2 STUDY SYNOPSIS

Name of Sponsor/Company:	Name of Study Treatment:	Name of Active Ingredient:
AstraZeneca AB	[^{14}C]AZD9977	AZD9977

Title of Study: A Phase I, Open-label Study of Absolute Bioavailability and Absorption-Distribution-Metabolism-Excretion (ADME) of [^{14}C]AZD9977 in Healthy Male Subjects

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Publication (Reference): None**Studied Period:** 21 Dec 2020 to 04 Feb 2021

Phase of Development: I

Objectives:

The primary objectives of the study were:

- To evaluate absolute bioavailability of a single oral dose of AZD9977 capsule.
- To determine the mass balance, rates and routes of elimination, after a single dose of carbon-14 [^{14}C]AZD9977 in healthy male subjects.
- To provide samples for metabolite profiling and structural identification from plasma, urine and faecal samples*.

The secondary objectives of the study were:

- To provide additional safety and tolerability information for AZD9977.
- To determine the pharmacokinetic (PK) of AZD9977 following single dose administration of [^{14}C]AZD9977 oral suspension and AZD9977 capsule on separate occasions.
- To determine the PK of [^{14}C]AZD9977 following single administration of [^{14}C]AZD9977 intravenous (IV) infusion.
- To determine the PK of total radioactivity following single administration of [^{14}C]AZD9977 IV infusion and [^{14}C]AZD9977 oral suspension.
- To evaluate the extent of distribution of total radioactivity into blood cells.

The exploratory objective of this study was:

- To provide samples to be stored for future analysis (if required).

*Metabolite profiling, identification and quantification are reported separately from the clinical study report as a standalone document.

Methodology:

This was a single centre, open-label, single-dose, 2-period, 3-regimen, non-randomised study in 8 healthy male subjects. Period 1 assessed the absolute bioavailability and evaluated the PK parameters of a single unlabelled oral dose of AZD9977 and a radiolabelled IV microdose of [^{14}C]AZD9977. Subjects were dosed with a single CCI oral dose of the AZD9977 capsule CCI, followed by CCI [^{14}C]AZD9977, containing not more than CCI, dosed as an IV microdose. Period 2 assessed the absorption, distribution, metabolism, and excretion (ADME) of [^{14}C]AZD9977. Subjects received a single oral dose of CCI [^{14}C]AZD9977, CCI as a suspension. Subjects took part in both study periods.

Subjects underwent preliminary screening procedures for the study at the screening visit (Day -28 to Day -2). Subjects were admitted in the evening on the day before dosing for both periods. Blood, urine (Periods 1 and 2) and faecal (and emesis if applicable; Period 2) samples were collected at regular intervals for PK, safety and mass balance analysis from Day -1 to the follow-up visit, as applicable.

In Period 1, subjects were dosed on the morning of Day 1. Following an overnight fast (minimum 10 h) subjects received a single oral dose of AZD9977 capsule. Subjects then received CCI [^{14}C]AZD9977 as a continuous 15 min IV infusion 2 h and 15 min after the oral dose. The end of the infusion coincided with the expected median oral t_{max} (2.5 h after the oral dose [see Section 11.2 of the clinical protocol for allowable window details). Subjects remained resident in the clinical unit until up to 72 h after dosing with the oral dose (up to Day 4).

There was a minimum washout of 7 days between dosing in Period 1 and Period 2.

