboratory evaluations in order to determine the nature and severity of the potential liver injury.

There are no adverse events of special interest (AESIs) for this study. Hypophosphatasia and nephrotoxicity will be monitored using laboratory alerts and review of AEs reported during this study. Details of HPP and nephrotoxicity monitoring during the conduct of the study are described in the Medical Monitoring Plan.

If the laboratory alerts indicate deterioration of the subject's renal function, the Investigator will be contacted to obtain relevant subject medical history, Investigator's assessment of clinical significance of the results, clinical course, and outcome. Based on the discussion between the Investigator and the Sponsor, further evaluation may be warranted including temporary discontinuation of the investigational product.

9.4. Adverse Event

9.4.1. Definition of Adverse Event

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

It is the responsibility of Investigators, based on their knowledge and experience, to determine those circumstances or abnormal laboratory findings which should be considered adverse events.

9.4.2. Serious Adverse Event

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or
- Is an important medical event.

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. Examples include allergic bronchospasm, convulsions, and blood dyscrasias or development of drug dependency or drug abuse.

Note:

- Procedures are not AEs or SAEs, but the reason for the procedure may be an AE or SAE.
- Preplanned (prior to signing the Informed Consent Form) procedures or treatments requiring hospitalizations for pre-existing conditions that do not worsen in severity are not SAEs.

9.4.3. Severity Assessment

The following definitions should be used to assess intensity of adverse events:

- Mild: Awareness of sign or symptom, but easily tolerated, ie, does not interfere with subject's usual function.
- Moderate: Discomfort enough to cause interference with usual activity.
- Severe: Incapacitating with inability to work or do usual activity, ie, interferes significantly with subject's usual function.

Severity vs. Seriousness: Severity is used to describe the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "seriousness," which is based on patient/event outcome at the time of the event.

9.4.4. Causality Assessment

The Investigator should assess causal relationship between an adverse event and the study drug on the basis of his/her clinical judgment and the following definitions. The causality assessment must be made on the basis of the available information and can be updated as new information becomes available.

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

or

  - The AE follows a reasonable temporal sequence from study drug administration and is a known reaction to the drug under study or its chemical group or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

9.4.5. Action Taken Regarding Study Drug(s)

- Dose Not Changed: No change in study drug dosage was made.
- Drug Withdrawn: The study drug was permanently stopped.
- Drug Interrupted: The study drug was temporarily stopped.
- Not Applicable: Subject died, study treatment had been completed prior to adverse event, or reaction/event occurred prior to start of treatment.

9.4.6. Other Action Taken for Adverse Event

- None.

  - No treatment was required.
- Medication required.
  - Prescription and/or over-the-counter medication was required to treat the adverse event.
- Hospitalization or prolongation of hospitalization required.
  - Hospitalization was required or prolonged because of the AE, whether or not medication was required.
- Other.

9.4.7. Adverse Event Outcome

- Recovered/Resolved
  - The subject fully recovered from the adverse event with no residual effect observed.
- Recovering/Resolving
  - The adverse event improved but has not fully resolved.
- Not recovered/Not resolved
  - The adverse event itself is still present and observable.
- Recovered/Resolved with sequelae
  - The residual effects of the adverse event are still present and observable.
  - Include sequelae/residual effects.
- Fatal
  - Fatal should be used when death is a direct outcome of the adverse event.
- Unknown

9.5. Serious Adverse Events Reporting–Procedure for Investigators

All SAEs will be reported in the CRF.

The following types of events should be reported by the Investigator in Electronic Data Capture (EDC) or on a Serious Adverse Event Report (SAVER) form if EDC is unavailable within 24 hours of awareness:

- SAEs (see Section 9.4.2 for definition)
- Hepatic events meeting combination abnormalities (ALT or AST ≥3 × ULN with simultaneous TBL ≥2 × ULN) (potential Hy's Law case), both serious and nonserious.

