2 STUDY SYNOPSIS

Name of Sponsor/Company: AstraZeneca AB	Name of Study Treatment: Savolitinib	Name of Active Ingredient: Savolitinib

Title of Study: A Phase I Open-label Study to Assess the Absolute Bioavailability of Savolitinib and Absorption, Distribution, Metabolism, Excretion of CCI [^{14}C]Savolitinib in Healthy Male Subjects

Principal Investigator: PPD

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Publication (Reference): None**Studied Period:** 13 Nov 2020 to 11 Jan 2021

Phase of Development: I

Objectives:

The primary objectives of the study were:

Part 1

- To evaluate absolute bioavailability of savolitinib in healthy male subjects after administration of a single oral dose of 600 mg tablet and 100 microgram (µg) [^{14}C]savolitinib intravenous (IV) solution.

Part 2

- To determine the mass balance, rates and routes of elimination of [^{14}C]savolitinib 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 of savolitinib.
- To determine the pharmacokinetics (PK) of savolitinib, [^{14}C]savolitinib, and metabolites M2 and M3 in plasma (Part 1) and savolitinib, metabolites M2 and M3 and total radioactivity in plasma and urine and total radioactivity in whole blood (Part 2).
- To compare the disposition of drug related total radioactivity in plasma to whole blood (Part 2).

The exploratory objectives of the study were:

- To quantify and identify the chemical structures of metabolites in plasma, urine and faeces.
- Collect and store DNA for future exploratory research into genes/genetic variations that may influence the PK of savolitinib.

Methodology:
This was a single centre, non-randomised, open-label, two-part study in healthy male subjects. Part 1 assessed the absolute bioavailability and evaluated the PK parameters of a single unlabelled oral dose and a radiolabelled IV microdose of savolitinib. Subjects were dosed with a single oral dose of 600 mg savolitinib (3 × 200 mg tablets), followed by 100 µg [^{14}C]savolitinib, containing not more than (NMT) 37.0 kBq [^{14}C], dosed as an IV microdose. Part 2 assessed absorption, distribution, metabolism and excretion (ADME) of [^{14}C]savolitinib following a single oral dose of 300 mg [^{14}C]savolitinib, containing NMT 4.1 MBq [^{14}C], as a solution. It was planned to enrol 8 healthy male subjects to ensure data in a minimum of 6 subjects.

Part 1

Part 1 was an open-label, non-randomised single oral dose followed by an IV microtracer assessment in 8 healthy male subjects.

All subjects underwent preliminary screening procedures to determine their eligibility for Parts 1 and 2 of the study at the screening visit (Day -28 to Day -2 of Part 1). Subjects were admitted to the clinical unit on the evening prior to IMP administration (Day -1) for confirmation of eligibility and baseline procedures. Subjects were dosed on the morning following admission (Day 1). Following an overnight fast (approximately 8 h), subjects consumed a high-fat breakfast and received a single oral dose of savolitinib approximately 30 min after the start of breakfast. Approximately 1.75 h post oral dose administration, IV infusion of microdose [^{14}C]savolitinib solution was started and continued for 15 min.

Subjects remained resident in the clinic until up to 72 h post-oral dose (up to Day 4).

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

The washout period between dose administrations in Part 1 and 2 was a minimum of 14 days.

Part 2

Part 2 was an open-label, non-randomised ADME assessment in the same 8 healthy male subjects who completed Part 1. Following a minimum washout period of 14 days, all subjects who participated in Part 1 of the study were admitted to the clinical unit for participation in Part 2 so that there were at least 4 subjects who completed Part 2 of the study. On Day 1 each subject received a single oral administration of 300 mg [^{14}C]savolitinib oral solution containing (NMT 4.1 MBq [^{14}C] on the morning of Day 1 after a high-fat breakfast.

