2. SYNOPSIS

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Study Title:
Drug-Drug Interaction Study of S-217622 in Healthy Adult Participants

Investigators and Study Centers: This study was a single-center study conducted in Japan.

Publication (reference): Not applicable

Studied Period:
From 09 Feb 2022 to 12 Mar 2022

Phase of Development: Phase 1

Objectives and Endpoints:

Objectives	Endpoints
Primary	
● To investigate the effects of a single dose of S-217622 on the pharmacokinetics (PK) of digoxin, rosuvastatin and metformin in Japanese healthy adult participants.	● Digoxin, rosuvastatin, and metformin: maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration after dosing ($AUC_{0\text{-}last}$), area under the plasma concentration-time curve extrapolated from time zero to infinity ($AUC_{0\text{-}inf}$), terminal elimination half-life ($t_{1/2,z}$), terminal elimination rate constant (λ_z), mean residence time (MRT), apparent total clearance (CL/F), and apparent volume of distribution in the terminal elimination phase (V_z/F)

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Secondary	
● To investigate the PK of a single dose of S-217622 in Japanese healthy adult participants. ● To investigate the safety and tolerability of a single dose of S-217622 in Japanese healthy adult participants.	● S-217622: C_{max}, T_{max}, area under the plasma concentration-time curve from time zero to 24 hours after dosing (AUC_{0-24}), and area under the plasma concentration-time curve from time zero to 96 hours after dosing (AUC_{0-96}) ● Adverse events (AEs), physical examination, laboratory tests (hematology, blood chemistry, coagulation test, and urinalysis), vital signs (systolic/diastolic blood pressure, pulse rate, respiratory rate, and body temperature), and 12-lead electrocardiogram (ECG)

Methodology:

The study was a single-center, single-arm, open-label study in Japanese healthy adult participants, consisting of Screening Period (Days −28 to −1), Hospitalization Period 1 (Days −1 to 5), Hospitalization Period 2 (Days 10 to 15), and Follow-up (Day 21 [+2]).

- Screening Period (Days −28 to −1)
  After obtaining informed consent, screening tests were performed to confirm the participant's eligibility for participation in the study.
- Hospitalization Period 1 (Days −1 to 5)
  Participants who were determined to be eligible based on the screening tests were enrolled into the study 1 day before administration of digoxin (a P-glycoprotein [P-gp] substrate), rosuvastatin (a breast cancer resistance protein [BCRP] and organic anion transporter polypeptide [OATP] 1B1/1B3 substate), and metformin (multidrug and toxin extrusion [MATE]1 and organic cation transporter [OCT]1 substrate), as a drug cocktail (Day −1). Participants were admitted on Day −1, received a single dose of the cocktail on Day 1 (in fasted state), and were discharged on Day 5 (hospitalization period: 6 days and 5 nights). Participants underwent the specified investigations and tests during hospitalization and were

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discharged after the investigations and tests scheduled on Day 5. All meals were normal meals.

– Hospitalization Period 2 (Days 10 to 15)
Participants who completed Hospitalization Period 1 were admitted 9 days after administration of the cocktail (Day 5 after discharge in Hospitalization Period 1) and 1 day before administration of study intervention (S-217622) (Day 10) in Hospitalization Period 2. Participants were admitted on Day 10, received a single dose of study intervention (S-217622) and the cocktail on Day 11 (in fasted state), and were discharged on Day 15 (hospitalization period: 6 days and 5 nights). Participants underwent the specified investigations and tests during hospitalization and were discharged after the investigations and tests scheduled on Day 15. All meals were normal meals.

– Follow-up (Day 21 [+2])
Participants who completed Hospitalization Period 2 underwent specified investigations and tests on Day 21 (+2).

Number of Participants (Planned and Analyzed):

Planned: 14

Assigned to study intervention: 14

Analyzed for PK:

- PK concentration population: 14
- PK parameter population: 14

Analyzed for safety (Safety analysis population): 14

Diagnosis and Main Criteria for Inclusion:

1. Inclusion criteria

- Male and female participants who had Japanese parents and were 20 to 55 years of age, inclusive, at the time of signing the informed consent.
- Body mass index (BMI) within the range 18.5 to 30.0, inclusive.
Weight ≥ 40 kg (for female).