Although pregnancy is not an AE, all pregnancies must be reported within 24 hours of the Investigator being aware of it (see Section 9.7).

All events (serious and nonserious) must be reported with Investigator's assessment of the event's seriousness, severity, and causality to the blinded study drug. For SAEs, a detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided. Specific or estimated dates of event onset, treatment, and resolution should be included when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed and include the results if available. Source documents (including medical reports) will be retained at the study site and should not be submitted to the Sponsor for SAE reporting purposes.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to nonurgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

In the event that eCRF is unavailable, report SAEs by faxing the paper SAVER Form to the CRO using the provided fax cover sheet and the appropriate fax number provided for your country. Once eCRF becomes available, please enter SAEs reported on the SAVER Form into eCRF as soon as possible. Please refer to eCRF Completion Guide for additional instructions.

Contact study medical monitor for questions regarding SAE reporting.

9.6. Notifying Regulatory Authorities, Investigators, and Institutional Review Board/Ethics Committee

Daiichi Sankyo and/or CRO will inform Investigators, Institutional Review Boards/Ethics Committees (IRBs/ECs), and regulatory authorities of any suspected unexpected serious Adverse reactions (SUSARs) occurring in other study sites or other studies of the investigational drug, as appropriate per local reporting requirements. Daiichi Sankyo and/or CRO will comply with any additional local safety reporting requirements. The section of "Reference Safety Information" in the current Investigator's Brochure should be referred to judge "Unexpected."

In the US, upon receipt of the Sponsor's notification of SUSARs that occurred with the study drug, unless delegated to the Sponsor, it is the Investigator's responsibility to inform the IRB per Sponsor's instruction.

In the European Economic Area states, it is the Sponsor's or CRO's responsibility to report SUSARs to all ECs.

9.7. Exposure In Utero During Clinical Studies

Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving or within 30 days of discontinuing the study drug. Although pregnancy is not technically an adverse event, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the Investigator, or designee, to report any pregnancy in a female subject using the Exposure In Utero (EIU) Reporting form within 24 hours of learning of the pregnancy. Please contact your study monitor to receive the EIU Reporting Form upon learning of a pregnancy. The Investigator should make every effort to follow the subject until completion of the pregnancy and complete the EIU Reporting Form with complete pregnancy outcome information, including

normal delivery and induced abortion. The adverse pregnancy outcome, either serious or nonserious, should be reported in accordance with study procedures. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (ie, postpartum complications, spontaneous or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the Investigator should follow the procedures for reporting SAEs outlined in Section 9.5.

9.8. Clinical Laboratory Evaluations

The clinical laboratory tests including hematology, coagulation, blood chemistry, and urinalysis will be performed as per the SoE (Table 3.1).

9.9. Vital Signs

Vital signs will be measured and recorded as per the SoE (Table 3.1).

Blood pressure and pulse rate will be measured after the subject has rested in a recumbent position for 5 minutes or more.

Information will be entered in the case report form on whether or not the parameter was measured, on what date the measurement is performed, and what the measurement results were for the following items: systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and body temperature.

9.10. Electrocardiograms

Twelve-lead ECGs in triplicate will be performed and recorded for every subject as per the SoE (Table 3.1). Vital signs will be collected after ECG measurements, and blood collection should occur after the vital signs (if indicated at the same timepoint).

The ECG will be measured after the subject has rested in a recumbent position for 5 minutes or more. Whether or not measurement is performed, on what date the measurement is performed, and what the results and findings are for the following parameters will be recorded: heart rate, PR interval, RR interval, QRS amplitude, and QT interval.

9.11. Physical Examinations

Physical examinations/assessments should be performed as per the SoE (Table 3.1).

Height and body weight will be performed only at Screening.