Subjects were admitted to the clinical unit on the evening prior to investigational medicinal product (IMP) administration (Day -1 of Part 2) for re-confirmation of eligibility and baseline procedures for Part 2 of the study. Subjects were dosed on the morning of Day 1 following an overnight fast (approximately 8 h). Subjects consumed a high-fat breakfast, and received a single oral dose of [^{14}C]savolitinib approximately 30 min after the start of breakfast. Subjects remained resident in the clinic until up to 168 h after dosing (up to Day 8). During the study, any vomitus was to be collected (if presented), analysed and the radioactivity recovered from this recorded. 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 administered dose 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. Once the discharge criteria or the planned residency period has been achieved, collection of all samples (blood, urine and faeces) would be stopped and the subjects would undergo discharge assessments. If mass balance criteria had not been met by all subjects on the morning of Day 8, then home collections of urine and/or faeces may be requested at the discretion of the investigator for the individual subject. Mass balance criteria was had not been met by 3 subjects so home collection of faeces was requested.

A subject was considered evaluable in Part 2 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 two consecutive days, whichever was sooner.

All subjects attended the clinical unit for a follow-up visit 14 to 21 days after discharge from the clinic (at least 14 days after the last dose of savolitinib).

Number of Subjects (Planned and Analysed):
A total of 8 subjects was planned, 8 subjects were enrolled (informed consent received), 8 subjects received treatment, 8 subjects completed the study and no subjects were withdrawn from the study following treatment.

In total, 8 subjects were included in the safety analysis set, and 8 subjects were included in the PK and mass balance analysis sets.

Diagnosis and Main Criteria for Inclusion:
Healthy male subjects between 30 and 65 years of age with a body mass index between 18.0 and 32.0 kg/m^2 inclusive and weight of at least 50 kg and no more than 100 kg inclusive, as measured at screening.

Test Product, Dose and Mode of Administration, Batch Number:
All subjects received the following IMP:

Part	Regimen	IMP	Dose	Route of Administration	Batch No.
1	A	savolitinib (AZD6094) film coated tablets 200 mg	600 mg (3 × 200 mg)	Oral, Fed	CCI [redacted]
1	B	[^{14}C]savolitinib (AZD6094) Solution for Infusion, 20 µg/mL (NMT 37.0 kBq/5 mL)	100 µg, NMT 37.0 kBq [^{14}C]	Intravenous Administration	CCI [redacted]
2	C	[^{14}C]savolitinib (AZD6094) Oral Solution, 300 mg (NMT 4.1 MBq)	300 mg NMT 4.1 MBq [^{14}C]	Oral, Fed	CCI [redacted]

^{14}C: carbon-14; NMT: not more than.
Tablets were administered with a total of 240 mL of water. If required, additional water in 50 mL aliquots was given with the IMP. The oral solution was administered in order to have a total volume of 240 mL of fluid (the dosing vessel was rinsed with tap water and the washings also ingested by the subject).

Reference Therapy, Dose and Mode of Administration, Batch Number:
Not applicable.

Duration of Treatment:
Subjects received a single oral dose of savolitinib tablets (600 mg) followed by an IV infusion of [^{14}C]savolitinib administered 1.75 h after the oral dose on one occasion in Part 1 and a single oral dose of [^{14}C]savolitinib oral solution on one dosing occasion in Part 2.

Criteria for Evaluation:

Mass Balance
The following mass balance parameters were estimated where possible:

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 savolitinib, M2 and M3 and [^{14}C]savolitinib in plasma and total radioactivity in plasma and whole blood 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:

Parameter	Definition
t_{lag}	Time prior to the first measurable concentration
t_{max}	Time of maximum observed concentration
C_{max}	Maximum observed concentration
AUC_{last}	Area under the curve from time 0 to the time of last measurable concentration
AUC	Area under the curve from time 0 extrapolated to infinity
$t_{1/2}$	Terminal elimination 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 where F (fraction of dose bioavailable) is unknown
CL_R	Renal clearance
V_z/F	Apparent volume of distribution based on the terminal phase calculated using AUC after a single extravascular administration where F (fraction of dose bioavailable) is unknown
MRT_{last}	Mean residence time from time 0 to time of the last measurable concentration
MRT	Mean residence time extrapolated to infinity

MPR C_{max}	Metabolite to parent ratio based on C_{max}
MPR AUC	Metabolite to parent ratio based on AUC
A_e[a]	Amount of savolitinib, M2 and M3 excreted in urine
F_e[a]	Amount of savolitinib, M2 and M3 excreted in urine expressed as a percentage of the radioactive dose administered
MAT	Mean absorption time of the unchanged drug in the systemic circulation
MAT_{last}	Mean absorption time of the unchanged drug in the systemic circulation determined using AUC_{last}
F	Absolute bioavailability based on AUC of oral formulation compared to IV adjusted for dose
F_{last}	Absolute bioavailability based on AUC_{last} of oral formulation compared to IV adjusted for dose

[a] A_e and F_e were calculated as an absolute and cumulative parameter per time interval and over the entire sampling duration using statistical SAS software.

