2. SYNOPSIS

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Study Title:
A Phase 1 Study of S-217622 in Healthy Adult Participants

Investigators and Study Centers:
This was a study in Japan which consisted of 7 parts: Parts 1, 4, 5, 6, and 7 were single-center studies, and Parts 2 and 3 were multicenter studies conducted in 2 study sites.

Publication (reference): Not applicable

Studied Period:
From 20 Jul 2021 to 10 Jun 2022

Phase of Development: Phase 1

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Part 1 • To investigate the safety and tolerability of S-217622 following single-dose administration in Japanese healthy adult male participants.	Part 1 • Adverse events (AEs), physical examination, laboratory tests (hematology, blood chemistry, serological, endocrinological, blood coagulation, and urinalysis), vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature), 12-lead electrocardiography (ECG), and Holter ECG
Part 2 • To investigate the safety and tolerability of S-217622 following multiple-dose administration in Japanese and White healthy adult male participants, as well as in Japanese healthy adult female participants.	Part 2 • AEs, physical examination, laboratory tests (hematology, blood chemistry, serological, endocrinological, blood coagulation, and urinalysis), vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature), and 12-lead ECG

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Part 3 • To investigate the effect of S-217622 on the pharmacokinetics (PK) of dexamethasone and prednisolone following multiple-dose administration in Japanese healthy adult male participants. • To investigate the PK of S-217622 following multiple-dose administration in Japanese healthy adult male participants.	Part 3 • Dexamethasone and prednisolone: 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) • S-217622: C_{max}, T_{max}, area under the plasma concentration-time curve over the dosing interval τ ($AUC_{0\text{-}\tau}$), $t_{1/2,z}$, and λ_z
Part 4 • To investigate the effect of food on the PK of S-217622 (125-mg tablets) following single-dose administration after a meal (high-calorie, high-fat) in Japanese healthy adult participants.	Part 4 • S-217622: C_{max}, T_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $t_{1/2,z}$, λ_z, MRT, CL/F, and V_z/F
Part 5 • To investigate the safety and tolerability of S-217622 (125-mg or 250-mg tablets) following multiple-dose administration in White healthy adult participants.	Part 5 • AEs, physical examination, laboratory tests (hematology, blood chemistry, blood coagulation, and urinalysis), vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature), and 12-lead ECG
Part 6 • To investigate the safety and tolerability of S-217622 (125-mg tablets) following multiple-dose administration in healthy elderly participants.	Part 6 • AEs, physical examination, laboratory tests (hematology, blood chemistry, blood coagulation, and urinalysis), vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature), and 12-lead ECG
Part 7 • To investigate the effect of S-217622 (125-mg tablets) on the PK of midazolam, cytochrome P450 (CYP) 3A substrate,	Part 7 • S-217622: C_{max}, T_{max}, and $AUC_{0\text{-}\tau}$ • Midazolam: C_{max}, T_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $t_{1/2,z}$, λ_z, MRT, CL/F, and V_z/F

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following multiple-dose administration in Japanese healthy adult participants.	
Secondary	
Part 1 • To investigate the PK of S-217622 following single-dose administration in Japanese healthy adult male participants. • To investigate the effect of food on the PK of S-217622 following single-dose administration after a meal (high-calorie, high-fat) in Japanese healthy adult male participants. • To investigate the effect of S-217622 on ECG parameters following single-dose administration in Japanese healthy adult male participants.	Part 1 • S-217622: C_{max}, T_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $t_{1/2,z}$, λ_z, MRT, CL/F, V_z/F, renal clearance (CL_R), and fraction of dose excreted in urine (Feu) • Heart rate (HR), corrected QT (QTc), PR, QRS, T-wave, and U-wave • Change from baseline in HR, QTc, PR, and QRS (ΔHR, ΔQTc, ΔPR, and ΔQRS) • Baseline- and placebo-adjusted HR, QTc, PR, and QRS (ΔΔHR, ΔΔQTc, ΔΔPR, and ΔΔQRS)
Part 2 • To investigate the PK of S-217622 following multiple-dose administration in Japanese and White healthy adult male participants, as well as in Japanese healthy adult female participants. • To compare the PK of S-217622 following multiple-dose administration in Japanese and White healthy adult male participants, as well as in Japanese healthy adult female participants. • To investigate the effect of S-217622 on the PK of midazolam, a CYP3A substrate, following multiple-dose administration in Japanese healthy adult male participants	Part 2 • S-217622: C_{max}, T_{max}, and $AUC_{0\text{-}\tau}$ • Midazolam: C_{max}, T_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $t_{1/2,z}$, λ_z, MRT, CL/F, and V_z/F
Part 3 • To investigate the safety and tolerability of S-217622 following multiple-dose administration in Japanese healthy adult male participants.	Part 3 • AEs, physical examination, laboratory tests (hematology, blood chemistry, and urinalysis), vital sings (systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature), and 12-lead ECG
Part 4 • To investigate the safety and tolerability of S-217622 (125-mg tablets) following single-dose administration in Japanese healthy adult participants.	Part 4 • AEs, physical examination, laboratory tests (hematology, blood chemistry, blood coagulation, and urinalysis), vital signs (systolic and diastolic blood pressure, pulse

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	rate, respiratory rate, and temperature), and 12-lead ECG
Part 5 • To investigate the PK of S-217622 (125-mg or 250-mg tablets) following multiple-dose administration in White healthy adult participants.	Part 5 • S-217622: C_{max}, T_{max}, $AUC_{0-\tau}$, $t_{1/2,z}$, and λ_z
Part 6 • To investigate the PK of S-217622 (125-mg tablets) following multiple-dose administration in healthy elderly participants.	Part 6 • S-217622: C_{max}, T_{max}, $AUC_{0-\tau}$, $t_{1/2,z}$, and λ_z
Part 7 • To investigate the safety and tolerability of coadministration of S-217622 (125-mg tablets) and midazolam in Japanese healthy adult participants.	Part 7 • AEs, physical examination, laboratory tests (hematology, blood chemistry, blood coagulation, and urinalysis), vital sings (systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature), and 12-lead ECG
Exploratory	
Part 2 • To investigate the effect of S-217622 on cytokines following multiple-dose administration in Japanese and White healthy adult male participants, as well as in Japanese healthy adult female participants.	Part 2 • Laboratory tests (cytokines)

No efficacy endpoints were established in this study.

Methodology:

This study consisted of 7 parts: Part 1 (SAD), Part 2 (MAD), Part 3 (DDI), Part 4 (FE), Part 5 (W-MAD), Part 6 (elderly), and Part 7 (DDI of S-217622 [125-mg tablets] with midazolam).

Part 1 (SAD)

Part 1 of this study was a single-center, randomized, double-blind, placebo-controlled study in Japanese healthy adult male participants, consisting of 6 cohorts (A, B, C, D, E, and J). In Cohort C, the effect of food was investigated in a 2-group, 2-period crossover design with administration of S-217622 and placebo. This study was a first-in-human study for S-217622; thus, administration was started from Cohort A at the lowest dose and proceeded to next cohorts after confirming the safety and tolerability

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at the end of each cohort according to the procedures for progression to the next cohort. Cohort A was divided into Cohorts A1 and A2, and Cohort J was divided into Cohorts J1 and J2. Cohort K was to be conducted at a dose lower than that in Cohort J contingent upon the occurrence of safety issues in Cohort J1. Cohort K, if conducted, was to be divided into Cohorts K1 and K2 in the same manner.