The physical examination will include an evaluation mainly of the respiratory, cardiovascular, gastrointestinal, dermatological, neurological, and musculoskeletal systems, as well as the eyes, ears, nose, and throat. The physical assessment may be expanded further to note any observations related to the subject's physical signs and symptoms. The physical assessment will be performed by a visiting nurse for the in-home visit (Visit 7).

9.12. Other Examinations

Not applicable.

10. OTHER ASSESSMENTS

10.1. COVID-19 Assessments

All confirmed or suspected COVID-19 infection events during the study must be recorded in the eCRF. Investigator should make every effort to collect or perform all required diagnostic tests to fully diagnose the suspected concomitant illnesses to confirm the definitive diagnosis if possible. The subject's consent may be required for some of the diagnostic tests as required by the local legal or regulatory needs or customary practices.

In the case of a moderate to severe COVID-19 infection or COVID-19 infection requiring treatment, study drug interruption should be considered by the Investigator in consultation with the medical monitor.

In an effort to ensure appropriate safety reporting of COVID-19 cases in accordance with Health Authority guidelines, the following process should be followed for cases that have occurred in the context of a clinical trial:

- All confirmed or suspected COVID-19 events must be recorded in the eCRF.
  - Subjects who test positive for COVID-19 should be reported as "Confirmed COVID-19," either as an AE or SAE.
  - Subjects whose medical history and clinical manifestations, signs, and possible exposure are consistent with COVID-19 but for whom no polymerase chain reaction or antibody test for COVID-19 is available should be reported as "Suspected COVID-19," either as an AE or SAE.
- The usual protocol mandated SAE reporting requirements should be followed for confirmed or suspected COVID-19 as done for any other AE, ie, the Investigator should assess whether any seriousness criteria are met per protocol, and appropriate protocol reporting requirements should be followed.
  - In the event that the Investigator assesses that a COVID-19 case does not meet any seriousness criteria as outlined in the protocol, it should be reported as a non-serious adverse event in the CRF.
- All study drug interruption or discontinuation due to the COVID-19 event must be recorded on the AE and drug administration eCRFs.
- For both serious or nonserious COVID-19-related AEs, the following information should be provided as applicable:
  - Date and laboratory results confirming the COVID-19 diagnosis (including viral antigen test and/or antiviral antibody serological test).
  - Clinical course of the case including presenting signs, symptoms, exposure, actions taken with the investigational products, medications used for treatment or prophylaxis of COVID-19, and outcome in relevant eCRF (eg, concomitant medication, AE).
  - Findings from diagnostic imaging (including computed tomography scan or other chest imaging).

11. STATISTICAL METHODS

11.1. General Statistical Considerations

Continuous variables will be summarized by the number of subjects, mean, standard deviation, median, and minimum and maximum values, unless otherwise specified. Categorical variables will be summarized by using frequency counts and percentages. In general, data will be summarized by treatment group.

Raw data will be presented with the exact precision with which they were collected.

There is no multiplicity adjustment.

11.2. Analysis Sets

- All Enrolled Subjects will include all subjects who sign the informed consent form.
- The Intent-to-treat Analysis Set will consist of all randomized subjects.
- Safety Analysis Set will include all subjects who received at least 1 dose of study drug.
- Per-protocol Analysis Set consists of all randomized subjects who received at least 1 dose of the study drug according to an automatic voice or web response system assignment and do not have important protocol deviations. Important protocol deviations are defined in the statistical analysis plan (SAP).
- Pharmacokinetic Analysis Set will include all subjects who receive at least 1 dose of study drug and have at least 1 measurable pharmacokinetic result.
- Biomarker Analysis Set will consist of all subjects who receive at least 1 dose of study drug and have at least 1 measurable biomarker assessment.

11.3. Study Population Data

Disposition and reasons for ending the treatment and discontinuing from the study will be summarized and listed for subjects in the enrolled analysis set.

Demographic and other baseline characteristics will be summarized for the Intent-to-treat Analysis Set.

11.4. Efficacy Analyses

Not applicable.