In Period 2, subjects were dosed on the morning of Day 1. Following an overnight fast (minimum 10 h) subjects received a single dose of [^{14}C]AZD9977 oral suspension. Subjects remained resident in the clinical unit until up to 168 h post-dose (up to Day 8). It was planned that subjects would be released as a group when all subjects had achieved a mass balance cumulative recovery of >90% or if <1% of the dose administered had been collected in urine and faeces within 2 separate, consecutive 24 h periods. This may have resulted in the subjects being discharged as a group prior to completion of the planned residency period. If the mass balance criteria were achieved during the planned residency period, collection of all samples (blood, urine and faeces) would have been stopped and subjects would have undergone discharge assessments. If the mass balance criteria were not met by all subjects on Day 8, the residency period for the subjects not achieving the mass balance criteria may have been extended up to a maximum of 48 h post-dose (Day 10). Only urine and/or faecal samples would have been collected during the extended residency period. If the mass balance criteria were still not met by Day 10, or if the extended residency period was not considered appropriate or necessary, then home collections of urine and/or faeces may have been requested at the discretion of the investigator for individual subjects.

Subjects attended the clinical unit for a follow-up visit between Day 15 and Day 18 post-final dose. For those subjects who would have continued home collections until the

mass balance criteria were met beyond Day 18, the follow-up visit would have taken place up to 7 days after the final home collection.

A subject was considered evaluable in Period 1 of the study if they had taken a full dose of study drug and provided PK samples for up to 72 h post-oral dose. The PK evaluability of subjects was assessed on a case by case basis.

A subject was considered evaluable in Period 2 of the study if they had provided mass balance and PK samples for up to 8 days after drug administration or had demonstrated >90% mass balance recovery, or had <1% of the administered dose eliminated in excreta for 2 consecutive days, whichever was the sooner.

Number of Subjects (Planned and Analysed):

Planned: 8, Enrolled: 8, Completed: 7, Discontinued: 1.

Overall, 8 subjects were dosed with investigational medicinal product (IMP) in Period 1 and were included in the safety analysis set for this treatment, and 7 subjects were dosed with IMP in Period 2 and were included in the safety analysis set for this treatment. All subjects were therefore included in the mass balance and PK analysis sets for Period 1, and 7 subjects were included in the mass balance and PK analysis sets for Period 2.

One subject withdrew due to personal reasons and only received one dose of IMP in Period 1 of the study.

Diagnosis and Main Criteria for Inclusion:

Healthy males aged 30 to 60 years at the time of signing informed consent with suitable veins for cannulation or repeated venepuncture. Body mass index 18.0 to 30.0 kg/m^2 (body weight at least 50.0 kg) as measured at screening. Must have had regular bowel movements (i.e., average stool production of ≥1 and ≤3 stools per day).

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

Subjects received CCI oral dose of the AZD9977 capsule CCI , followed by CCI [^{14}C]AZD9977, containing CCI dosed as an IV microdose CCI in Period 1. Capsules were administered with a total of 240 mL of water.

In Period 2, subjects received a single oral dose of CCI [^{14}C]AZD9977, containing CCI , as a suspension. Immediately after administration of the oral suspension, the dosing vessel was rinsed with water and subjects consumed the rinse solution. Subjects then consumed further water to a total volume of 240 mL (including the dosing volume and volume used to rinse the dosing vessel).

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

Not applicable.

Duration of Treatment:

Subjects received a single oral dose of the AZD9977 capsule followed by an IV infusion of [^{14}C]AZD9977 solution administered 2 h and 15 min after the oral dose on one occasion in Period 1 and a single oral dose of [^{14}C]AZD9977 oral suspension on one occasion in Period 2. The IV dose was infused over 15 min. There was a minimum washout of 7 days between dosing in Period 1 and Period 2. Subjects attended the clinical unit for a follow-up visit between Day 15 and Day 18 post-final dose.