- Cohorts A1 and A2 (20 mg, single-dose administration):

  A single dose of S-217622 20 mg or placebo was administered in the fasted state.
- Cohort B (70 mg, single-dose administration):

  A single dose of S-217622 70 mg or placebo was administered in the fasted state.
- Cohort C1 (250 mg, single-dose administration, investigation of the effect of food):

  A single dose of S-217622 250 mg or placebo was administered in the fasted state in Period 1 and after breakfast (high-calorie, high-fat) in Period 2.
- Cohort C2 (250 mg, single-dose administration, investigation of the effect of food):

  A single dose of S-217622 250 mg or placebo was administered after breakfast (high-calorie, high-fat) in Period 1 and in the fasted state in Period 2.
- Cohort D (500 mg, single-dose administration):

  A single dose of S-217622 500 mg or placebo was administered in the fasted state.
- Cohort E (1000 mg, single-dose administration):

  A single dose of S-217622 1000 mg or placebo was administered in the fasted state.
- Cohorts J1 and J2 (2000 mg, single-dose administration):

  A single dose of S-217622 2000 mg or placebo was administered in the fasted state.
- Cohorts K1 and K2 (1500 mg, single-dose administration) (if conducted):

  A single dose of S-217622 1500 mg or placebo was to be administered in the fasted state.

In Cohorts A, B, D, E, and J, 8 eligible participants were randomly assigned to the S-217622 group (6 participants) or the placebo group (2 participants). Cohort A was

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divided into Cohorts A1 and A2. In Cohort A1, 2 participants were randomly assigned to the S-217622 group (1 participant) or the placebo group (1 participant). In Cohort A2, after confirming that there were no safety issues until 24 hours postdose in Cohort A1, 6 participants (5 in the S-217622 group, 1 in the placebo group) received the study intervention on Day 4 of Cohort A1. Cohort J was divided into Cohorts J1 and J2. In Cohort J1, 2 participants were randomly assigned to the S-217622 group (1 participant) or the placebo group (1 participant). In Cohort J2, after confirming that there were no safety issues until 48 hours postdose in Cohort J1, remaining 6 participants (5 in S-217622 group, 1 in placebo group) received the study intervention. For each cohort, the study period consisted of a screening period (Day −28 to Day −1), a hospitalization period (Day −1 to Day 7), follow-up 1 (Day 9 [+2]), and follow-up 2 (Day 15 [+2]).

In Cohort C (250 mg) which was divided into Cohorts C1 and C2, the effect of food was investigated in a 2-group, 2-period crossover design with administration of S-217622 and placebo. In Cohorts C1 and C2, 5 eligible participants were randomly assigned to the S-217622 group (4 participants) or the placebo group (1 participant), respectively. For each cohort, the study period consisted of a screening period (Day −28 to Day −1), a hospitalization period of Period 1 (Day −1 to Day 7), follow-up 1 (Day 9 [+2]), a hospitalization period of Period 2 (Day 14 to Day 21), follow-up 2 (Day 23 [+2]), and follow-up 3 (Day 29 [+2]). An interval between doses of Period 1 (Day 1) and Period 2 (Day 15) was 14 days or longer.

Part 2 (MAD)

Part 2 of this study was a multicenter, randomized, double-blind (open-label for midazolam in Cohort G), placebo-controlled study in Japanese and White healthy adult male participants and in Japanese healthy adult female participants, consisting of 5 cohorts (F to H, N and O). Cohort F was initiated according to the procedures for progression to the next cohort, after confirming the safety and tolerability of a single dose that would ensure the estimated maximum exposure per day at the dosage to be used in Cohort F, which was deduced by a simulation. The simulation was performed based on the PK results of S-217622 up to Period 1 of Cohort C to determine the appropriateness of the dosage to be used in Cohort F. Cohort G was initiated according to the procedures for progression to the next cohort, after confirming the safety and tolerability of S-217622 for 24 hours after the intervention (Day 2) in Cohort E and 24 hours after the last intervention (Day 6) in Cohort F, and judging whether progression was possible. Cohort H was initiated according to the procedures

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for progression to the next cohort, after confirming the safety and tolerability of S-217622 for 24 hours after the last intervention (Day 6) in Cohort F, and judging whether progression was possible. Cohort O was initiated according to the procedures for progression to the next cohort, after confirming the safety and tolerability of S-217622 for 24 hours after the last intervention (Day 6) in Cohort N and judging whether progression was possible.

The dose and duration of administration in Part 2 were modified based on the PK results of Part 1. The study interventions were administered in the fasted state as follows.

- Cohort F (once daily, multiple-dose administration):

  S-217622 or placebo was administered once daily for 5 days in Japanese healthy adult male participants. A loading dose of S-217622 375 mg was administered only on Day 1. After that, S-217622 125 mg was administered on Day 2 to Day 5.
- Cohort G (once daily, multiple-dose administration, investigation of DDI of S-217622 [suspension] with midazolam):

  S-217622 or placebo was administered once daily for 6 days in Japanese healthy adult male participants. A loading dose of S-217622 750 mg was administered only on Day 1. After that, S-217622 250 mg was administered on Day 2 to Day 6. Midazolam syrup 1 mL was administered alone on Day –2 and concomitantly with S-217622 or placebo on Day 6.
- Cohort H (once daily, multiple-dose administration):

  S-217622 or placebo was administered once daily for 5 days in White healthy adult male participants. A loading dose of S-217622 375 mg was administered only on Day 1. After that, S-217622 125 mg was administered on Day 2 to Day 5.
- Cohort N (once daily, multiple-dose administration):

  S-217622 (125-mg tablets) or placebo was administered once daily for 5 days in Japanese healthy adult female participants. A loading dose of S-217622 375 mg was administered only on Day 1. After that, S-217622 125 mg was administered on Day 2 to Day 5.
- Cohort O (once daily, multiple-dose administration):

  S-217622 (250-mg tablets) or placebo was administered once daily for 5 days in Japanese healthy adult female participants. A loading dose of S-217622

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750 mg was administered only on Day 1. After that, S-217622 250 mg was administered on Day 2 to Day 5.

In each cohort of Part 2, 11 eligible participants were randomly assigned to the S-217622 group (8 participants) or the placebo group (3 participants). For Cohorts F, H, N, and O, the study period consisted of a screening period (Day −28 to Day −1), a hospitalization period (Day −1 to Day 9), and follow-up (Cohorts F and H, Day 13 [+2]; Cohorts N and O, Day 13 [−2, +5]).

For Cohort G, the study period consisted of a screening period (Day −28 to Day −3), a hospitalization period (Day −3 to Day 10), and follow-up (Day 14 [+2]).

Part 3 (DDI)

Part 3 of this study was a multicenter, single-arm, open-label study in Japanese healthy adult male participants, consisting of 2 cohorts (L and M). Part 3 was initiated after confirming the safety and tolerability of S-217622 at the dose used in Cohort G of Part 2.

- Cohort L (once daily, multiple-dose administration, investigation of DDI of S-217622 with dexamethasone):

  S-217622 (250-mg tablets) was administered once daily for 5 days in Japanese healthy adult male participants. A loading dose of S-217622 750 mg was administered only on Day 1. After that, S-217622 250 mg was administered on Day 2 to Day 5. Dexamethasone 1 mg was administered alone on Day –2, concomitantly with S-217622 on Day 5, and alone again on Day 9 and Day 14.
- Cohort M (once daily, multiple-dose administration, investigation of DDI of S-217622 with prednisolone):

  S-217622 (250-mg tablets) was administered once daily for 5 days in Japanese healthy adult male participants. A loading dose of S-217622 750 mg was administered only on Day 1. After that, S-217622 250 mg was administered on Day 2 to Day 5. Prednisolone 10 mg was administered alone on Day –2, concomitantly with S-217622 on Day 5, and alone again on Day 9 and Day 14.

For Cohort L and Cohort M, the study period consisted of a screening period (Day −28 to Day −3), a hospitalization period (Day −3 to Day 15), follow-up 1 (Day 18 [+2]), and follow-up 2 (Day 32 [−2, +7]).

Part 4 (FE)

Part 4 of this study was a single-center, randomized, open-label, 2-group 2-period crossover study in Japanese healthy adult participants.

- Cohort P1 (375 mg, single-dose administration, investigation of the effect of food):

  A single dose of three S-217622 125-mg tablets was administered in the fasted state in Period 1 and after breakfast (high-calorie, high-fat) in Period 2.
- Cohort P2 (375 mg, single-dose administration, investigation of the effect of food):

  A single dose of three S-217622 125-mg tablets was administered after breakfast (high-calorie, high-fat) in Period 1 and in the fasted state in Period 2.