11.5. Pharmacokinetic/Pharmacodynamic/Biomarker Analyses

11.5.1. Pharmacokinetic Analyses

Pharmacokinetic analyses will be based on Pharmacokinetic Analyses Set.

The following PK parameters will be calculated by noncompartmental methods from the DS-1211a concentration-time data: maximum plasma concentration, minimum plasma

concentration, time to reach maximum plasma concentration, and if appropriate area under the plasma concentration-time curve (AUC), terminal elimination half-life, The apparent total body clearance, and apparent volume of distribution at steady state. The PK analysis will be conducted in compliance with DSI Noncompartmental Analysis Guidelines.

Plasma concentration of DS-1211a and PK parameters will be summarized by treatment group using descriptive statistics, including the mean, geometric mean, standard deviation, coefficient of variation percentage or median.

Finally, plasma concentration data for DS-1211a collected from the study may also be analyzed by means of nonlinear mixed-effect modeling. Results from the analysis will be reported in a separate standalone report.

11.5.2. Pharmacodynamic Analyses

See Section 11.5.3.

11.5.3. Biomarker Analyses

All biomarker analyses will be based on Biomarker Analysis Set. Observed values at each assessment and the absolute change and percentage change from baseline will be numerically summarized for primary and exploratory biomarkers by treatment group over time. The 95% confidence interval will be presented for percentage change from baseline in ALP, PPi, and PLP. The baseline of biomarker data is defined as the last nonmissing assessment collected prior to the first dose of study medication.

Difference in primary and exploratory biomarkers between active doses and placebo will be summarized by descriptive statistics.

11.5.4. Pharmacogenetic (Inherited Genetic) Analyses

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[redacted]

11.6. Safety Analyses

Safety analysis will be performed by using the Safety Analysis Set and subjects will be analyzed according to their actual treatment received. The baseline value for clinical laboratory, vital sign, and ECG values is defined as the last nonmissing value prior to the first dose of study medication.

11.6.1. Adverse Event Analyses

Treatment-emergent adverse events (TEAEs) are defined as events that start on or after the first dose of study drug or start prior to but then worsen after the first dose of study drug. Treatment-emergent adverse events will be analyzed by treatment group.

AEs will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects reporting TEAEs will be calculated overall, by system

organ class, by preferred term, and by treatment group. TEAEs will be further summarized by severity and relationship to study drug. Similarly, the number and percentage of subjects reporting treatment-emergent SAEs will be tabulated, as well as TEAEs leading to discontinuation of study treatments.

A by-subject AE (including treatment emergent) data listing including but not limited to verbatim term, preferred term, system organ class, severity Common Toxicity Criteria for Adverse Event grade, and relationship to study treatment will be provided. Deaths, other SAEs, and other significant AEs, including those leading to discontinuation of study treatments, will be listed.

AEs due to COVID-19 will be summarized and listed.

11.6.2. Clinical Laboratory Evaluation Analyses

Descriptive statistics will be provided for the clinical laboratory results by scheduled time of evaluation and by treatment group for the safety population, as well as for the change from baseline. In addition, mean change from baseline will be presented by treatment group for the maximum and minimum post-treatment values and the values at the end of treatment visit.

The number and percentage of subjects with laboratory interval values meeting Hy's law criteria will be summarized. Laboratory results from HPP and nephrotoxicity monitoring will be analyzed.

11.6.3. Vital Sign Analyses

Descriptive statistics will be provided for the vital sign measurements by scheduled time of evaluation and by treatment group for the safety population, as well as for the change from baseline.

11.6.4. Electrocardiogram Analyses

Descriptive statistics will be provided for the ECG measurements by scheduled time of evaluation and by treatment group for the safety population, as well as for the change from baseline. In addition, the number and percentage of subjects with ECG interval values meeting the criteria will be tabulated (eg, QTc $\leq$ 450 ms, > 450 to $\leq$ 480 ms, > 480 ms to $\leq$ 500 ms, and > 500 ms). Data from ECG will also be presented in the data listings.

