2 STUDY SYNOPSIS

Name of Sponsor/Company:	Name of Study Treatment:	Name of Active Ingredient:
AstraZeneca AB	[^{14}C]AZD9833	AZD9833

Title of Study: A Randomised, Open-Label Study to Determine the Relative Bioavailability of Different Oral AZD9833 Tablet Formulations and an AZD9833 Oral Solution, the Effect of Food on the Pharmacokinetics of an Oral AZD9833 Tablet Formulation, and the Absolute Bioavailability of AZD9833 Following Co-Administration of an Oral AZD9833 Tablet Formulation with a Single Radiolabelled Intravenous Microdose of [^{14}C]AZD9833, in Healthy Post-Menopausal Female Subjects at Two Dose Levels

Principal Investigator: PPD

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Publication (Reference): None

Studied Period 17 Sep 2020 to 07 Jan 2021

Phase of Development: I

Objectives:

The primary objectives of the study were:

- To determine the relative bioavailability of AZD9833 following single dose oral administration of AZD9833 tablet formulations at 2 different dose levels and an oral solution formulation at 1 dose level, in the fasted state
- To determine the relative bioavailability of AZD9833 following single dose oral administration of an AZD9833 late phase studies tablet administered in the fed and fasted state at 2 different dose levels

The secondary objectives of the study were:

- To determine the absolute bioavailability of AZD9833 following single dose oral administration of an AZD9833 late phase studies tablet co-administered with a single radiolabelled intravenous (IV) microdose of carbon-14 [^{14}C]AZD9833
- To provide additional safety and tolerability information for oral AZD9833 formulations

The exploratory objective of the study was:

- To explore the relationship between exposure and pharmacokinetic (PK) parameters and properties of the active pharmaceutical ingredient and/or formulation. This work is reported separately to the clinical study report

Methodology:

This was a single centre, open-label, randomised, single dose study in healthy post-menopausal female subjects. It was planned to enrol 32 subjects into 4 cohorts of 8 subjects per cohort. Subjects in Cohorts 1 and 2 received a total of 4 administrations of the 75 mg dose level, and subjects in Cohorts 3 and 4 received a total of 3 administrations of the 300 mg dose level. Subjects received either a single oral dose of AZD9833 on up to 4 separate occasions, in either the fed or fasted state. It was planned that for half the subjects, on 1 fasted dosing occasion, the oral dose would be co-administered with a radiolabelled IV microdose of [^{14}C]AZD9833, however due to an IV batch failure 2 subjects did not receive the IV microdose as scheduled. There was a minimum 7-day washout between periods.

Number of Subjects (Planned and Analysed):

A total of 32 subjects were enrolled and treated in the study as planned, and 29 subjects completed the study. Three (9.4%) subjects withdrew from the study, PPD and 2 (6.3%) subjects randomised to 75 mg AZD9833 were withdrawn due to adverse events (AEs) considered to be not related to the investigational medicinal product (IMP).

All 32 subjects were included in the safety analysis and PK analysis sets. In addition, a PK analysis subset was defined which included all the subjects in the PK analysis set with the exception of PPD (300 mg AZD9833 film-coated tablet [late phase] + 100 µg [14C]AZD9833 Solution for Infusion). Consequently, the subject did not complete at least one of the relevant test and reference comparisons. The PK analysis subset was used for formal statistical analysis of PK parameters.

Diagnosis and Main Criteria for Inclusion:

Healthy post-menopausal females between 50 and 70 years of age with a body mass index between 19.0 and 35.0 kg/m^2 and minimum weight 50 kg and maximum weight 100 kg, as measured at screening.

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

The subjects received the following test IMPs in the fasted/fed state:

Regimen	IMP Dose and Prandial State	Route of Administration	AZ Batch Number	Quotient Batch Numbers
A	100 µg (5 mL of 20 µg/mL [^{14}C]AZD9833 Solution for Infusion [NMT 22.8 kBq])[a]	IV administration, fasted	N/A	CCI , CCI , CCI , CCI , CCI , CCI , CCI
B	75 mg (3×25 mg) - AZD9833 film-coated tablet 25 mg (RC) (Phase 1)	Oral administration, fasted	L012922	CCI
C	75 mg (50 mL of 1.5 mg/mL) AZD9833 Oral Solution	Oral administration, fasted	N/A	CCI , CCI , CCI , CCI , CCI , CCI , CCI , CCI , CCI , CCI
D	75 mg (3×25 mg) - AZD9833 film-coated tablet 25 mg (DC) (late phase)	Oral administration, fasted	L014077	CCI
E	75 mg (3×25 mg) - AZD9833 film-coated tablet 25 mg (DC) (late phase)	Oral administration, fed	L014077	CCI
F	300 mg (3×100 mg) - AZD9833 film-coated tablet 100 mg (RC) (Phase 1)	Oral administration, fasted	L012923	CCI
G	300 mg (2×150 mg) - AZD9833 film-coated tablet 150 mg (DC) (late phase)	Oral administration, fasted	L014078	CCI
H	300 mg (2×150 mg) - AZD9833 film-coated tablet 150 mg (DC) (late phase)	Oral administration, fed	L014078	CCI