Of the 14 eligible participants, 7 each were randomly assigned to Cohorts P1 and P2. For each cohort, the study period consisted of a screening period (Day −28 to Day −1), a hospitalization period of Period 1 (Day −1 to Day 8), follow-up 1 (Day 15 [±1]), a hospitalization period of Period 2 (Day 21 to Day 29), and follow-up 2 (Day 36 [±1]). An interval between the dosing of Period 1 (Day 1) and of Period 2 (Day 22) was 21 days or longer.

Part 5 (W-MAD)

Part 5 of this study was a single-center, randomized, double-blind, placebo-controlled study in White healthy adult participants, consisting of 2 cohorts (Q and R). Cohort R was initiated according to the procedures for progression to the next cohort, after confirming the safety and tolerability of S-217622 24 hours after the last intervention (Day 6) in Cohort Q and judging whether progression was possible.

- Cohort Q (once daily, multiple-dose administration):

  S-217622 (125-mg tablets) or placebo was administered once daily for 5 days in White healthy adult participants. A loading dose of S-217622 375 mg was administered on Day 1 only. After that, S-217622 125 mg was administered on Day 2 to Day 5.
- Cohort R (once daily, multiple-dose administration):

  S-217622 (250-mg tablets) or placebo was administered once daily for 5 days in White healthy adult participants. A loading dose of S-217622 750 mg was administered on Day 1 only. After that, S-217622 250 mg was administered on Day 2 to Day 5.

In each cohort of Part 5, 12 eligible participants were randomly assigned to the S-217622 group (8 participants) or the placebo group (4 participants). The study period of Cohorts Q and R consisted of a screening period (Day −28 to Day −1), a hospitalization period (Day −1 to Day 9), and follow-up (Day 13 [+2]).

Part 6 (elderly)

Part 6 of this study was a single-center, randomized, double-blind, placebo-controlled study in healthy elderly participants.

- Cohort S (once daily, multiple-dose administration):

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S-217622 (125-mg tablets) or placebo was administered once daily for 5 days in healthy elderly participants. A loading dose of S-217622 375 mg was administered only on Day 1. After that, S-217622 125 mg was administered on Day 2 to Day 5.

Maximum of 16 eligible participants were randomly assigned to the S-217622 group or the placebo group in a ratio of 2:1. The study period of Cohort S consisted of a screening period (Day −28 to Day −1), a hospitalization period (Day −1 to Day 9), and follow-up (Day 13 [+2]).

Part 7 (DDI of S-217622 [125-mg tablets] with midazolam)

Part 7 of this study was a single-center, single-arm, open-label study in Japanese healthy adult participants.

- Cohort T (once daily, multiple-dose administration, investigation of DDI of S-217622 [125-mg tablets] with midazolam):

  S-217622 (125-mg tablets) was administered once daily for 5 days in Japanese healthy adult participants. A loading dose of S-217622 375 mg was administered only on Day 1. After that, S-217622 125 mg was administered on Day 2 to Day 5. Midazolam syrup 1 mL was administered alone on Day –2, and concomitantly with t S-217622 on Day 5.

The study period of Cohort T consisted of a screening period (Day −28 to Day −3), a hospitalization period (Day −3 to Day 9), and follow-up (Day 13 [+2]).

Number of Participants (Planned and Analyzed):

Planned:

Part 1 (SAD)

Eight evaluable participants each (6 in the S-217622 group, 2 in the placebo group) in Cohorts A, B, D, E, and J and 10 evaluable participants (8 in the S-217622 group, 2 in the placebo group) in Cohort C were planned to be enrolled to achieve 50 participants (or 52 participants if Cohort K was to be conducted) in total.

Part 2 (MAD)

Eleven evaluable participants each (8 in the S-217622 group, 3 in the placebo group) in Cohorts F to H, N, and O were planned to be enrolled to achieve 55 participants in total.

Part 3 (DDI)

Fourteen evaluable participants in each Cohorts L and M were planned to be enrolled to achieve 28 participants in total.

Part 4 (FE)

Fourteen evaluable participants in Cohort P were planned to be enrolled.

Part 5 (W-MAD)

Twelve evaluable participants each (8 in the S-217622 group, 4 in the placebo group) in Cohorts Q and R were planned to be enrolled to achieve 24 participants in total.

Part 6 (elderly)

Up to 16 participants (10 or 11 in the S-217622 group, 4 or 5 in the placebo group) in Cohort S were planned to be enrolled to achieve 14 evaluable participants in total.

Part 7 (DDI of S-217622 [125-mg tablets] with midazolam)

Fourteen evaluable participants in Cohort T were planned to be enrolled.

Enrolled:

A total of 751 participants.

All Randomized:

Part 1 (SAD)

A total of 50 participants (Cohort K was not conducted).

Part 2 (MAD)

A total of 55 participants.

Part 3 (DDI)

A total of 28 participants.

Part 4 (FE)

A total of 14 participants.

Part 5 (W-MAD)

A total of 24 participants.

Part 6 (elderly)

A total of 16 participants (11 in the S-217622 group, 5 in the placebo group).

Part 7 (DDI of S-217622 [125-mg tablets] with midazolam)

A total of 14 participants.

Analyzed for PK:

PK concentration population and PK parameter population

Part 1 (SAD)

A total of 38 participants.

Part 2 (MAD)

A total of 40 participants.

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Part 3 (DDI)

A total of 28 participants.

Part 4 (FE)

A total of 14 participants.

Part 5 (W-MAD)

A total of 16 participants.

Part 6 (elderly)

A total of 11 participants.

Part 7 (DDI of S-217622 [125-mg tablets] with midazolam)

A total of 14 participants.

Analyzed for Safety:

All randomized participants were included in each part.

Diagnosis and Main Criteria for Inclusion:

1. Inclusion criteria

- Japanese healthy adult male participants (Cohorts A to G, J, L, and M), White healthy adult male participants (Cohort H), Japanese healthy adult female participants (Cohorts N and O), Japanese healthy adult participants (Cohorts P and T), or White healthy adult participants (Cohorts Q and R) who were 20 to 55 years of age inclusive, or healthy elderly participants (Cohort S) who were 65 years of age or older inclusive, at the time of signing the informed consent form (ICF).
- Body mass index (BMI) had to be within the range of ≥ 18.5 and ≤ 30.0 at screening. Weight had to be ≥ 40 kg for female participants.
- In Cohorts F and H, adjustment was made to allocate Japanese and White healthy adult male participants evenly with respect to the age and BMI (age, ±10 years; BMI, ±15%).

2. Exclusion criteria

- Participants who were not healthy, were not able to comply with the study requirements, had any condition requiring medication and/or other treatment, or were considered inappropriate to participate in the study.

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- For Cohorts G and T, participants who had acute angle-closure glaucoma or myasthenia gravis.
- For Cohorts L and M, participants who had cataract, glaucoma, or hypertension.

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

The following study drugs were orally administered as described in Methodology.

Part	Cohort	Study intervention	Packaging Lot No.	Expiration date
SAD/MAD	A to J	S-217622 suspension	[redacted]	[redacted]
	N	S-217622 tablet 125 mg	[redacted]	[redacted]
	O	S-217622 tablet 250 mg	[redacted]	[redacted]
DDI	L and M	S-217622 tablet 250 mg	[redacted]	[redacted]
FE	P	S-217622 tablet 125 mg	[redacted]	[redacted]
W-MAD	Q	S-217622 tablet 125 mg	[redacted]	[redacted]
	R	S-217622 tablet 250 mg	[redacted]	[redacted]
Elderly	S	S-217622 tablet 125 mg	[redacted]	[redacted]
DDI of S-217622 [125-mg tablets] with midazolam	T	S-217622 tablet 125 mg	[redacted]	[redacted]

Duration of Treatment:

Part 1 (SAD)

Cohorts A1, A2, B, D, E, and J; 1 day (Day 1) for the single dose of S-217622.

Cohorts C1 and C2; 2 days (Day 1 in Period 1 and Day 15 in Period 2) for the single doses of S-217622.