11.7. Other Endpoint Analysis

Not applicable.

11.8. Interim Analyses

Not applicable.

11.8.1. Data Monitoring Committee

A Data Monitoring Committee (DMC) will not be involved in the management of this clinical study.

11.9. Sample Size Determination

Sample size is not based on statistical consideration but is chosen on the basis of feasibility and clinical consideration from biomarker results (intra- and intersubject variability and dose responses) of the completed Phase 1 healthy volunteer studies. CCI [redacted]

11.10. Statistical Analysis Process

The clinical study will be analyzed by the Sponsor or its agent/CRO.

The SAP will provide the statistical methods and definitions for the analysis of the safety and biomarker data, as well as describe the approaches to be taken for summarizing other clinical study information such as subject disposition, demographic and baseline characteristics, study drug exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused, and spurious data will be addressed.

The SAP will be finalized prior to database lock to preserve the integrity of the statistical analysis and clinical study conclusions.

All statistical analyses will be performed by using SAS® Version 9.4 or higher (SAS Institute, Cary, NC 27513).

12. DATA INTEGRITY AND QUALITY ASSURANCE

12.1. Monitoring and Inspections

The Sponsor/CRO monitor and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (eg, CRFs, source data, and other pertinent documents).

The verification of adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH Good Clinical Practice (GCP) and local regulations on the conduct of clinical research will be accomplished through a combination of onsite visits by the monitor and review of study data remotely. The frequency of the monitoring visit will vary based on the activity at each study site. The monitor is responsible for inspecting the CRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the CRFs. Detailed information is provided in the monitoring plan.

The monitor will communicate deviations from the protocol, SOPs, GCP, and applicable regulations to the Investigator and will ensure that appropriate action (s) designed to prevent recurrence of the detected deviations is taken and documented.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed to the satisfaction of the Sponsor and documented.

In accordance with ICH GCP and the Sponsor's audit plans, this study site may be selected for audit by representatives from the Sponsor. Audit of study site facilities (eg, pharmacy, drug storage areas, laboratories) and review of study-related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. The Investigator should respond to audit findings. In the event that a regulatory authority informs the Investigator that it intends to conduct an inspection, the Sponsor shall be notified immediately.

12.2. Data Collection

DSI or a designee will supply eCRFs. An eCRF must be completed for each subject who signs an ICF and undergoes any screening procedure. If a subject is not treated, the reason must be recorded on the eCRF. All data collected during the study will be recorded in this individual, subject-specific eCRF. Instructions will be provided for the completion of the eCRF and any corrections made will be automatically documented via the EDC software's "audit trail."

Completion of the eCRF should be kept current to enable the monitor to review the subject's status throughout the course of the study. All information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood. The eCRF will be completed, reviewed, and signed off or e-signed by the Investigator/designee. The Investigator will sign and date the indicated places on the eCRF via the EDC system's electronic signature. These signatures will indicate that the Investigator inspected or reviewed the data on the eCRF, the data queries, and the site notifications, and agrees with the content.

12.3. Data Management

Each subject will be identified in the database by a unique subject identifier as defined by the Sponsor.

To ensure the quality of clinical data across all subjects and study sites, a Clinical Data Management review will be performed on subject data according to specifications given to Sponsor/CRO. Data will be vetted both electronically and manually for CRFs and the data will be electronically vetted by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated within the EDC application. During this review, subject data will be checked for consistency, completeness, and any apparent discrepancies. CRFs queries will be raised and resolved within the EDC application.

Data received from external sources such as central laboratories will be reconciled to the clinical database.

Serious adverse events and nonserious AEs potentially meeting Hy's Law in the clinical database will be reconciled with the safety database.

All AEs will be coded by using MedDRA. Prior and concomitant medications will be coded by using the World Health Organization Drug Reference List.