Criteria for Evaluation:

Mass Balance

The following mass balance parameters were estimated where possible:

Mass Balance Parameters (Period 2 only)

Parameter	Definition
$A_{e(urine)}$	Amount of total radioactivity excreted in urine
$F_{e(urine)}$	Amount of total radioactivity excreted in urine expressed as a percentage of the radioactive dose administered
$CumA_{e(urine)}$	Cumulative amount of total radioactivity excreted in urine
$CumF_{e(urine)}$	Cumulative amount of total radioactivity excreted in urine expressed as a percentage of the radioactive dose administered
$A_{e(faeces)}$	Amount of total radioactivity eliminated in faeces
$F_{e(faeces)}$	Amount of total radioactivity eliminated in faeces expressed as a percentage of the radioactive dose administered
$CumA_{e(faeces)}$	Cumulative amount of total radioactivity eliminated in faeces
$CumF_{e(faeces)}$	Cumulative amount of total radioactivity eliminated in faeces expressed as a percentage of the radioactive dose administered
$A_{e(total)}$	Amount of total radioactivity excreted in urine and faeces combined
$F_{e(total)}$	Amount of total radioactivity excreted in urine and faeces combined expressed as a percentage of the radioactive dose administered
$CumA_{e(total)}$	Cumulative amount of total radioactivity excreted in urine and faeces combined
$CumF_{e(total)}$	Cumulative amount of total radioactivity excreted in urine and faeces combined expressed as a percentage of the radioactive dose administered

Pharmacokinetics

The PK parameters for AZD9977 (Periods 1 and 2) and [^{14}C]AZD9977 (Period 1) in plasma and total radioactivity in plasma (Periods 1 and 2) and whole blood (Period 2) were estimated where possible and appropriate for each subject by non-compartmental analysis methods using Phoenix® WinNonlin® software (v8.0 or a more recent version, Certara USA, Inc., USA). Plasma PK parameters examined and their definitions are provided below:

Plasma and Urine Pharmacokinetic Parameters (Period 1)

Parameter	Definition
t_{lag}	Time prior to the first measurable concentration (AZD9977)
t_{max}	Time of maximum observed concentration
C_{max}	Maximum observed concentration
AUC_{0-t}	Area under the curve from time 0 to the time of last measurable concentration
AUC_{0-inf}	Area under the curve from time 0 extrapolated to infinity
$AUC_{\%extrap}$[a]	Area under the curve from time of the last measurable concentration to infinity as a percentage of the area under the curve extrapolated to infinity
$t_{1/2}$	Terminal half-life
λ_z	First order rate constant associated with the terminal (log-linear) portion of the curve
CL	Total body clearance calculated after a single intravenous administration ([^{14}C]AZD9977)
CL/F	Total body clearance calculated after a single extravascular administration (AZD9977)
CL_R	Renal clearance calculated using plasma AUC (AZD9977 and [^{14}C]AZD9977)

Parameter	Definition
V_z	Volume of distribution based on the terminal phase calculated using $AUC_{0\text{-}inf}$ after a single intravenous administration ([^{14}C]AZD9977)
V_{ss}	Volume of distribution at steady state after a single intravenous administration ([^{14}C]AZD9977)
V_z/F	Apparent volume of distribution based on the terminal phase calculated using $AUC_{0\text{-}inf}$ after a single extravascular administration (AZD9977)
$MRT_{0\text{-}t}$	Mean residence time from time 0 to time of the last measurable concentration (AZD9977 and [^{14}C]AZD9977)
$MRT_{0\text{-}inf}$	Mean residence time extrapolated to infinity (AZD9977 and [^{14}C]AZD9977)
F	Absolute bioavailability
$A_{e(urine)}$	Amount of unchanged AZD9977 and [^{14}C]AZD9977 excreted in urine
$F_{e(urine)}$	Amount of unchanged AZD9977 and [^{14}C]AZD9977 excreted in urine expressed as a percentage of the radioactive dose administered
$CumA_{e(urine)}$	Cumulative amount of unchanged AZD9977 and [^{14}C]AZD9977 excreted in urine
$CumF_{e(urine)}$	Cumulative amount of unchanged AZD9977 and [^{14}C]AZD9977 excreted in urine expressed as a percentage of the radioactive dose administered
λ_z lower[a]	Lower limit on time for values to be included in the calculation of λ_z
λ_z upper[a]	Upper limit on time for values to be included in the calculation of λ_z
tlast[a]	Time of last observed (quantifiable) concentration
$\lambda_z N$[a]	Number of data points used for λ_z determination
λ_z span ratio[a]	Time period over which λ_z was determined as ratio of $t½\lambda_z$
Rsq[a]	Statistical measure of fit for the regression used for λ_z determination
Rsq adj[a]	Statistical measure of fit for the regression used for λ_z determination adjusted for the number of used data points

[a] these values were listed but omitted from the descriptive statistics.