Part 2 (MAD)

Cohorts F, H, N, and O; 5 days (Days 1 to 5) for the multiple doses of S-217622 once daily.

Cohort G; 6 days (Days 1 to 6, concomitantly with midazolam on Day 6) for the multiple doses of S-217622 once daily.

Part 3 (DDI)

Cohorts L and M; 5 days (Days 1 to 5, concomitantly with dexamethasone or prednisolone on Day 5) for the multiple doses of S-217622 once daily.

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Part 4 (FE)

Cohorts P1 and P2; 2 days (Day 1 in Period 1 and Day 22 in Period 2) for the single doses of S-217622.

Part 5 (W-MAD)

Cohorts Q and R; 5 days (Days 1 to 5) for the multiple doses of S-217622 once daily.

Part 6 (elderly)

Cohort S; 5 days (Days 1 to 5) for the multiple doses of S-217622 once daily.

Part 7 (DDI of S-217622 [125-mg tablets] with midazolam)

Cohort T; 5 days (Days 1 to 5, concomitantly with midazolam on Day 5) for the multiple doses of S-217622 once daily.

Reference Therapy, Dose and Mode of Administration, Lot Number:

The following reference therapies were orally administered as described in Methodology.

Part	Cohort	Study intervention	Packaging Lot No.	Expiration date
SAD/MAD	A to J	Placebo suspension	[redacted]	[redacted]
	G	Midazolam syrup	[redacted]	[redacted]
	N	S-217622 tablet Placebo-B	[redacted]	[redacted]
	O	S-217622 tablet Placebo-D	[redacted]	[redacted]
DDI	L	Dexamethasone tablet	[redacted]	[redacted]
	M	Prednisolone tablet	[redacted]	[redacted]
W-MAD	Q	S-217622 tablet Placebo-B	[redacted]	[redacted]
	R	S-217622 tablet Placebo-D	[redacted]	[redacted]
Elderly	S	S-217622 tablet Placebo-B	[redacted]	[redacted]
DDI of S-217622 [125-mg tablets] with midazolam	T	Midazolam syrup	[redacted]	[redacted]

Criteria for Evaluation:

Safety Assessment:

Safety was assessed through physical examination, vital signs, 12-lead ECG, laboratory tests, and risk monitoring for suicidal ideation and suicide-related behavior using Columbia-Suicide Severity Rating Scale (C-SSRS). All AEs and serious AEs (SAEs) were collected from the date of signing of the ICF until completion of the follow-up.

PK Assessment:

Part 1 (SAD)

For PK parameters of S-217622, C_{max}, T_{max}, $AUC_{0\text{-}last}$, area under the plasma concentration-time curve from time zero to 144 hours postdose ($AUC_{0\text{-}144}$), $AUC_{0\text{-}inf}$, $t_{1/2,z}$, λ_z, MRT, CL/F, V_z/F, fraction of dose excreted in urine from time 0 to 144 hours ($Feu_{0\text{-}144}$) and CL_R (except for Cohort J for $Feu_{0\text{-}144}$ and CL_R) were determined.

Part 2 (MAD)

For PK parameters of S-217622 in Cohorts F to H, C_{max}, T_{max}, and $AUC_{0\text{-}\tau}$ were determined after the first and 5th day of multiple-dose administration (Days 1 and 5).

For PK parameters of midazolam in Cohort G, C_{max}, T_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, $t_{1/2,z}$, λ_z, MRT, CL/F and V_z/F were determined after each administration of midazolam (Days −2 and 6).

For PK parameters of S-217622 in Cohorts N and O, C_{max}, T_{max}, $AUC_{0\text{-}\tau}$, and plasma concentration of S-217622 were determined 24 hours postdose (C_{24}) after the first day of multiple-dose administration (Day 1) and C_{max}, T_{max}, $AUC_{0\text{-}\tau}$, $t_{1/2,z}$, λ_z, and C_{24} were determined after the 5th day of multiple-dose administration (Day 5).

Part 3 (DDI)

For PK parameters of S.217622, C_{max}, T_{max}, and $AUC_{0\text{-}\tau}$ were determined after the first day of multiple-dose administration (Day 1), and C_{max}, T_{max}, $AUC_{0\text{-}\tau}$, $t_{1/2,z}$, and λ_z were determined for the 5th day of multiple-dose administration (Day 5).

For PK parameters of dexamethasone and prednisolone in Part 3, C_{max}, T_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, $t_{1/2,z}$, λ_z, MRT, CL/F, and V_z/F were determined after each administration of dexamethasone and prednisolone (Days −2, 5, 9, and 14).

Part 4 (FE)

For PK parameters of S-217622, C_{max}, T_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, $t_{1/2,z}$, λ_z, MRT, CL/F, and V_z/F were determined.

Part 5 (W-MAD)

For PK parameters of S-217622, C_{max}, T_{max}, $AUC_{0\text{-}\tau}$, and C_{24} were determined after the first day of multiple-dose administration (Day 1), and C_{max}, T_{max}, $AUC_{0\text{-}\tau}$, $t_{1/2,z}$, λ_z, and C_{24} were determined for the 5th day of multiple-dose administration (Day 5).

Part 6 (elderly)

For PK parameters of S-217622, C_{max}, T_{max}, $AUC_{0\text{-}\tau}$, and C_{24} were determined after the first day of multiple-dose administration (Day 1), and C_{max}, T_{max}, $AUC_{0\text{-}\tau}$, $t_{1/2,z}$, λ_z, and C_{24} were determined for the 5th day of multiple-dose administration (Day 5).

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Part 7 (DDI of S-217622 [125-mg tablets] with midazolam)

For PK parameters of S-217622, C_{max}, T_{max}, and $AUC_{0-\tau}$ were determined after the first and the 5th day of multiple-dose administration (Days 1 and 5).

For PK parameters of midazolam, 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 after each administration of midazolam (Days −2 and 5).

Statistical Methods:

Safety Analyses:

AEs were coded and classified by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0. The number and proportion of participants who experienced treatment-emergent adverse events (TEAE), TEAEs with an outcome of death, serious TEAEs other than deaths, and TEAE leading to discontinuation of the study intervention were summarized by cohort and study intervention and by food condition for each time point. The number and proportion of participants who experienced TEAEs in each category of severity and outcome were summarized by SOC and PT for each cohort and each study intervention. Treatment-related TEAEs were summarized in the same manner as TEAEs.

For laboratory test values and vital signs, summary statistics of measurement values and each change from baseline were calculated by cohort and study intervention and by food condition for each time point. For qualitative parameters of urinalysis, shift tables using baseline and each measurement value were created by cohort and study intervention and by food condition for each time point.

For 12-lead ECG, findings were summarized by cohort and study intervention and by food condition for each time point using shift tables. Summary statistics of measurement values and each change from baseline in ECG parameters were calculated by cohort and study intervention and by food condition for each time point.

For C-SSRS, the number and proportion of participants who experienced suicide attempt or suicidal ideation were summarized by cohort and study intervention and by food condition.

PK Analyses:

Plasma and Urine Concentrations

Plasma concentration data of S-217622, midazolam, dexamethasone, and prednisolone were listed and summarized by treatment and nominal sampling time.

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The summary statistics and plasma concentration profiles of S-217622, midazolam, dexamethasone, and prednisolone were presented appropriately. Urine volume and urine concentration data of S-217622 were listed.

PK Parameters

The PK parameters were calculated for each participant by treatment and day, based on the plasma concentration data of S-217622, midazolam, dexamethasone, and prednisolone, urine concentration data of S-217622, and urine volume according to the non-compartmental method. For PK analyses, actual sampling time was used in Parts 1 (SAD), 2 (MAD), 3 (DDI), 5 (W-MAD), and 6 (elderly), and nominal sampling time was used in Parts 4 (FE) and 7 (DDI of S-217622 [125-mg tablets] with midazolam).

Statistical Methods for PK Analyses

For Part 1 (SAD), dose proportionality, dose independency, and effect of food on the PK of S-217622 suspension were assessed using a power model or an analysis of variance (ANOVA).