Data that may potentially unblind the treatment assignment will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, prior to unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available.

12.4. Study Documentation and Storage

The Investigator will maintain a Signature List of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Signature List.

Investigators will maintain a confidential screening log of all potential study candidates that includes limited information of the subjects and the date and outcome of screening/rescreening process.

Investigators will be expected to maintain an Enrollment Log of all subjects enrolled in the study indicating their assigned study number.

Investigators will maintain a confidential subject identification code list. This confidential list of names of all subjects allocated to study numbers on enrolling in the study allows the Investigator to reveal the identity of any subject when necessary.

Source documents are original documents, data, and records from which the subject’s CRF data are obtained. These include, but are not limited to, hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, X-rays, and correspondence.

Records of subjects, source documents, monitoring visit logs, data correction forms, CRFs, inventory of study drug, regulatory documents (eg, protocol and amendments, IRB/EC correspondence and approvals, approved and signed informed consent forms, Investigator’s Agreement, clinical supplies receipts, distribution and return records), and other Sponsor

correspondence pertaining to the study must be kept in appropriate study files at the study site (Trial Master File). Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by the institution or study site policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

12.5. Recordkeeping

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (Trial Master File) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Essential documents contained in the Trial Master File include:

- Subject files containing completed CRFs, informed consent forms, and supporting copies of source documentation (if kept).
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the EC/IRB and the Sponsor.
- Records related to the study drug(s) including acknowledgment of receipt at study site, accountability records and final reconciliation and applicable correspondence.

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

All study-related essential documentation will be retained by the Investigator until at least 3 years (or as applicable for local requirements) after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years (or as applicable for local requirements) have lapsed since the formal discontinuation of clinical development of the investigational drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

Subject's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution, or private practice.

No study document should be destroyed without prior written agreement between Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify Sponsor in writing of the new responsible person and/or the new location.

13. FINANCING AND INSURANCE

13.1. Finances

Prior to starting the study, the Principal Investigator and/or institution will sign a clinical study agreement with the CRO on behalf of DSI. This agreement will include the financial information agreed upon by the parties.

13.2. Reimbursement, Indemnity, and Insurance

The Sponsor provides insurance for study subjects to make available compensation in case of study-related injury.

Reimbursement, indemnity, and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

14. PUBLICATION AND PUBLIC DISCLOSURE OF CLINICAL TRIAL INFORMATION

Daiichi Sankyo is committed to meeting the highest standards of publication and public disclosure of information arising from clinical trials sponsored by the company. We will comply with applicable United States (US), European Union (EU), and Japanese policies for public disclosure of the clinical trial protocol and clinical trial results, and for sharing of clinical trial data. We follow the principles set forward in "Good Publication Practice for Communicating Company-Sponsored Medical Research (GPP3)", and publications will adhere to the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" established by the International Council of Medical Journal Editors (ICMJE).

In order to ensure that we are in compliance with the public disclosure policies and the ICMJE recommendations, and to protect proprietary information generated during the study, all publications (manuscripts, abstracts, or other public disclosure) based on data generated in this study must be accepted, reviewed, and approved in writing by the Sponsor prior to submission.

15. ETHICS AND STUDY ADMINISTRATIVE INFORMATION

15.1. Compliance Statement, Ethics, and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonization (ICH) consolidated Guideline E6 for GCP (CPMP/ICH/135/95), and applicable regulatory requirement(s) including the following:

- European Commission Directive (2001/20/EC Apr 2001) and/or;
- European Commission Directive (2005/28/EC Apr 2005) and/or;
- US Food and Drug Administration GCP Regulations: Code of Federal Regulations Title 21, parts 11, 50, 54, 56 and 312 as appropriate and/or;
- Other applicable local regulations.

15.2. Subject Confidentiality

The Investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.

For EU study sites, the Sponsor will observe the rules laid down in the European Data Protection Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and the free movement of such data.

