2. SYNOPSIS

Sponsor: Shionogi B.V.	**Individual Study Table** **Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product Not applicable	**Volume:**	
Name of Active Ingredient: S-217622	**Page:**	

Study Title:
A Single-group, Phase 1, Open-label Study to Investigate the Absorption, Distribution, Metabolism and Excretion of [^{14}C]-S-217622 Following Oral Dose Administration as a Suspension in Healthy Adult Male Participants

Investigators and Study Centres: This was a single-site study conducted at [redacted] a contract research organisation on behalf of the sponsor. The principal investigator was [redacted].

Publication (reference): Not applicable

Studied Period:
From [redacted]

Phase of Development: Phase 1

Objectives:

The primary objectives of the study were:

- To determine the mass balance recovery after administration of a single dose of 375 mg carbon-14 labelled S-217622 ([^{14}C]-S-217622) Oral Suspension in the fasted state
- To determine the whole blood and plasma concentrations of total radioactivity
- To assess the pharmacokinetics (PK) of total radioactivity and S-217622 after administration of a single dose of 375 mg [^{14}C]-S-217622 Oral Suspension in the fasted state

The secondary objectives of the study were:

- To characterise and identify metabolites of S-217622 in plasma, urine and faeces[a]
- To determine the routes and rates of elimination of [^{14}C]-S-217622
- To evaluate the extent of distribution of total radioactivity into blood cells
- To assess the safety and tolerability of S-217622 following administration of a single dose of 375 mg [^{14}C]-S-217622 Oral Suspension

[a] Metabolite profiling and identification will be reported separately from this clinical study report as a standalone document

Methodology: This was a single-centre, open-label, single-arm study in healthy adult male study participants to assess the mass balance recovery, absorption,

Sponsor: Shionogi B.V.	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product Not applicable	**Volume:**	
Name of Active Ingredient: S-217622	**Page:**	

metabolism, and excretion of S-217622 following a single oral administration of 375 mg [^{14}C]-S-217622 Oral Suspension in a fasted state. Six healthy adult male participants were enrolled to receive a single dose of 375 mg [^{14}C]-S-217622 Oral Suspension (12.2 mg/g [active pharmaceutical ingredient/total oral suspension]), containing not more than (NMT) 3.5 megabecquerel (MBq), after an overnight fast of at least 10 hours. A participant who had received a single dose of 375 mg [^{14}C]-S-217622 Oral Suspension and had provided mass balance and PK samples for up to 504 hours postdose (Day 22), or had demonstrated > 90% mass balance recovery, or had < 1% of the administered dose eliminated in excreta for each of 2 consecutive days (and therefore < 2% collected in a single 48-hour period), whichever occurred soonest, was evaluated. No replacement of participants was planned for this study.

Number of Participants (Planned and Analysed):

Planned: 6

Enrolled: 6

Analysed for PK, mass balance and safety: 6

Diagnosis and Main Criteria for Inclusion:

Healthy males aged ≥ 30 to ≤ 65 years inclusive at the time of signing informed consent with a body mass index of ≥ 18.0 to ≤ 32.0 kg/m^2 (inclusive). Participants were required to have regular bowel movements (ie, average stool production of ≥ 1 and ≤ 3 stools per day).

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

Test Product:

[^{14}C]-S-217622 Oral Suspension

Dose and Mode of Administration:

375 mg [^{14}C]-S-217622 Oral Suspension (12.2 mg/g [active pharmaceutical ingredient/total oral suspension]), expressed as the free drug equivalent, containing NMT 3.5 MBq, oral administration in the fasted state. The actual amount of radioactivity received by each participant was 3.41257 MBq.

Batch Number:

[redacted]

Duration of Treatment:

Single administration (1 day)

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

Not applicable.

Sponsor: Shionogi B.V.	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product Not applicable	**Volume:**	
Name of Active Ingredient: S-217622	**Page:**	

Criteria for Evaluation:

Mass Balance and Pharmacokinetics Assessment:

Venous blood samples were collected and processed to isolate plasma. Pharmacokinetic analysis was carried out on whole blood (total radioactivity only) and plasma (total radioactivity and S-217622) samples.

Urine and faecal samples were collected for total radioactivity and metabolite profiling and structural identification.

Mass Balance Parameters: The amount of total radioactivity eliminated/excreted in the urine, faeces, and urine and faeces combined was calculated (A_{eu}, A_{ef}, and A_{etotal}) and also expressed as a percentage of the radioactive dose administered (F_{eu}, F_{ef}, and F_{etotal}). The respective cumulative amounts were also determined ($CumA_{eu}$, $CumF_{eu}$, $CumA_{ef}$, $CumF_{ef}$, $CumA_{etotal}$, and $CumF_{etotal}$).