Plasma, Whole Blood and Urine Pharmacokinetic Parameters (Period 2)

Parameter	Definition
t_{lag}	Time prior to the first measurable concentration
t_{max}	Time of maximum observed concentration
C_{max}	Maximum observed concentration
$AUC_{0\text{-}t}$	Area under the curve from time 0 to the time of last measurable concentration
$AUC_{0\text{-}inf}$	Area under the curve from time 0 extrapolated to infinity
$AUC_{\%extrap}$[a]	Area under the curve from time of the last measurable concentration to infinity as a percentage of the area under the curve extrapolated to infinity
$t_{1/2}$	Terminal half-life
λ_z	First order rate constant associated with the terminal (log-linear) portion of the curve
CL/F	Total body clearance calculated after a single extravascular administration (AZD9977)
CL_R	Renal clearance calculated using plasma AUC (AZD9977)
V_z/F	Apparent volume of distribution based on the terminal phase calculated using AUC after a single extravascular administration (AZD9977)
$MRT_{0\text{-}t}$	Mean residence time from time 0 to time of the last measurable concentration (AZD9977)
$MRT_{0\text{-}inf}$	Mean residence time extrapolated to infinity (AZD9977)
$A_{e(urine)}$	Amount of unchanged AZD9977 excreted in urine
$F_{e(urine)}$	Amount of unchanged AZD9977 excreted in urine expressed as a percentage of

Parameter	Definition
	the radioactive dose administered
$CumA_{e(urine)}$	Cumulative amount of unchanged AZD9977 excreted in urine
$CumF_{e(urine)}$	Cumulative amount of unchanged AZD9977 excreted in urine expressed as a percentage of the radioactive dose administered
λ_z lower[a]	Lower limit on time for values to be included in the calculation of λ_z
λ_z upper[a]	Upper limit on time for values to be included in the calculation of λ_z
tlast[a]	Time of last observed (quantifiable) concentration
$\lambda_z N$[a]	Number of data points used for λ_z determination
λ_z span ratio[a]	Time period over which λ_z was determined as ratio of $t½\lambda_z$
Rsq[a]	Statistical measure of fit for the regression used for λ_z determination
Rsq adj[a]	Statistical measure of fit for the regression used for λ_z determination adjusted for the number of used data points

[a] these values were listed but omitted from the descriptive statistics.

Safety

The evaluation of safety parameters comprised analysis of adverse events (AEs), laboratory variables (haematology, clinical chemistry and urinalysis), vital signs, electrocardiograms (ECGs), body weight and physical examination findings.

Statistical Methods:

Descriptive statistics were considered adequate for a study of this type. Summary statistics (i.e. n, geometric mean, geometric standard deviation [SD], geometric coefficient of variation [CV%], arithmetic mean, arithmetic SD, arithmetic CV%, minimum, median and maximum) were presented for mass balance, PK, and safety data as appropriate.

Summary – Conclusions:

Mass Balance Results

Following administration of a single oral CCI dose of [^{14}C]AZD9977, an average of 94.1% of the total radioactivity administered was recovered in excreta (48.9% in faeces and 45.2% in urine) over a 168 h sampling period, with 47.4% being excreted within 24 h post-dose.

Only 16.4% of the faecal recovery was excreted in the first 48 h post dose, with the remainder excreted between 48 h and 168 h. This may suggest that the majority of faecal recovery was due to biliary elimination and not unabsorbed drug.