Safety

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

Statistical Methods:

No formal statistical analysis was performed for the safety, mass balance or PK data. Data were presented with descriptive summary statistics (e.g. number of subjects with an observation, mean, standard deviation, median, minimum and maximum). Additional statistics were provided for PK-related data (concentrations and PK parameters), including coefficient of variation (CV%), geometric mean and geometric CV%.

Summary – Conclusions:

Pharmacokinetic Results (Part 1)

Oral Administration

The key geometric mean (geometric coefficient of variation [CV%]) PK parameters for plasma following dosing with a single oral dose of 600 mg savolitinib are summarised below:

Analyte	Savolitinib	Savolitinib M2	Savolitinib M3
Parameter (units)	**(N = 8)**	**(N = 8)**	**(N = 8)**
t_{max}[a] (h)	3.500 (1.50-6.00)	4.000 (2.00-6.00)	4.000 (2.00-6.00)
C_{max} (ng/mL)	2360 (21.0)	562 (59.3)	221 (44.0)
AUC_{last} (ng h/mL)	14500 (31.1)	4130 (25.2)	1640 (32.9)
AUC (ng h/mL)	14500 (31.3)	4190 (24.9)	1660 (32.5)
$t_{1/2}$ (h)[b]	6.057 (4.109)	13.689 (10.209)	8.528 (3.979)
λ_z (1/h)[b]	0.14457 (0.05502)	0.08469 (0.05574)	0.09892 (0.04866)

Analyte	Savolitinib	Savolitinib M2	Savolitinib M3
Parameter (units)	**(N = 8)**	**(N = 8)**	**(N = 8)**
CL/F (L/h)[b]	43.0 (11.5)	NC	NC
V_z/F (L)[b]	328 (108)	NC	NC
MRT_{last} (h)	6.708 (33.2)	8.067 (33.8)	8.219 (34.0)
MRT (h)	6.799 (33.7)	8.994 (41.0)	8.819 (36.4)
MPR C_{max} (N/A)	NC	0.249 (53.0)	0.089 (29.3)
MPR AUC (N/A)	NC	0.301 (40.5)	0.109 (16.8)
MAT_{last} (h)	2.94 (48.9)	N/A	N/A
MAT (h)	2.72 (49.3)	N/A	N/A
F_{last} (%)	69.9 (6.7)	N/A	N/A
F (%)	68.8 (7.5)	N/A	N/A

%CV = coefficient of variation; IV = intravenous; N/A = not applicable; NC = not calculated
[a] Median (range)
[b] Arithmetic mean (SD)

Following administration of a single oral 600 mg tablet, the initial appearance of savolitinib was rapid with quantifiable concentrations from 0.5 h and the resultant median t_{max} was 3.5 h. The estimated plasma half-life was 5.27 h.

Formation of the metabolites savolitinib M2 and savolitinib M3 was rapid with plasma concentrations evident from between 0.5 and 1 h post-dose, with a median t_{max} of 4 h for both metabolites.

Based on the geometric mean metabolite to parent ratios for AUC, savolitinib M2 and savolitinib M3 accounted for approximately 30% and 11%, respectively, of savolitinib.

Geometric mean plasma elimination half-life for the metabolites savolitinib M2 and savolitinib M3 was longer than for the parent suggesting elimination of the metabolites was not formation rate limited.

The geometric mean absolute bioavailability of savolitinib was 69.9% and 68.8%, based on AUC_{last} and AUC, respectively.