Pharmacokinetic Parameters: The following PK parameters were estimated where possible and appropriate: time of maximum observed concentration (T_{max}); maximum observed concentration (C_{max}); area under the curve (AUC) from time 0 to the time of the last measurable concentration ($AUC_{0\text{-}last}$); AUC from time 0 extrapolated to infinity ($AUC_{0\text{-}inf}$); AUC from the time of the last measurable concentration to infinity as a percentage of the $AUC_{0\text{-}inf}$ (AUC_{extrap}); terminal elimination half-life ($t_{1/2}$); first order rate constant associated with the terminal (log-linear) portion of the curve (λ_z); total body clearance calculated after a single extravascular administration where F (fraction of dose bioavailable) is unknown (CL/F); apparent volume of distribution based on the terminal phase calculated using $AUC_{0\text{-}inf}$ after a single extravascular administration where F is unknown (V_z/F); mean residence time (MRT) from time 0 to time of last measurable concentration ($MRT_{0\text{-}last}$); MRT from time 0 extrapolated to infinity ($MRT_{0\text{-}inf}$), ratio of plasma S-217622 to plasma total radioactivity based on C_{max} (R C_{max}) and based on $AUC_{0\text{-}inf}$ (R AUC); and whole blood to plasma total radioactivity ratio based on C_{max} (WB:P C_{max}), on $AUC_{0\text{-}last}$ (WB:P $AUC_{0\text{-}last}$), and on $AUC_{0\text{-}inf}$ (WB:P $AUC_{0\text{-}inf}$).

Safety Assessment:

Safety evaluations were based on the incidence, severity, and type of adverse events (AEs), 12-lead electrocardiogram (ECG) results, vital signs measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature), safety laboratory tests (clinical chemistry, haematology, and urinalysis), and physical examinations.

Sponsor: Shionogi B.V.	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product Not applicable	**Volume:**	
Name of Active Ingredient: S-217622	**Page:**	

Statistical Methods:

No formal statistical analysis was planned for mass balance, PK, or safety data in this study. Descriptive statistics are considered adequate for a study of this type.

Summary of Results:

Mass Balance and Pharmacokinetics:

The mean cumulative amount of total radioactivity recovered in urine and faeces following a single administration of [^{14}C]-S-217622 to healthy male participants is presented in the following table:

Collection Interval (hours)	**$CumF_{eu}$ (%)**	**$CumF_{ef}$ (%)**	**$CumF_{etotal}$ (%)**
0 - 6[a]	2.631	-	-
0 - 12[a]	5.732	-	-
0 - 24	9.545	3.314	12.859
0 - 48	15.310	14.031	29.341
0 - 72	19.237	20.317	39.554
0 - 96	21.440	35.714	57.154
0 - 120	22.859	42.822	65.681
0 - 144	23.860	47.840	71.701
0 - 168	24.495	52.636	77.131
0 - 192	24.898	55.354	80.252
0 - 216	25.201	58.405	83.607
0 - 240	25.394	60.381	85.775
0 - 264	25.537	61.675	87.211
0 - 288	25.644	62.310	87.954
0 - 312	25.711	63.553	89.264
0 - 336	25.764	64.045	89.809
0 - 360	25.780	64.557	90.338
0 - 384	25.785	64.585	90.370
0 - 408	25.788	64.645	90.433
0 - 432	25.789	64.724	90.514
0 - 456	25.791	64.769	90.560
Collection Interval (hours)	**$CumA_{eu}$ (mg equivalents)**	**$CumA_{ef}$ (mg equivalents)**	**$CumA_{etotal}$ (mg equivalents)**
0 - 456	98.3	247	345

[a] urine only

Sponsor: Shionogi B.V.	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product Not applicable	**Volume:**	
Name of Active Ingredient: S-217622	**Page:**	

The geometric mean (geometric coefficient of variation [CV%]) whole blood and plasma PK parameters following a single administration of 375 mg [^{14}C]-S-217622 to healthy male participants are presented in the following table. Due to a missing sample within the T_{max} range for one participant, all exposure parameter summaries (together with summaries for derived parameters) are based on 5 participants' data.