Pharmacokinetic Results

Pharmacokinetic Results: Intravenous Microtracer (Period 1)

The key geometric mean (geometric CV%) plasma PK parameters for [^{14}C]AZD9977 and total radioactivity, and for AZD9977, following administration of a single oral dose of CCI AZD9977 CCI capsules, followed by a 15 min CCI [^{14}C]AZD9977 IV infusion in the fasted state are summarised in the following tables:

Analyte PK Parameter (units)[a]	[^{14}C]AZD9977 (n=8)	Total Radioactivity (n=8)
t_{max}[a] (h)	0.251 (0.11-0.33)	0.294 (0.25-3.75)
C_{max} (pmol/L)	12500 (23.3)	13800 (33.7)
AUC_{0-t} (pmol /L)	17600 (35.5)	33800 (57.5)
AUC_{0-inf} (pmol /L)	17700 (35.5)	36000 (54.4)
$t_{1/2}$ (h)	4.22 (101.6)	36.7 (60.3)
CL (L/h)	14.2 (35.5)	NC
CL_R (L/h)	5.61 (40.4)	NC
V_z (L)	86.2 (103.0)	NC
V_{ss} (L)	37.8 (15.8)	NC
MRT_{0-t} (h)	2.56 (37.6)	7.62 (6.7)
MRT_{0-inf} (h)	2.67 (40.0)	14.7 (47.7)

CV%: coefficient of variation, n: number of subjects included in the analysis, NC: not calculated
[a] Median (range)

Analyte PK Parameter (units)	AZD9977 (n=8)
t_{lag}[a] (h)	0.250 (0.00-0.27)
t_{max}[a] (h)	1.250 (0.75-2.50)
C_{max} (nmol/L)	2160 (27.7)
AUC_{0-48} (nmol h/L)	9000 (24.9)
AUC_{0-t} (nmol h/L)	9070 (25.9)
AUC_{0-inf} (nmol.h/L)	9180 (26.9)
$t_{1/2}$ (h)	12.3 (90.6)
CL/F (L/h)	27.3 (26.9)
CL_R (L/h)	5.46 (26.7)
V_z/F (L)	485 (84.9)
MRT_{0-t} (h)	5.607 (29.2)
MRT_{0-inf} (h)	6.372 (38.9)
F (%)	51.978 (24.6)

CV%: coefficient of variation, n: number of subjects included in the analysis
[a] Median (range)

Following CCI [^{14}C]AZD9977 administered via a 15 min IV infusion, concentration vs time profiles of [^{14}C]AZD9977 tended to be consistent with typical IV infusion administration. Maximum concentrations were reached by the end of infusion at a median t_{max} of 0.25 h. The C_{max} for [^{14}C]AZD9977 was 12500 pmol/L, which was 9% lower than that observed for total radioactivity (13800 pmol/L). Following C_{max}, concentrations showed a rapid distribution phase followed by an elimination phase with geometric mean half-life of 4.22 h, which is consistent with the proposed effective half-life.

The volume of distribution (86.2 L) observed following the IV infusion was higher than total body water indicating distribution into tissue.

Total clearance of [^{14}C]AZD9977 (14.2 L/h) was lower than typical hepatic blood flow rates. The renal clearance value observed of 5.61 L/h and approximately 39.9% of the dose was excreted unchanged in the urine.

Exposure to [^{14}C]AZD9977 accounted for 52% and 49% of circulating plasma total radioactivity based on AUC_{0-t} and AUC_{0-inf}, respectively. The geometric mean apparent terminal half-life for total radioactivity in plasma (36.7 h) was longer than that observed for [^{14}C]AZD9977 (4.22 h). In 1 subject PPD) the total radioactivity half-life

(31.68 h) was similar to that for [^{14}C]AZD9977 terminal half-life (27.45 h), in the remaining 7 subjects the total radioactivity half-life was longer than that for the [^{14}C]AZD9977.