For Part 2 (MAD), dose proportionality, and comparison of exposure between the initial and last doses in Japanese healthy adult male participants, comparison of PK between Japanese and White healthy adult male participants, effect of S-217622 suspension on the PK of midazolam, and dose proportionality, dose independency, and comparison of exposure between the initial and last doses in Japanese healthy adult female participants were assessed using ANOVA.

For Part 3 (DDI), the effect of S-217622 on the PK of dexamethasone and prednisolone was assessed using ANOVA.

For Part 4 (FE), the effect of food on the PK of S-217622 tablets was assessed using ANOVA.

For Part 5 (W-MAD), dose proportionality, dose independency, and comparison of exposure between the initial and last doses in White healthy adult participants were assessed using ANOVA.

For Part 6 (elderly), comparison of exposure between the initial and last doses in healthy elderly participants were assessed using ANOVA.

For Part 7 (DDI of S-217622 [125-mg tablets] with midazolam), assessment of the effect of S-217622 tablets on the PK of midazolam, and comparison of exposure of S-217622 between the initial and last doses were made using ANOVA.

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Summary of Results:

Safety:

No deaths, other serious TEAEs, suicidal ideations, or suicide attempts were reported during this study. The safety observations in each part were summarized below.

Part 1 (SAD)

- In Japanese healthy adult male participants in the fasted state, 2 TEAEs were reported in 2 of 6 participants (33.3%) in the S-217622 70 mg group, 6 TEAEs were reported in 6 of 6 participants (100.0%) in the S-217622 1000 mg group, and 11 TEAEs were reported in 6 of 6 participants (100.0%) in the S-217622 2000 mg group. Of these, all 12 events of high density lipoprotein decreased (6 events each in the S-217622 1000 mg and 2000 mg groups) and 1 event each of headache, nausea, vomiting, faeces soft, and chills in the S-217622 2000 mg group were considered related to S-217622. Other TEAEs were considered not related to S-217622. No TEAEs were reported in the S-217622 20, 250, or 500 mg groups or placebo group.
- No TEAEs were reported in the fed state.
- All TEAEs were categorized as mild.
- No clinically significant findings or trends related to S-217622 were identified in laboratory parameters, vital signs, 12-lead ECG, C-SSRS, or other safety observations, except for the changes reported as TEAEs.
- No apparent trends related to S-217622 were identified over time in laboratory parameters, vital signs, 12-lead ECG, or other safety observations, except for transient changes in lipid parameters including decrease in high density lipoprotein cholesterol (HDL-C) and increase in triglycerides in a dose dependent manner.

Part 2 (MAD)

- In Japanese healthy adult male participants, 12 TEAEs were reported in 7 of 8 participants (87.5%) in the S-217622 125 mg group (ie, the group who received S-217622 at the loading dose of 375 mg on Day 1 and at the maintenance dose of 125 mg on Days 2 to 5). Of these, 7 events of high density lipoprotein decreased reported in 7 of 8 participants (87.5%) were considered related to S-217622. Other TEAEs were considered not related to S-217622. No TEAEs were reported in the placebo group.
- In Japanese healthy adult male participants, 33 TEAEs were reported in 8 of 8 participants (100.0%) in the S-217622 250 mg + midazolam group (ie, the

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group who received S-217622 at the loading dose of 750 mg on Day 1 and at the maintenance dose of 250 mg on Days 2 to 6, with midazolam alone on Day −2 and concurrently with midazolam at 2mg on Day 6), and 1 TEAE was reported in 1 of 3 participants (33.3%) in the placebo + midazolam group. Of these, 25 TEAEs were considered related to the study interventions; 7 events of high density lipoprotein decreased, 6 events of headache, 2 events of blood triglycerides increased, and 1 event each of nausea, vomiting, rash, feeling hot, pyrexia, and C-reactive protein increased were considered related to S-217622, and 4 events of somnolence were considered related to midazolam. Other TEAEs were considered not related to the study interventions. Only the TEAE occurred in the placebo + midazolam group was diarrhoea, which was reported in 1 of 3 participants (33.3%) and considered not related to the study interventions.

- In White healthy adult male participants, 19 TEAEs were reported in 8 of 8 participants (100.0%) in the S-217622 125 mg group. Of these, 9 TEAEs were considered related to S-217622; 7 events of high density lipoprotein decreased and 2 events of headache. Other TEAEs were considered not related to S-217622. Only the TEAE occurred in the placebo group was diarrhoea, which was reported in 1 of 3 participants (33.3%) and considered not related to the study intervention.
- In Japanese healthy adult female participants, 11 TEAEs were reported in 5 of 8 participants (62.5%) in the S-217622 125 mg group, 11 TEAEs were reported in 8 of 8 participants (100.0%) in the S-217622 250 mg group (ie, the group who received S-217622 at the loading dose of 750 mg on Day 1 and at the maintenance dose of 250 mg on Days 2 to 5), and 3 TEAEs were reported in 3 of 6 participants (50.0%) in the pooled placebo group. Of these, all TEAEs reported in the S-217622 groups and 1 TEAE reported in the pooled placebo group were considered related to the study intervention.
- In Japanese healthy adult male participants, 1 event each of moderate nausea and rash occurred in the S-217622 250 mg + midazolam group. These moderate TEAEs were considered related to S-217622 and resolved following medical interventions. All other TEAEs reported in Part 2 were categorized as mild.
- In Japanese healthy adult male participants, 1 event each of moderate rash, mild headache, and mild feeling hot were reported as TEAEs leading to discontinuation of study intervention, all of which occurred in 1 participant in

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the S-217622 250 mg + midazolam group and were considered related to S-217622. The rash was resolved after 9 days from the onset with medical interventions, and the headache and feeling hot were resolved without medical interventions after 1 day and 4 days from the onset, respectively.

- No clinically significant findings or trends related to S-217622 were identified in laboratory parameters, vital signs, 12-lead ECG, C-SSRS, or other safety observations, except for the changes reported as TEAEs.
- No apparent trends related to S-217622 were identified over time in laboratory parameters, vital signs, 12-lead ECG, or other safety observations, except for a transient decrease in HDL-C and a transient increase in triglycerides in a dose dependent manner.

Part 3 (DDI)

- In Japanese healthy adult male participants, 13 TEAEs were reported in 9 of 14 participants (64.3%) in the S-217622 250 mg + dexamethasone group (ie, the group who received S-217622 at the loading dose of 750 mg on Day 1 and at the maintenance dose of 250 mg on Days 2 to 5, with dexamethasone alone on Day −2, concomitantly with dexamethasone at 1mg on Day 5, and with dexamethasone alone again on Day 9 and Day 14), and 14 TEAEs were reported in 14 of 14 participants (100.0%) in the S-217622 250 mg + prednisolone group (ie, the group who received S-217622 at the loading dose of 750 mg on Day 1 and at the maintenance dose of 250 mg on Days 2 to 5, with prednisolone alone on Day −2, concomitantly with prednisolone at 10 mg on Day 5, and with prednisolone alone again on Day 9 and Day 14). Except for 1 event each of atrioventricular block and blood triglycerides increased reported in the S-217622 250 mg + dexamethasone group, which were considered not related to the study interventions, all other TEAEs were considered related to S-217622 but not to dexamethasone nor prednisolone.
- Coadministration of S-217622 with dexamethasone or prednisolone did not increase the frequency of TEAEs compare to dexamethasone or prednisolone alone.
- All TEAEs were categorized as mild.
- No clinically significant findings or trends related to S-217622 were identified in laboratory parameters, vital signs, 12-lead ECG, or other safety observations, except for the changes reported as TEAEs.

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- No apparent trends related to S-217622 were identified over time in laboratory parameters, vital signs, 12-lead ECG, or other safety observations, except for transient changes in lipid parameters including decrease in HDL-C and increase in triglycerides.