IV Administration

The key geometric mean (geometric CV%) plasma PK parameters for [^{14}C]savolitinib following dosing with 100 µg IV [^{14}C]savolitinib are summarised below:

Analyte	[^{14}C] savolitinib
Parameter (units)	**(N = 8)**
t_{max}[a] (h)	0.250 (0.17-0.33)
C_{max} (pg/mL)	1670 (18.7)
AUC_{last} (pg.h/mL)	3450 (25.1)
AUC (pg h/mL)	3510 (24.4)

Analyte	[^{14}C] savolitinib
Parameter (units)	**(N = 8)**
$t_{1/2}$[b] (h)	3.521 (1.242)
λ_z[b] (1/h)	0.21910 (0.07755)
CL[b] (L/h)	29.2 (6.42)
V_z[b] (L)	139 (21.3)
MRT_{last} (h)	3.63 (31.1)
MRT (h)	3.96 (30.1)

[a] Median (range)
[b] Arithmetic mean (SD)

Following single IV administration of 100 µg [^{14}C] savolitinib, median t_{max} was observed at the end of infusion at 0.250 hours post-dose.

The estimated plasma half-live was 3.521 hours.

The arithmetic mean (SD) volume of distribution and total clearance was 139 L (21.3) and 29.2 L/h (6.42), which was appreciably lower than total body water and lower than typical hepatic and renal plasma flow rates, respectively.

Pharmacokinetic and Mass Balance Results (Part 2)

The key geometric mean (geometric coefficient of variation [CV%]) PK parameters for plasma and whole blood following dosing with a single oral dose of 300 mg [^{14}C]savolitinib are summarised below:

Analyte	Savolitinib	Savolitinib M2	Savolitinib M3	Total Radioactivity	
Matrix	**Plasma**	**Plasma**	**Plasma**	**Plasma**	**Whole Blood**
Parameter (units)	**N = 8**	**N = 8**	**N = 8**	**N = 8**	**N = 8**
t_{max}[a] (h)	1.000 (0.50-4.00)	2.250 (0.50-4.00)	2.000 (0.50-4.00)	3.000 (1.50-4.00)	3.000 (1.50-3.00)
C_{max}[c] (ng/mL)	1240 (25.9)	318 (36.4)	118 (21.5)	4050 (15.7)	2720 (17.2)
AUC_{last}[c] (ng h/mL)	7100 (34.0)	2170 (15.6)	804 (29.7)	36800 (16.3)	22000 (13.1)
AUC[c] (ng h/mL)	7110 (34.0)	2210 (16.4)	821 (31.0)	38600 (16.0)	22400, 27300 [n=2][d]
$t_{1/2}$ (h) [b]	6.562 (7.680)	13.482 (11.254)	10.103 (12.022)	5.507 (1.220)	3.34, 3.85 [n=2][d]
λ_z (1/h) [b]	0.16766 (0.07214)	0.08648 (0.06252)	0.12779 (0.06910)	0.13100 (0.02710)	0.1802, 0.2074 [n=2][d]
CL/F (L/h)[b]	44.2 (14.3)	NC	NC	7.80 (1.32)	10.9, 13.3 [n=2][d]
V_z/F (L) [b]	338 (253)	NC	NC	61.8 (16.5)	60.4, 63.9 [n=2][d]
MRT_{last} (h)	5.254 (26.4)	6.663 (27.1)	6.433 (29.9)	NC	NC

Analyte	Savolitinib	Savolitinib M2	Savolitinib M3	Total Radioactivity	
MRT (h)	5.353 (27.7)	7.837 (40.4)	7.386 (44.7)	NC	NC
MPR C_{max} (NA)	NC	0.267 (43.1)	0.091 (29.1)	NC	NC
MPR AUC (NA)	NC	0.324 (40.7)	0.110 (19.4)	NC	NC
CL_R (mL/min)	1.20 (29.8)	8.586 (19.9)	2.03 (24.2)	NC	NC

N/A = not applicable; NC = not calculated
[a] Median (range)
[b] Arithmetic mean (SD)
[c] ng equivalents for total radioactivity
[d] individual values (n=2)

Cumulative mass balance parameters of total radioactivity are summarised for all subjects below:

Parameter (units)	Urine (N=8)	Faeces (N=8)	Total (N=8)
$CumA_e$ (mg equivalents)	166 [9.90]	114 [15.1]	280 [16.1]
$CumF_e$ (%)	55.736 [3.329]	38.409 [5.088]	94.145 [5.416]

All values are Mean [SD]

Following single oral administration of 300 mg [^{14}C]savolitinib solution to healthy male volunteers an average of 94.1% of the radioactivity administered was recovered in excreta over the sampling period. The majority of total radioactivity (approximately 55.7%) was recovered in the urine indicating renal excretion was the main route of elimination following oral dosing.