Following administration of a single oral dose of CCI AZD9977 capsule to healthy male subjects, AZD9977 was rapidly absorbed with plasma concentrations quantifiable from 0.25 and 0.5 h and a median t_{max} of 1.25 h. Absolute bioavailability of AZD9977 following oral dosing was 52%; however, the individual F values ranged from 30.91% to 68.35% and the lowest F value was for a subject who likely had an underestimate of IV AUC thus the corresponding mean could also be an overestimation.

The renal clearance for the oral dose (5.46 L/h) was similar to that observed for IV. Approximately 20% of the dose was excreted unchanged in the urine which was approximately half of that recovered following the IV dose which is consistent with the absolute bioavailability.

The estimated plasma half-life was 12.3 h, which was longer than that observed following the IV dose (4.22 h).

Pharmacokinetic Results: ADME (Period 2)

Key PK parameters for AZD9977 in plasma and total radioactivity in plasma and whole blood following administration of a single oral dose of CCI [^{14}C]AZD9977 in the fasted state are summarised below:

Analyte	AZD9977	Total Radioactivity	
Matrix PK Parameter (units)	Plasma (n=7)	Plasma (n=7)	Whole Blood (n=7)
t[a] (h)	0.00 (0.00-0.00)	0.000 (0.00-0.00)	0.000 (0.00-0.00)
t_{max}[a] (h)	0.500 (0.50-1.00)	0.750 (0.50-1.00)	0.750 (0.50-1.00)
C_{max} (nmol/L)	3210 (32.2)	3820 (27.8)	2610 (32.3)
AUC_{0-48} (nmol/L)	9270 (22.9)	NC	NC
AUC_{0-t} (nmol/L)	9280 (23.0)	19400 (17.4)	12600 (26.0)
AUC_{0-inf} (nmol/L)	9060 (23.8) [n=6]	20400 (17.9)	12800 (33.2) [n=5]
$t_{1/2}$ (h)	6.65 (98.6) [n=6]	6.80 (34.7)	3.34 (52.5) [n=5]
CL/F (L/h)	28.6 (23.8) [n=6]	NC	NC
CL_R (L/h)	5.44 (28.0)	NC	NC
V_z/F (L)	274 (95.1) [n=6]	NC	NC
MRT_{0-t} (h)	3.821 (24.7)	6.086 (9.8)	5.242 (31.1)
MRT_{0-inf}(h)	4.056 (28.9) [n=6]	7.653 (14.1)	5.429 (38.8) [n=5]

CV%: coefficient of variation, n: number of subjects included in the analysis, NC: not calculated
[a] Median (range)

Following administration of a single oral dose of CCI [^{14}C]AZD9977 suspension, AZD9977 was rapidly absorbed, with plasma concentrations quantifiable from 0.25 h and a median t_{max} of 0.5 h.

The renal clearance and the percentage of AZD9977 excreted in Period 2 were similar to that of the oral dose in Period 1, at 5.44 L/h and 19.8%, respectively.

The estimated plasma half-life of AZD9977 was 6.65 h, which was shorter than the observed $t_{1/2}$ noted in Period 1 (12.3 h).

Exposure to AZD9977 accounted for 47.8% and 44.4% of circulating plasma total radioactivity based on AUC_{0-t} and AUC_{0-inf}, respectively. The geometric mean apparent terminal half-life (6.65 h) for total radioactivity in plasma (6.80 h) was similar to that

observed for AZD9977 (6.65 h). The limit of quantification for the total radioactivity was 48.7 nmol/L whilst the limit for AZD9977 was 2 nmol/L. However, the limit of quantification for the total radioactivity was 48.7 nmol/L whereas the limit for AZD9977 was 2 nmol/L, which suggests that the profile may have been truncated before the terminal phase of the profile; in 5 of the 7 subjects, the last quantifiable concentration of AZD9977 was later than that for total radioactivity.