2. Exclusion criteria

- Participants whose systolic blood pressure at rest was outside the range of 90 to 140 mmHg or diastolic blood pressure was outside the range of 50 to 90 mmHg, or participants whose pulse rate was outside the range of 50 to

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100 bpm at screening or on admission and were considered ineligible for the study by the investigator.

- Any of the following abnormal values at screening or on admission:
  - Total bilirubin: > 1.5 × institutional upper limit of normal (ULN)
  - Alanine aminotransferase (ALT): > 1.5 × institutional ULN
  - Aspartate aminotransferase (AST): > 1.5 × institutional ULN
  - Creatinine clearance (CLcr) (Cockcroft-Gault formula) < 90 mL/min
- Participants who had a QT interval corrected using Fridericia's formula (QTcF) of ≥ 450 msec for males or ≥ 470 msec for females measured on 12-lead ECG or a heart rate (HR) that was outside the range of 50 to 95 bpm after resting in a supine position for 3 minutes at screening, on admission, or before administration, and were considered ineligible for the study by the investigator.
- Positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (reverse transcriptase polymerase chain reaction [RT-PCR] method, transcription-mediated amplification [TMA] method, or antigen test) at screening or Day −1.
- Sensitivity to heparin or heparin-induced thrombocytopenia.
- Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the investigator, contraindicated participation in the study (except for those with seasonal allergy without allergic symptoms).

Test Product, Dose and Mode of Administration, Lot Number:

1. Test Product

Intervention Name	S-217622 Tablet 125 mg	Digoxin	Rosuvastatin	Metformin
Type	Drug	Drug	Drug	Drug
Dosage Form	Tablet	Tablet	Tablet	Tablet
Unit Dose Strengths	Each tablet contained 125 mg of S-217622.	Each tablet contained 0.25 mg of digoxin.	Each tablet contained 2.5 mg of rosuvastatin.	Each tablet contained 500 mg of metformin hydrochloride.

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Dosage Levels	Administered 4 tablets of S-217622 125 mg on Day 11.	Administered 1 tablet of digoxin 0.25 mg on Days 1 and 11.	Administered 1 tablet of rosuvastatin 2.5 mg on Days 1 and 11.	Administered 1 tablet of metformin 500 mg on Days 1 and 11.
Route of Administration	Oral	Oral	Oral	Oral
Use	Experimental	Concomitant drug	Concomitant drug	Concomitant drug
Sourcing	Provided centrally by the sponsor.	Purchased by the study center.		
Packaging and Labeling	Each tablet was packed in a press through pack (PTP) sheet, and 3 sheets were packed in an individual carton. Each carton was labeled as required per Japanese requirement.	Each carton was labeled as required per Japanese requirement.		
Dosing Instructions	The cocktail and/or study intervention were administered in fasted state. Participants were not allowed to eat for at least 10 hours before administration of the cocktail and/or study intervention and for at least 4 hours after administration of the cocktail and/or study intervention. Drinking was prohibited from 1 hour before to 2 hours after dosing, with the exception of the water (240 mL) to be taken when taking the cocktail and study intervention, after which time water was allowed ad libitum.			

2. Dose and Mode of Administration

The study interventions were administrated as shown the table above.