Part 4 (FE)

- In Japanese healthy adult participants, 5 TEAEs were reported in 5 of 13 participants (38.5%) who received S-217622 375 mg in the fasted state and 11 TEAEs were reported in 8 of 14 participants (57.1%) who received S-217622 375 mg in the fed state. Of these, 11 events of high density lipoprotein decreased (4 events in the fasted state and 7 events in the fed state), 3 events of headache (1 event in the fasted state and 2 events in the fed state), and 1 event of nausea (in the fed state) were considered related to S-217622. The COVID-19 reported in the fed state was considered not related to S-217622.
- All TEAEs were categorized as mild.
- In the fed state, 1 event of mild COVID-19 was reported as a TEAE leading to discontinuation of study intervention. The participant received study intervention in the fed state on Day 1 and discontinued the study prior to receiving the study intervention in the fasted state. This event was considered not related to S-217622 and resolved without medical interventions after 9 days from the onset.
- No clinically significant findings or trends related to S-217622 were identified in laboratory parameters, vital signs, 12-lead ECG, or other safety observations, except for the changes reported as TEAEs.
- No apparent trends related to S-217622 were identified over time in laboratory parameters, vital signs, 12-lead ECG, or other safety observations, except for transient changes in lipid parameters including decrease in HDL-C and increase in triglycerides.

Part 5 (W-MAD)

- In White healthy adult participants, 8 TEAEs were reported in 7 of 8 participants (87.5%) in the S-217622 125 mg group (ie, the group who received S-217622 at the loading dose of 375 mg on Day 1 and at the maintenance dose of 125 mg on Days 2 to 5), 17 TEAEs were reported in 7 of 8 participants (87.5%) in the S-217622 250 mg group (ie, the group who received S-217622 at the loading dose of 750 mg on Day 1 and at the maintenance dose of 250 mg on Days 2 to 5), and 5 TEAEs were reported in 3

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of 8 participants (37.5%) in the pooled placebo group. Of these, 12 events of high density lipoprotein decreased (5 events in the S-217622 125 mg group and 7 events in the S-217622 250 mg group), and 3 events of headache and 1 event of blood triglycerides increased in the S-217622 250 mg group were considered related to S-217622. Other TEAEs were considered not related to S-217622. No treatment-related TEAEs were reported in the pooled placebo group.

- All TEAEs were categorized as mild.
- No clinically significant findings or trends related to S-217622 were identified in laboratory parameters, vital signs, 12-lead ECG, or other safety observations, except for the changes reported as TEAEs.
- No apparent trends related to S-217622 were identified over time in laboratory parameters, vital signs, 12-lead ECG, or other safety observations, except for transient changes in lipid parameters including decrease in HDL-C and increase in triglycerides in a dose dependent manner.

Part 6 (elderly)

- In healthy elderly participants, 15 TEAEs were reported in 6 of 11 participants (54.5%) in the S-217622 125 mg group (ie, the group who received S-217622 at the loading dose of 375 mg on Day 1 and at the maintenance dose of 125 mg on Days 2 to 5) and 4 TEAEs were reported in 2 of 5 participants (40.0%) in the placebo group. Of these, 5 events each of high density lipoprotein decreased and nausea, 3 events of headache, and 1 event of C-reactive protein increased were considered related to S-217622. One event of blood creatine phosphokinase increased reported in the S-217622 125 mg group was considered not related to S-217622. All TEAEs reported in the placebo group were considered related to the study intervention.
- Except for 1 event of moderate constipation reported in the placebo group, all TEAEs were categorized as mild.
- No clinically significant findings or trends related to S-217622 were identified in laboratory parameters, vital signs, 12-lead ECG, or other safety observations, except for the changes reported as TEAEs.
- No apparent trends related to S-217622 were identified over time in laboratory parameters, vital signs, 12-lead ECG, or other safety observations, except for transient changes in lipid parameters including decrease in HDL-C and increase in triglycerides.

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Part 7 (DDI of S-217622 [125-mg tablets] with midazolam)

- In Japanese healthy adult participants, 21 TEAEs were reported in 11 of 14 participants (78.6%) in the S-217622 125 mg + midazolam group (ie, the group who received S-217622 at the loading dose of 375 mg on Day 1 and at the maintenance dose of 125 mg on Days 2 to 5, with midazolam alone on Day −2 and concurrently with midazolam at 2mg on Day 5). Of these, 20 TEAEs were considered related to the study interventions; 8 events of high density lipoprotein decreased, 2 events of somnolence, and 1 event of blood triglycerides increased were considered related to S-217622; and 8 events of somnolence and 1 event of diarrhoea were considered related to midazolam. One event of arthropod sting was considered not related to the study interventions.
- Of the 10 events of somnolence that were reported in Cohort T, 8 were reported on Day 5 (after coadministration) and considered related to midazolam and 2 were reported on Day 3 and Day 4 (before coadministration) and considered related to S-217622.
- All TEAEs were categorized as mild.
- No clinically significant findings or trends related to S-217622 were identified in laboratory parameters, vital signs, 12-lead ECG, or other safety observations, except for the changes reported as TEAEs.
- No apparent trends related to S-217622 were identified over time in laboratory parameters, vital signs, 12-lead ECG, or other safety observations, except for transient changes in lipid parameters including decrease in HDL-C and increase in triglycerides.

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PK:

Part 1 (SAD)

- Following the single-dose administration of the suspension formulation of S-217622 to Japanese healthy adult male participants at 20 to 2000 mg in the fasted state, the median T_{max} of S-217622 ranged from 1.50 to 4.00 hours.
- The geometric mean $t_{1/2,z}$ of S-217622 ranged from 42.2 to 48.1 hours across the dose groups in the fasted state.
- The C_{max}, $AUC_{0\text{-}144}$, and $AUC_{0\text{-}inf}$ of S-217622 in the dose range of 20 to 500 mg and at a dose of 2000 mg exhibited a modest to moderate inter-individual variability (coefficient of variation for geometric mean [CV% Geometric Mean] ranged from 8.5% to 24.3%). At a dose of 1000 mg, the inter-individual variability of the PK parameters was higher than those at other doses; CV% Geometric Mean of C_{max}, $AUC_{0\text{-}144}$, and $AUC_{0\text{-}inf}$ were 39.1%, 34.4%, and 35.5%, respectively.
- The C_{max} and area under the plasma concentration-time curve (AUC) of S-217622 increased in an almost dose-proportional manner across the dose range of 20 to 2000 mg in the fasted state. The increase ratio of geometric mean of C_{max} from 1000 mg to 2000 mg was less than the dose ratio.
- In the dose range of 20 to 2000 mg, there were no clear relationship between the dose and $t_{1/2,z}$, MRT, CL/F, or V_z/F of S-217622 in the fasted state. In the dose range of 20 to 1000 mg, the CL_R of S-217622 tended to increase as the dose increased, however, the difference of CL_R across the dose range of 20 to 1000 mg was considered to have minimal effect on the PK of S-217622.
- The geometric mean of $F_{eu0\text{-}144}$ of S-217622 ranged from 12.9% to 21.8% across the dose range of 20 to 1000 mg.
- Following the single-dose administration of S-217622 to Japanese healthy adult male participants at 250 mg in the fasted and fed states, concomitant food intake reduced the C_{max} of S-217622 by 15% and delayed the T_{max} of S-217622 from 2.50 hours in the fasted state to 8.00 hours in the fed state, but did not affect the $AUC_{0\text{-}last}$ or $AUC_{0\text{-}inf}$ of S-217622. These results showed that there was no clinically meaningful difference in the exposures to S-217622 between the fasted and fed states.