The Investigator must ensure that the subject's anonymity is maintained. On the CRFs or other documents submitted to the Sponsor or the CRO, subjects should be identified by a unique subject identifier as designated by the Sponsor. Documents that are not for submission to the Sponsor or the CRO (eg, signed ICF) should be kept in strict confidence by the Investigator.

In compliance with ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/EC direct access to review the subject's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above-named representatives without violating the confidentiality of the subject.

15.3. Informed Consent

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent in writing from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or any study drugs are administered. Subjects should be given the opportunity to ask questions and receive satisfactory answers to their inquiries and should have adequate time to decide whether or not to participate in the study. The written ICF should be prepared in the local language(s) of the potential subject population.

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that

have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the EC or IRB prior to being provided to potential subjects.

The subject's written informed consent should be documented in the subject's medical records. The ICF should be signed and personally dated by the subject and by the person who conducted the informed consent discussion (not necessarily the Investigator). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject. The date and time (if applicable) that informed consent was given should be recorded on the CRF.

If the subject cannot read, then according to ICH GCP Guideline, Section 4.8.9, an impartial witness should be present during the entire informed consent discussion. This witness should sign the ICF after the subject has consented to the subject's participation and, if possible, signed the ICF. By signing the ICF, the witness attests that the information in the ICF and any other written information was adequately explained to and apparently understood by the subject and that informed consent was freely given by the subject.

Suggested model text for the ICF for the study and any applicable subparts (genomic, PK, etc) are provided in the Sponsor's ICF template for the Investigator to prepare the documents to be used at his or her study site.

For study sites in the US, an additional consent (or section of the main consent) is required for the Health Insurance Portability and Accountability Act.

15.4. Regulatory Compliance

The study protocol, subject information and consent form, the Investigator Brochure, any subject written instructions to be given to the subject, available safety information, subject recruitment procedures (eg, advertisements), information about payments and compensation available to the subjects, and documentation evidencing the Investigator's qualifications should be submitted to the EC or IRB for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the SAP.

The Sponsor will appoint a Coordinating Investigator. Among other possible duties, the Coordinating Investigator will be responsible for reviewing and approving the Final Clinical Study Report and testifying to the accuracy of the description of the study conduct. Because the Coordinating Investigator should have personal knowledge of the conduct of the study, he or she will normally be chosen from among those Investigators who have enrolled and treated at least one subject. However, where an Investigator has special knowledge of the field or of the trial, the Coordinating Investigator can be chosen prior to enrollment of the first subject. In all cases, the Coordinating Investigator must be chosen prior to locking the database.

The Investigator and/or Sponsor must submit and, where necessary, obtain approval from the EC or IRB for all subsequent protocol amendments and changes to the ICF. The Investigator should notify the EC or IRB of deviations from the protocol or SAEs occurring at the study site and other AE reports received from the Sponsor/CRO in accordance with local procedures.

As required by local regulations, the Sponsor's local Regulatory Affairs group or representative to whom this responsibility has been delegated will ensure all legal aspects are covered, and approval from the appropriate regulatory bodies obtained, prior to study initiation. If changes to the initial protocol and other relevant study documents are made, this representative will also ensure that any revised documents required for submission are submitted to regulatory authorities and implementation of these changes happen only after approval by the relevant regulatory bodies.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Regulatory Authority(ies) in any area of the world, or if the Investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational drug, the Sponsor should be informed immediately.

In addition, the Investigator will inform the Sponsor immediately of any urgent safety measures taken by the Investigator to protect the study subjects against any immediate hazard, and of any suspected/actual serious GCP noncompliance that the Investigator becomes aware of.

15.5. Protocol Deviations

The Investigator should conduct the study in compliance with the protocol agreed to by Sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRBs/ECs.