Exposure to savolitinib, savolitinib M2 and savolitinib M3 accounted for approximately 18.4%, 5.7% and 2.1%, respectively, of circulating plasma total radioactivity based on geometric mean AUC. The sum of the analytes measured accounted for approximately 26.3% of the circulating plasma total radioactivity.

The geometric mean whole blood to plasma total radioactivity concentration ratios ranged from 0.85 at 0.25 h to 0.56 at 16 h indicating non-preferential distribution of total radioactivity to the cellular components of whole blood and that the majority of the drug is distributed into the plasma compartment.

Safety Results

Following dosing with 600 mg savolitinib and 100 µg IV [^{14}C]savolitinib in Part 1 and 300 mg oral [^{14}C]savolitinib in Part 2 there were no deaths, serious adverse events (SAEs) or AEs leading to subject withdrawal. Overall, all regimens were well tolerated in 8 healthy males under the conditions of this study.

All reported AEs were reported as mild in severity and the majority were not-related to the IMP with only 1 (12.5%) subject reporting possibly related AEs PPD following 600 mg savolitinib and 100 µg IV [^{14}C]savolitinib and PPD following 300 mg oral [^{14}C]savolitinib. The majority of AEs resolved without intervention and all AEs were resolved prior to completion of the study.

There were no significant clinical laboratory, vital signs or ECGs findings. One subject was noted to have a clinically significant physical examination finding PPD after discharge from the clinical unit which was also reported as an AE at follow up.

Conclusions

Pharmacokinetic Conclusions (Part 1)

- The geometric mean absolute bioavailability of savolitinib was 68.8%.
- Following a single IV administration of 100 µg [^{14}C]savolitinib, the median t_{max} was observed at the end of infusion, at 0.25 h post-start of infusion.
- For the IV dose, the estimated plasma half-life was 3.52 h for [^{14}C]savolitinib.
- The arithmetic mean (SD) volume of distribution was 139 L (21.3) and total clearance was 29.2 L/h (6.42).
- Following a single oral dose of 600 mg savolitinib in tablet form, the median t_{max} was 3.5 h post-dose for savolitinib and 4 h for both savolitinib M2 and savolitinib M3.
- The estimated arithmetic mean plasma half-lives were 6.06 h for savolitinib, 13.7 h for savolitinib M2 and 8.5 h for savolitinib M3.
- Based on the geometric mean metabolite to parent ratios for AUC, savolitinib M2 and savolitinib M3 accounted for approximately 30% and 11%, respectively, of savolitinib.

Pharmacokinetic and Mass Balance Conclusions (Part 2)

- Following a single oral administration of 300 mg [^{14}C]savolitinib solution to healthy male volunteers an average of 94.1% of the radioactivity administered was recovered in excreta (in urine and faeces) over the sampling period.
- The majority of total radioactivity (approximately 55.7%) was recovered in the urine indicating renal excretion was the main route of elimination following oral dosing.
- Exposure to savolitinib, savolitinib M2 and savolitinib M3 accounted for approximately 18.4%, 5.7% and 2.1%, respectively, of circulating plasma total radioactivity based on geometric mean AUC. The sum of the analytes measured accounted for approximately 26.3% of the circulating plasma total radioactivity.
- The geometric mean whole blood to plasma total radioactivity concentration ratios ranged from 0.85 at 0.25 h to 0.56 at 16 h and appeared to decrease over time.
- Approximately 3.1% of the administered dose was excreted as unchanged in the savolitinib urine and the geometric mean renal clearance was 1.20 L/h.

Safety Conclusions

- Single doses of savolitinib and [^{14}C]savolitinib were well tolerated in 8 healthy male subjects.
- There were no deaths, SAEs or AEs leading to withdrawal reported during the study.
- All AEs were reported as mild in severity and the majority of which were not related to the IMP.
- There were no significant clinical laboratory, vital signs or ECG results.

Date of Report: 16 Aug 2021