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Part 2 (MAD)

- Following the multiple-dose administration of the suspension formulation of S-217622 to Japanese healthy adult male participants at 375/125 mg for 5 days (ie, the loading dose of 375 mg on Day 1 and the maintenance dose of 125 mg on Days 2 to 5) in Cohort F and at 750/250 mg for 6 days (ie, the loading dose of 750 mg on Day 1 and the maintenance dose of 250 mg on Days 2 to 6, with midazolam alone on day −2 and concurrently with midazolam at 2 mg on Day 6) in Cohort G, the geometric least squares mean ratios of the C_{max} and $AUC_{0-\tau}$ of S-217622 (Cohort G/Cohort F) were 1.52 and 1.69 on Day 1, and 2.18 and 2.24 on Day 5, respectively.
- Following the multiple-dose administration of the suspension formulation of S-217622 to Japanese healthy adult male participants at 375/125 mg for 5 days and at 750/250 mg for 6 days, and to White healthy adult male participants at 375/125 mg for 5 days, the C_{max} and $AUC_{0-\tau}$ of S-217622 slightly increased on Day 5 than on Day 1.
- Following the multiple-dose administration of the suspension formulation of S-217622 to Japanese and White healthy adult male participants at 375/125 mg for 5 days, the geometric least squares mean ratios of the C_{max} and $AUC_{0-\tau}$ of S-217622 (White/Japanese) were 0.77 and 0.72 on Day 1, and 0.87 and 0.86 on Day 5, respectively.
- Following the multiple-dose administration of the suspension formulation of S-217622 at 750/250 mg once daily for 6 days, with midazolam alone on Day −2 and concurrently with midazolam at 2mg on Day 6, to Japanese healthy adult male participants, the C_{max}, AUC_{0-last}, and AUC_{0-inf} of midazolam coadministered with S-217622 were increased by 2.78-, 7.23-, and 8.80-fold, respectively, when compared with those following the single-dose administration of midazolam alone. These results showed that S-217622 is a strong CYP3A inhibitor.
- Following the multiple-dose administration of the tablet formulation of S-217622 to Japanese healthy female participants at 375/125 mg for 5 days in Cohort N and at 750/250 mg for 5 days in Cohort O, the median T_{max} of S-217622 ranged from 2.00 to 3.50 hours between the dose groups on Days 1 and 5.
- The geometric means of $t_{1/2,z}$ of S-217622 after the last dose on Day 5 were 51.4 hours in Cohort N and 48.7 hours in Cohort O.

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- The C_{max} and $AUC_{0-\tau}$ of S-217622 exhibited a modest to moderate inter-individual variability (CV% Geometric Mean ranged from 12.0% to 21.0%) between the dose groups of Cohorts N and O.
- The C_{max} and $AUC_{0-\tau}$ of S-217622 increased in a dose-proportional manner between the dose groups of Cohorts N and O on Days 1 and 5.
- There was no clear relationship between the dose and $t_{1/2,z}$ of S-217622 in Cohorts N and O.
- The C_{max} and $AUC_{0-\tau}$ of S-217622 on Day 5 were 1.25- and 1.39-fold of those on Day 1, respectively, in Cohort N. Those on Day 5 were 1.40- and 1.58-fold of those on Day 1, respectively, in Cohort O.

Part 3 (DDI)

- Following the multiple-dose administration of the tablet formulation of S-217622 at 750/250 mg once daily for 5 days, with dexamethasone alone on Day −2, concurrently with dexamethasone at 1 mg on Day 5, and with dexamethasone alone again on Day 9 and Day 14, to Japanese healthy adult male participants in Cohort L, the C_{max}, AUC_{0-last}, and AUC_{0-inf} of dexamethasone coadministered with S-217622 on Day 5 increased by 1.47-, 3.18-, and 3.47-fold, respectively, when compared with those following the single-dose administration of dexamethasone alone on Day −2. The C_{max}, AUC_{0-last}, and AUC_{0-inf} of dexamethasone following the single-dose administration of dexamethasone on Day 9 (5th day after the last S-217622 dose) were 1.24-, 2.45-, and 2.38-fold, respectively, and those on Day 14 (10th day after the last S-217622 dose) were 1.17-, 1.56-, and 1.58-fold, respectively, when compared with those following the single-dose administration of dexamethasone alone on Day −2. These results suggested that the effect of S-217622 on the PK of dexamethasone was diminished over time, after the last administration of S-217622.
- Following the multiple-dose administration of the tablet formulation of S-217622 at 750/250 mg once daily for 5 days, with prednisolone alone on Day −2, concurrently with prednisolone at 10 mg on Day 5, and with prednisolone alone again on Day 9 and Day 14, to Japanese healthy adult male participants in Cohort M, the AUC_{0-last} and AUC_{0-inf} of prednisolone coadministered with S-217622 on Day 5 increased by 1.24- and 1.25-fold, respectively, when compared with those following the single-dose administration of prednisolone alone on Day −2. The 90% confidence intervals (CIs) of geometric least squares mean ratios of the C_{max} on Day 5 and those of

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the C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ on Day 9 (5th day after the last S-217622 dose) and Day 14 (10th day after the last S-217622 dose) were contained within 0.8000 and 1.2500. These results suggested that there was no meaningful effect of S-217622 on the PK of prednisolone.

- Following the multiple-dose administration of the tablet formulation of S-217622 to Japanese healthy adult male participants at 750/250 mg for 5 days in Cohorts L and M, the medians of T_{max} of S-217622 were 2.50 and 3.00 hours on Day 1, respectively, and 4.00 hours on Day 5 in both cohorts. The geometric means of C_{max} of S-217622 in Cohort L were 32.4 µg/mL on Day 1 and 43.9 µg/mL on Day 5 and those in Cohort M were 33.1 µg/mL on Day 1 and 52.3 µg/mL on Day 5. The geometric means of $AUC_{0\text{-}\tau}$ of S-217622 in Cohort L were 545.2 µg·hr/mL on Day 1 and 852.8 µg·hr/mL on Day 5 and those in Cohort M were 553.7 µg·hr/mL on Day 1 and 997.3 µg·hr/mL on Day 5. The geometric means of $t_{1/2,z}$ of S-217622 after the last dose on Day 5 in Cohorts L and M were 46.7 and 55.9 hours, respectively.

Part 4 (FE)

- Following the single-dose administration of the tablet formulation of S-217622 to Japanese healthy adult participants at 375 mg in the fasted and fed states, the food intake increased the AUC of S-217622 by approximately 25%, delayed the T_{max} of S-217622 from 2.50 hours in the fasted state to 6.00 hours in the fed state, but did not affect the C_{max} of S-217622. These results showed that there was no clinically meaningful difference in the exposures to S-217622 between the fasted and fed states.

Part 5 (W-MAD)

- Following the multiple-dose administration of the tablet formulation of S-217622 to White healthy adult participants at 375/125 mg for 5 days in Cohort Q and at 750/250 mg for 5 days in Cohort R, the median T_{max} of S-217622 ranged from 2.25 to 3.25 hours between the dose groups on Days 1 and 5.
- The geometric means of $t_{1/2,z}$ of S-217622 after the last dose on Day 5 were 57.6 hours in Cohort Q and 53.2 hours in Cohort R.
- The C_{max} and $AUC_{0\text{-}\tau}$ of S-217622 exhibited a modest to moderate inter-individual variability (CV% Geometric Mean ranged from 13.4% to 21.5%) between the dose groups.

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- The C_{max} and $AUC_{0-\tau}$ of S-217622 increased in a less than dose-proportional manner between the dose groups on Days 1 and 5. The geometric least squares mean ratios of C_{max} and $AUC_{0-\tau}$ were less than the dose ratio.
- There was no clear relationship between the dose and $t_{1/2,z}$ of S-217622.
- The C_{max} and $AUC_{0-\tau}$ of S-217622 on Day 5 were 1.26- and 1.46-fold of those on Day 1, respectively, in Cohort Q. Those on Day 5 were 1.45- and 1.61-fold of those on Day 1, respectively, in Cohort R.

Part 6 (elderly)

- Following the multiple-dose administration of the tablet formulation of S-217622 to healthy elderly participants at 375/125 mg for 5 days, the medians of T_{max} of S-217622 were 2.00 hours on Day 1 and 3.00 hours on Day 5.
- The geometric means of C_{max} of S-217622 were 19.7 µg/mL on Day 1 and 23.8 µg/mL on Day 5. The geometric means of $AUC_{0-\tau}$ of S-217622 were 319.2 µg·hr/mL on Day 1 and 446.1 µg·hr/mL on Day 5.
- The geometric means of $t_{1/2,z}$ of S-217622 after the last dose on Day 5 were 58.9 hours.
- The C_{max} and $AUC_{0-\tau}$ of S-217622 exhibited a modest to moderate inter-individual variability (CV% Geometric Mean ranged from 17.1% to 24.0%).
- The C_{max} and $AUC_{0-\tau}$ of S-217622 on Day 5 were 1.21- and 1.40-fold of those on Day 1, respectively.