The geometric mean whole blood to plasma total radioactivity concentration ratios ranged from 0.431 at 12 h to 0.724 at 3 h, and at 24 h the ratio was 1.476. There were no notable time dependent differences in the ratios, with the exception of the 24 h time point, where the ratios were greater than 1, although that was only based on 4 subjects.

Safety Results

Single doses of CCI AZD9977 and CCI IV [14C]AZD9977 in Period 1 and CCI oral [^{14}C]AZD9977 in Period 2 were well tolerated by healthy subjects in this study. A total of 4 treatment-emergent adverse events (TEAEs) were reported, all of which were mild and resolved by the end of study; 2 of the TEAEs (headache and nausea) were considered to be possibly related to the IMP. There were no deaths, serious adverse events or other significant AEs reported and no AEs led to discontinuation of the IMP. There were no clinically significant findings in vital signs, ECGs, clinical laboratory evaluations or physical examinations.

Conclusions

Mass Balance and Pharmacokinetics

Period 1

- Following CCI [^{14}C]AZD9977 IV infusion maximum concentrations for [^{14}C]AZD9977 were reached by the end of infusion (median t_{max} 0.25 h).
- The geometric mean volume of distribution of [^{14}C]AZD9977 was 86.2 L.
- The geometric mean total clearance of [^{14}C]AZD9977 was 14.2 L/h and renal clearance was 5.61 L/h.
- An average of 39.9% of the dose was recovered as [^{14}C]AZD9977 in the urine over the 72 h sampling period.
- The geometric mean terminal plasma half-life of [^{14}C]AZD9977 was 4.22 h and for total radioactivity was 36.7 h.
- Exposure to [^{14}C]AZD9977 accounted for 52% and 49% of circulating plasma total radioactivity based on $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$, respectively.
- Absolute bioavailability of AZD9977 following oral dosing was 52%.
- Following a single oral dose of CCI AZD9977 capsule, the median t_{max} was 1.25 h for AZD9977.
- The renal clearance of AZD9977 was 5.46 L/h and approximately 20% was recovered unchanged in the urine.
- The estimated terminal half-life for AZD9977 was 12.3 h.

Period 2

- Following administration of a single oral CCI dose of [^{14}C]AZD9977 suspension in the fasted state, an average of 94.1% of the radioactivity administered was recovered in excreta over a 168-h sampling period.
- The mean total recovery of radioactivity from urine and faeces were 45.2 % and 48.9%, respectively, following oral dosing.
- Approximately 19.8% of the dose was excreted as unchanged AZD9977 in the urine and the renal clearance of AZD9977 was 5.44 L/h.
- Following administration of CCI dose of [^{14}C]AZD9977 oral suspension, the median t_{max} for AZD9977 was of 0.5 h.
- Exposure to AZD9977 accounted for 47% and 44% of circulating plasma total radioactivity based on AUC_{0-t} and AUC_{0-inf}, respectively.
- The geometric mean apparent terminal half-life for AZD9977 was 6.80 h and for total radioactivity was 6.65 h.
- The geometric mean whole blood to plasma total radioactivity concentration ratios ranged from 0.431 at 12 h to 0.724 at 3 h and at 24 h the ratio was 1.476.

Safety

- A total of 4 TEAEs were reported by 3 subjects, 2 of which were considered possibly related to the IMP.
- There were no serious or severe AEs, or early withdrawals due to IMP related AEs.
- No clinically significant abnormalities were observed in terms of clinical safety parameters.
- No clinically significant trends were noted for any of the safety laboratory parameters that were performed.
- No subjects met the safety stopping criteria.
- There were no new safety concerns discovered during this study.
- Single doses of CCI oral AZD9977, CCI IV [^{14}C]AZD9977 and CCI oral [^{14}C]AZD9977 under the conditions of the trial were found to be safe and well tolerated by the subjects.

Date of Report: 12 Jan 2022