Analyte	**Total Radioactivity**	**Total Radioactivity**	**S-217622**
Matrix	**Whole Blood**	**Plasma**	**Plasma**
Number of Participants	**N = 6**	**N = 6**	**N = 6**
T_{max}[a] (h)	2.500 (1.00 - 3.00) [n = 5]	2.500 (1.00 - 4.00) [n = 5]	2.033 (1.00 - 3.00) [n = 5]
C_{max}[b] (µg/mL)	10.1 (17.8%) [n = 5]	19.3 (12.8%) [n = 5]	19.3 (9.0%) [n = 5]
$AUC_{0\text{-}last}$[b] (µg.h/mL)	604.9 (27.8%) [n = 5]	1138 (25.8%) [n = 5]	1031 (27.1%) [n = 5]
$AUC_{0\text{-}inf}$[b] (µg.h/mL)	621.5 (27.2%) [n = 5]	1154 (26.0%) [n = 5]	1034 (27.4%) [n = 5]
AUC_{extrap} (%)	2.575 (30.8%) [n = 5]	1.361 (23.9%) [n = 5]	0.164 (144.0%) [n = 5]
$t_{1/2}$ (h)	45.3 (13.4%)	50.1 (10.6%)	39.7 (17.9%)
λ_z (1/h)	0.01530 (13.4%)	0.01385 (10.6%)	0.01744 (17.9%)
CL/F (L/h)	NA	NA	0.363 (27.4%) [n = 5]
Vz/F (L)	NA	NA	21.2 (18.1%) [n = 5]
$MRT_{0\text{-}last}$ (h)	61.6 (13.2%) [n = 5]	68.2 (11.0%) [n = 5]	61.7 (12.0%) [n = 5]
$MRT_{0\text{-}inf}$ (h)	68.2 (12.6%) [n = 5]	72.7 (11.3%) [n = 5]	62.6 (13.3%) [n = 5]
R C_{max}	NA	NA	1.00 (9.4%) [n = 5]
R AUC	NA	NA	0.896 (2.5%) [n = 5]
WB:P C_{max}	0.522 (5.8%) [n = 5]	NA	NA
WB:P $AUC_{0\text{-}last}$	0.532 (7.8%) [n = 5]	NA	NA
WB:P $AUC_{0\text{-}inf}$	0.538 (6.9%) [n = 5]	NA	NA

NA = not applicable
[a] median (range)
[b] µg equivalents for total radioactivity

Sponsor: Shionogi B.V.	**Individual Study Table** **Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product Not applicable	**Volume:**	
Name of Active Ingredient: S-217622	**Page:**	

Safety:

Single administrations of 381 mg [^{14}C]-S-217622 containing 3.4 MBq were safe and well tolerated when administered under the conditions of this study. No severe treatment-emergent adverse events (TEAEs), treatment-related TEAEs, serious TEAEs, or TEAEs leading to death or study discontinuation were reported during the study. Mild headache was the only TEAE reported, which occurred on Day 1 of the study and resolved without treatment after approximately 2 hours. This event was considered to be unrelated to the study intervention. There were no clinically significant findings in clinical laboratory evaluations, vital signs, ECGs, or physical examinations.

Sponsor: Shionogi B.V.	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product Not applicable	**Volume:**	
Name of Active Ingredient: S-217622	**Page:**	

CONCLUSIONS

Mass Balance and Pharmacokinetics Conclusions:

Following administration of a single planned dose of 375 mg [^{14}C]-S-217622 Oral Suspension (actual dose approximately 381 mg) in the fasted state to healthy male participants, approximately 90.560% of the radioactivity administered was recovered in excreta over a 456-hour sampling period.

Of the overall 90.560% of total radioactivity recovered, the majority (64.769%) was recovered in the faeces, with the remaining 25.791% recovered in the urine.

The substantial excretion of total radioactivity via the faecal route between 48 and 456 hours postdose (50.738%), combined with the 25.791% excreted in the urine over the full sampling period, suggests that S-217622 was well absorbed and that, the majority of elimination was via the biliary route with some contribution from renal elimination.

Exposure to S-217622 accounted for 89.6% of circulating plasma total radioactivity based on $AUC_{0\text{-}inf}$, indicating that S-217622 was the main circulating component in the plasma following oral administration.

The geometric mean whole blood to plasma total radioactivity concentration ratios, whole blood to plasma ratios based on C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$, and association of total radioactivity with red blood cells calculations indicated little to no distribution of total radioactivity into the cellular components of whole blood, with no notable time-dependent differences in the ratios.

Safety Conclusions:

A single dose of 381 mg [^{14}C]-S-217622 (containing 3.4 MBq) administered as an oral suspension following an overnight fast of a minimum of 10 hours, was safe and well tolerated by healthy male participants in this study. No new safety concerns were identified for S-217622 after a single oral dose.

Overall, the changes in the clinical safety assessments were unremarkable.

Date of Report: [redacted]