A deviation to any protocol procedure or waiver to any stated criteria will not be allowed in this study except where necessary to eliminate immediate hazard(s) to the subject. Sponsor must be notified of all intended or unintended deviations to the protocol (eg, inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

The Investigator or a person designated by the Investigator should document and explain any deviation from the approved protocol.

If a subject was ineligible or received the incorrect dose or study treatment and had at least 1 administration of study drug, data should be collected for safety purposes.

If applicable, the Investigator should notify the EC or IRB of deviations from the protocol in accordance with local procedures.

15.6. Supply of New Information Affecting the Conduct of the Study

When new information becomes available that may adversely affect the safety of subjects or the conduct of the study, the Sponsor will inform all Investigators involved in the clinical study, ECs/IRBs, and regulatory authorities of such information, and when needed, will amend the protocol and/or subject information.

The Investigator should immediately inform the subject whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participation in the study. The communication should be documented on medical records, for example, and it should be confirmed whether the subject is willing to remain in the study.

If the subject information is revised, it must be reapproved by the IEC/IRB. The Investigator should obtain written informed consent to continue participation with the revised written information even if subjects were already informed of the relevant information. The Investigator or other responsible personnel who provided explanations and the subject should sign and date the revised ICF.

15.7. Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the Investigator by Daiichi Sankyo or the CRO. Also, the Sponsor will ensure the timely submission of amendments to regulatory authorities.

A global protocol amendment will affect study conduct at all study sites in all regions of the world. Such amendments will be incorporated into a revised protocol document. Changes made by such amendments will be documented in a Summary of Changes document. These protocol amendments will undergo the same review and approval process as the original protocol.

A local protocol amendment will affect study conduct at a particular study site(s) and/or in a particular region/country. Sponsor approval of local amendments will be clearly documented.

A protocol amendment may be implemented after it has been approved by the IRB/EC and by regulatory authorities, unless implementation is allowed without this approval by local regulations.

15.8. Study Termination

The Sponsor has the right to terminate the study at any time and the study termination may also be requested by (a) competent authority/ies.

15.9. Data and Safety Monitoring Board

Not applicable.

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17. APPENDICES

17.1. CYP Inhibitors and Inducers

Table 17.1 lists the generic names of strong CYP3A4 inhibitors and inducers. Table 17.2 lists the generic names of CYP2C19 inhibitors and inducers.

Table 17.1: CYP3A4 Inhibitors/Inducers

Inhibitor/Inducer Type	Generic Drug Name	Allowance
Strong Inhibitor	Ketoconazole Voriconazole Itraconazole Clarithromycin Telithromycin Indinavir Ritonavir Nelfinavir Saquinavir Mibefradil Idelalisib Tucatinib Ribociclib Grapefruit Juice	Use is prohibited during the study.
Strong Inducer	Rifampin (rifampicin) Phenytoin Fosphenytoin Phenobarbital Carbamazepine Apalutamide Enzalutamide Lumacaftor Lumacaftor-ivacaftor Mitotane Primidone St John's Wort	Use is prohibited during the study.

Note: Moderate and weak CYP3A4 inhibitors and inducers are allowed (https://drug-interactions.medicine.iu.edu/MainTable.aspx)

Table 17.2: CYP2C19 Inhibitors/Inducers

Inhibitor/Inducer Type	Generic Drug Name	Allowance
Strong Inhibitors	Fluvoxamine Fluconazole Ticlopidine	Use is prohibited during the study.
Moderate Inhibitors	Esomeprazole Fluoxetine	Use is allowed.
Weak Inhibitors	Armodafinil Citalopram Cimetidine Felbamate Isoniazid Luliconazole Modafinil Omeprazole Pantoprazole Oral contraceptives	Use is allowed.
Strong Inducers	Rifampin (rifampicin) Apalutamide	Use is prohibited during the study.

17.2. Highly Effective Contraception

Methods considered to be highly effective contraception include:[15]

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Complete sexual abstinence (evaluate in relation to the preferred and usual lifestyle choice of the study participant)


CCl