3. Packaging Lot Number

S-217622 Tablet 125 mg: [redacted]

Digoxin : [redacted]

Rosuvastatin : [redacted]

Metformin : [redacted]

Duration of Treatment:

1 day for the single dose of S-217622

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Reference Therapy, Dose and Mode of Administration, Lot Number: Not applicable		
Criteria for Evaluation: **Pharmacokinetics Assessment:** As the PK parameters of S-217622, C_{max}, T_{max}, AUC_{0-24} and AUC_{0-96} were determined. As the PK parameters of digoxin, rosuvastatin, and metformin, C_{max}, T_{max}, AUC_{0-last}, AUC_{0-inf}, $t_{1/2,z}$, λ_z, MRT, CL/F, and V_z/F were determined. **Safety Assessment:** Adverse events, physical examinations, clinical laboratory test, vital signs, and 12-lead ECG. All AEs/SAEs were collected from the date of signing of the informed consent form (ICF) or start of intervention until the completion of follow-up.		
Statistical Methods: **Pharmacokinetic Analyses:** Pharmacokinetic analyses were performed on the PK concentration population or the PK parameter population. Plasma concentration data of S-217622, digoxin, rosuvastatin, and metformin were listed and summarized by treatment and nominal sampling time. Pharmacokinetic parameters of digoxin, rosuvastatin, and metformin after the cocktail administration (Day 1) or coadministration of S-217622 and the cocktail (Day 11) were compared using analysis of variance (ANOVA) with dosing conditions (administration of the cocktail or in combination with S-217622) as a fixed effect and participant as a random effect, using the MIXED procedure in SAS. The primary parameters were C_{max}, AUC_{0-last}, and AUC_{0-inf} ratio of digoxin, rosuvastatin, and metformin, respectively. If the 90% confidence intervals (CIs) for the geometric least squares (GLS) means ratios of these parameters were within the range of 0.8000 and 1.2500, it was considered that coadministration of S-217622 did not affect the PK of digoxin, rosuvastatin, or metformin. **Safety Analyses:** All safety analyses were performed on the safety analysis set. Adverse events were classified by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA), Version 24.1. The number and proportion of participants who experienced treatment-emergent AEs		

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(TEAEs), deaths, other serious TEAEs, and TEAEs leading to treatment discontinuation were summarized.

For clinical laboratory test, vital signs, and 12-lead ECG parameters, summary statistics were calculated for measured values and changes from baseline at each measurement time point scheduled after enrollment.

Summary of Results:

Pharmacokinetics:

- Coadministration with S-217622 500 mg increased digoxin C_{max} 2.17-fold, $AUC_{0\text{-last}}$ 1.30-fold, and $AUC_{0\text{-inf}}$ 1.31-fold compared with digoxin without S-217622, suggesting weak P-gp inhibition by S-217622 500 mg.
- Coadministration with S-217622 500 mg increased rosuvastatin C_{max} 1.97-fold, $AUC_{0\text{-last}}$ 1.64-fold, and $AUC_{0\text{-inf}}$ 1.65-fold compared with rosuvastatin without S-217622, suggesting weak BCRP and OATP1B1/1B3 inhibition by S-217622 500 mg.
- The GLS mean ratios of C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ (metformin + S-217622 / metformin) were close to 1 and their 90% CIs were all contained within the range of 0.8000 to 1.2500, suggesting no MATE1 and OCT1 inhibition by S-217622 500 mg.
- The C_{max} and $AUC_{0\text{-24}}$ of S-217622 following single-dose administration of 500 mg S-217622 on Day 11 were almost the same as the exposures of Day 5 following once daily multiple-dose administration of S-217622 375 mg on Day 1 and 125 mg on Days 2 to 5.

Safety:

- No deaths, SAEs or other significant TEAEs were reported in the study.
- The only TEAE in this study was diarrhoea that occurred in 1 participant (7.1%) each in Period 1 and Period 2. These events were mild and resolved during the study and were not considered treatment-related.
- No clinically significant abnormal results were observed in laboratory tests, vital signs, or 12-lead ECGs in the study.

CONCLUSIONS

Pharmacokinetics Conclusions:

A single administration of S-217622 500 mg in combination of digoxin, rosuvastatin, and metformin showed weak inhibition against P-gp, BCRP and OATP1B1/1B3, and no inhibition against MATE1 or OCT1.

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Safety Conclusions: A single administration of S-217622 500 mg in combination of digoxin, rosuvastatin, and metformin was considered to cause no significant safety issues.		
Date of Report: 30 May 2022		