Part 7 (DDI of S-217622 [125-mg tablets] with midazolam)

- Following the multiple-dose administration of the tablet formulation of S-217622 to Japanese healthy adult participants at 375/125 mg for 5 days, the medians of T_{max} of S-217622 were 4.00 hours on Day 1 and 3.00 hours on Day 5.
- The geometric means of C_{max} of S-217622 were 18.1 µg/mL on Day 1 and 21.9 µg/mL on Day 5. The geometric means of $AUC_{0-\tau}$ of S-217622 were 306.3 µg·hr/mL on Day 1 and 424.5 µg·hr/mL on Day 5.
- The C_{max} and $AUC_{0-\tau}$ of S-217622 on Day 5 were 1.21- and 1.39-fold of those on Day 1, respectively.
- Following the multiple-dose administration of the tablet formulation of S-217622 at 375/125 mg once daily for 5 days, with midazolam alone on Day −2 and concurrently with midazolam at 2 mg on Day 5, to Japanese healthy adult participants, the C_{max}, AUC_{0-last}, and AUC_{0-inf} of midazolam

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increased by 2.80-, 6.90-, and 6.77-fold, respectively, when compared with those following the single-dose administration of midazolam alone. These results showed that S-217622 is a strong CYP3A inhibitor.

CONCLUSIONS

Safety Conclusions:

Overall, S-217622 was safe and well tolerated in the following:

- when single-dose administration of S-217622 suspension up to 2000 mg to Japanese healthy adult male participants
- when multiple-dose administration of S-217622 suspension at 375/125 mg for 5 days to Japanese and White healthy adult male participants (ie, a loading dose of 375 mg on Day 1 and a maintenance dose of 125 mg on Days 2 to 5)
- when multiple-dose administration of S-217622 suspension at 750/250 mg for 6 days with midazolam to Japanese healthy adult male participants (ie, a loading dose of 750 mg on Day 1 and a maintenance dose of 250 mg on Days 2 to 6, with midazolam alone on Day −2 and concurrently with midazolam at 2 mg on Day 6)
- when multiple-dose administration of S-217622 tablet at 750/250 mg for 5 days with dexamethasone or prednisolone to Japanese healthy adult male participants (ie, a loading dose of 750 mg on Day 1 and a maintenance dose of 250 mg on Days 2 to 5, with dexamethasone or prednisolone alone on Day −2, concurrently with dexamethasone at 1 mg or prednisolone at 10 mg on Day 5, and with dexamethasone or prednisolone alone again on Day 9 and Day 14)
- when multiple-dose administration of S-217622 tablet at 375/125 mg or 750/250 mg for 5 days to Japanese healthy adult female participants and White healthy adult participants (ie, a loading dose of 375 mg or 750 mg on Day 1 and a maintenance dose of 125 mg or 250 mg on Days 2 to 5)
- when multiple-dose administration of of S-217622 tablet at 375/125 mg for 5 days to healthy elderly participants (ie, a loading dose of 375 mg on Day 1 and a maintenance dose of 125 mg on Days 2 to 5)
- when multiple-dose administration of S-217622 tablet at 375/125 mg for 5 days with midazolam to Japanese healthy adult participants (ie, a loading dose of 375 mg on Day 1 and a maintenance dose of 125 mg on Days 2 to 5,

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with midazolam alone on Day −2 and concurrently with midazolam at 2 mg on Day 5)

PK Conclusions:

The exposures (C_{max} and AUC) to S-217622 increased in an almost dose-proportional manner following the single-dose administration of the suspension formulation of S-217622 to Japanese healthy adult male participants at 20 to 2000 mg in the fasted state, and following the multiple-dose administration of the suspension and tablet formulations of S-217622 to Japanese healthy adult participants at 375/125 mg and 750/250 mg for 5 days in the fasted state.

Part 1 (SAD)

Following the single-dose administration of the suspension formulation of S-217622 to Japanese healthy adult male participants at 250 mg, no clinically meaningful difference in exposures were observed between the fasted and fed states.

Part 2 (MAD)

Following the multiple-dose administration of the suspension formulation of S-217622 to Japanese and White healthy adult male participants at 375/125 mg for 5 days, the exposure to S-217622 was slightly lower in White healthy adult male participants than in Japanese healthy adult male participants.

Following the multiple-dose administration of the suspension formulation of S-217622 at 750/250 mg once daily for 6 days, with midazolam alone on Day −2 and concurrently with midazolam at 2 mg on Day 6, to Japanese healthy adult male participants, the $AUC_{0\text{-}inf}$ of midazolam was increased by 8.80-fold compared with that following the single-dose administration of midazolam alone. The result showed that S-217622 is a strong CYP3A inhibitor.

Part 3 (DDI)

Following the multiple-dose administration of the tablet formulation of S-217622 at 750/250 mg once daily for 5 days, with dexamethasone alone on Day −2, concurrently with dexamethasone at 1 mg on Day 5, and with dexamethasone alone again on Day 9 and Day 14, to Japanese healthy adult male participants, the $AUC_{0\text{-}inf}$ of dexamethasone coadministered with S-217622 on Day 5 increased 3.47-fold when compared with that following the single-dose administration of dexamethasone alone on Day −2. The $AUC_{0\text{-}inf}$ of dexamethasone following the single-dose administration of dexamethasone on Day 9 (5th day after the last S-217622 dose) was 2.38-fold and

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that on Day 14 (10th day after the last S-217622 dose) was 1.58-fold, when compared with that following the single-dose administration of dexamethasone alone on Day −2. These results suggested that the effect of S-217622 on the PK of dexamethasone was diminished over time, after the last administration of S-217622.

Following the multiple-dose administration of the tablet formulation of S-217622 at 750/250 mg once daily for 5 days, with prednisolone alone on Day −2, concurrently with prednisolone at 10 mg on Day 5, and with prednisolone alone again on Day 9 and Day 14, to Japanese healthy adult male participants, the $AUC_{0\text{-inf}}$ of prednisolone coadministered with S-217622 on Day 5 increased 1.25-fold, when compared with that following the single-dose administration of prednisolone alone on Day −2. The 90% CIs of geometric least squares mean ratios of the C_{max} on Day 5 and those of the C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ on Day 9 (5th day after the last S-217622 dose) and Day 14 (10th day after the last S-217622 dose) were contained within the range of 0.8000 and 1.2500. These results suggested that there was no meaningful effect of S-217622 on the PK of prednisolone.

Part 4 (FE)

Following single-dose administration of the tablet formulation of S-217622 to Japanese healthy adult participants at 375 mg , no clinically meaningful difference in exposures were observed between the fasted and fed states.

Part 5 (W-MAD)

Following the multiple-dose administration of the tablet formulation of S-217622 to White healthy adult participants at 375/125 mg for 5 days and at 750/250 mg for 5 days in the fasted state, the exposures (C_{max} and AUC) to S-217622 increased in a less than dose-proportional manner.

Part 6 (elderly)

Following the multiple-dose administration of the tablet formulation of S-217622 to healthy elderly participants at 375/125 mg for 5 days in the fasted state, the medians of T_{max} of S-217622 were 2.00 hours on Day 1 and 3.00 hours on Day 5. The C_{max} and $AUC_{0\text{-}\tau}$ of S-217622 on Day 5 were 1.21- and 1.40-fold of those on Day 1, respectively. The geometric means of $t_{1/2,z}$ of S-217622 after the last dose on Day 5 were 58.9 hours.

Part 7 (DDI of S-217622 [125-mg tablets] with midazolam)

Following the multiple-dose administration of the tablet formulation of S-217622 at 375/125 mg once daily for 5 days, with midazolam alone on Day −2 and concurrently with midazolam at 2 mg on Day 5, to Japanese healthy adult participants, the $AUC_{0\text{-inf}}$

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of midazolam was increased by 6.77-fold compared with that following the single-dose administration of midazolam alone. The result showed that S-217622 is a strong CYP3A inhibitor.		
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