DC: direct compression, IMP: investigational medicinal product, NMT: not more than, RC: roller compaction

[a] [^{14}C]AZD9833 IV microtracer was administered as a 15 min infusion starting 2 h 45 min post-oral dosing and finishing at around the predicted tmax (3 h)

A total of 240 mL of water was given 1 h following oral administration.

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

Not applicable.

Duration of Treatment:

Subjects received a total of up to 4 administrations as either a single oral dose of AZD9833 on up to 4 separate occasions, or as a single oral dose of AZD9833 on 3 occasions and a single oral dose of AZD9833 co-administered with a single radiolabelled IV microdose of [^{14}C]AZD9833 on 1 occasion.

Subjects had a follow-up phone call 5 to 7 days after the final dose.

Criteria for Evaluation:

Pharmacokinetics

The following PK parameters for plasma concentrations of AZD9833 and [^{14}C]AZD9833 were estimated where possible and appropriate for each subject and regimen by non-compartmental analysis methods using Phoenix® WinNonlin® software (v8.0, Certara USA, Inc., USA):

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-t}	The area under the concentration-time curve from dosing to the last measurable concentration
AUC_{0-inf}	The area under the concentration-time curve from dosing 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	Total body clearance calculated after a single IV administration (IV dose only)
CL/F	Total body clearance calculated after a single extravascular administration where F (fraction of dose bioavailable) is unknown (oral dose only)
V_z	Volume of distribution based on the terminal phase calculated using AUC_{0-inf} after a single IV administration (IV dose only)
V_z/F	Apparent volume of distribution based on the terminal phase calculated using AUC_{0-inf} after a single extravascular administration where F (fraction of dose bioavailable) is unknown (oral dose only)
MRT_{0-t}	Mean residence time from time 0 to time of the last measurable concentration
MRT_{0-inf}	Mean residence time extrapolated to infinity
F AUC_{0-t}	Absolute bioavailability based on AUC_{0-t}
F AUC_{0-inf}	Absolute bioavailability based on AUC_{0-inf}
F_{rel} C_{max}	Relative bioavailability based on C_{max}
F_{rel} AUC_{0-t}	Relative bioavailability based on AUC_{0-t}
F_{rel} AUC_{0-inf}	Relative bioavailability based on AUC_{0-inf}

Safety

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

Statistical Methods:

Formal statistical analysis was performed on the PK parameters C_{max}, AUC_{0-t} and AUC to assess the relative bioavailability and food effect of AZD9833 for 2 separate dose levels. The PK parameters underwent a natural logarithmic transformation and were analysed using mixed effect modelling techniques. The model included terms for treatment (ie regimen), period and sequence fitted as fixed effects and subject within sequence fitted as a random effect.

Summary – Conclusions:

Pharmacokinetic Results

Relative Bioavailability in the Fasted State

Geometric mean (geometric coefficient of variation [CV%]) plasma PK parameters for AZD9833 following single oral doses of AZD9833 to healthy post-menopausal female subjects, in the fasted state, are summarised in the following table:

Regimen Treatment Dose (mg)	B Phase 1 tablet (fasted) 75 mg N=15	C Oral solution (fasted) 75 mg N=15	D Late Phase tablet (fasted) 75 mg N= 15	F Phase 1 tablet (fasted) 300 mg N=15	G Late Phase tablet (fasted) 300 mg N=16
Parameter					
t_{max}[a] (h)	6.000 (2.00-6.20)	6.000 (2.00-6.22)	4.000 (2.00-6.04)	2.007 (2.00-8.00)	4.000 (2.02-6.00)
C_{max} (ng/mL)	32.2 (34.2)	34.3 (39.6)	30.6 (44.1)	184 (22.8)	182 (18.4)
AUC_{0-t} (ng h/mL)	611 (39.2)	620 (33.6)	568 (34.0)	2980 (21.4)	2950 (18.6) [n=15]
AUC (ng h/mL)	671 (40.4)	688 (36.9)	636 (35.1)	3180 (22.2)	3190 (19.2) [n=15]
$t_{1/2}$ (h)	21.440 (15.0)	22.245 (32.6)	23.335 (18.3)	19.460 (12.2)	21.111 (17.6) [n=15]
λ_z (1/h)	0.03233 (15.0)	0.03116 (32.6)	0.02970 (18.3)	0.03562 (12.2)	0.03283 (17.6) [n=15]
CL/F (L/h)	112 (40.4)	109 (36.9)	118 (35.1)	94.3 (22.2)	94.1 (19.2) [n=15]
V_z/F (L)	3460 (35.0)	3500 (31.6)	3970 (34.5)	2650 (22.0)	2870 (21.1) [n=15]
MRT_{0-t} (h)	21.011 (6.9)	21.018 (6.8)	21.208 (6.7)	18.709 (8.3)	18.807 (8.9) [n=15]
MRT (h)	28.341 (12.4)	29.372 (14.8)	29.977 (15.0)	23.795 (13.7)	24.894 (14.9) [n=15]
F_{rel} vs Phase 1 tablet C_{max} (%)	NA	NA	99.016 (23.5) [n=14]	NA	97.174 (18.9) [n=15]
F_{rel} vs Phase 1 tablet AUC_{0-t} (%)	NA	NA	95.731 (10.9) [n=14]	NA	99.077 (11.0) [n=15]
F_{rel} vs Phase 1 tablet AUC (%)	NA	NA	97.264 (10.6) [n=14]	NA	100.173 (10.5) [n=15]
F_{rel} vs Oral solution C_{max} (%)	97.595 (36.0) [n=14]	NA	95.031 (36.2) [n=14]	NA	NA
F_{rel} vs Oral Solution AUC_{0-t} (%)	102.422 (13.2) [n=14]	NA	98.270 (11.8) [n=14]	NA	NA

Regimen Treatment Dose (mg)	B Phase 1 tablet (fasted) 75 mg N=15	C Oral solution (fasted) 75 mg N=15	D Late Phase tablet (fasted) 75 mg N= 15	F Phase 1 tablet (fasted) 300 mg N=15	G Late Phase tablet (fasted) 300 mg N=16
Parameter					
F_{rel} vs Oral Solution AUC (%)	101.498 (13.4) [n=14]	NA	99.252 (12.6) [n=14]	NA	NA

%CV = coefficient of variation; N = number of subjects in the dataset, unless otherwise stated;
n = number of subjects with an observation; NA = not applicable
a Median (range)

When dosed in the fasted state, plasma concentrations of AZD9833 were evident from the first sampling timepoint (0.5 h) for all subjects for all regimens (unless there was evidence of carryover and in those cases quantifiable pre-dose concentrations represented <5% of the corresponding C_{max} result).

Following administration of AZD9833 at 75 mg in the late phase tablet formulation in the fasted state (Regimen D), median t_{max} was 4 h compared with 6 h for the Phase 1 tablet and oral solution. At the 300 mg dose level, the median t_{max} occurred later for the late phase tablet (4 h) compared with Phase 1 tablet (2 h).

The geometric mean $t_{1/2}$ estimates were similar across all formulations and dose levels with geometric mean values ranging from 19.460 h to 23.335 h.

Exposure was similar when comparing the late phase tablet with the Phase 1 tablet. Geometric mean relative bioavailability (F_{rel}), based on C_{max}, AUC_{0-t} and AUC was 98.74% (87.42, 111.53), 95.71% (90.93%, 100.73%) and 97.41% (92.59%, 102.48%) at the 75 mg level, respectively and 96.64% (86.88%, 107.50%), 99.33% (94.80%, 104.08%) and 100.42% (96.16%, 104.88%) at the 300 mg dose level, respectively.

Systemic exposure to AZD9833 following administration of Phase 1 tablets was similar to the oral solution at the 75 mg dose level with geometric mean F_{rel} C_{max}, F_{rel} AUC_{0-t} and F_{rel} AUC estimates of 97.47% (86.30%, 110.09%), 103.02% (97.88%, 108.43%) and 102.11% (97.05%, 107.42%), respectively.

When comparing the late phase tablet with the oral solution, at the 75 mg level in the fasted state, geometric mean relative bioavailability (F_{rel}) indicated that systemic exposure was similar with values of 96.24% (85.25%, 108.65%), 98.59% (93.69%, 103.75%) and 99.46% (94.56%, 104.61%), based on C_{max}, AUC_{0-t} and AUC, respectively.

Relative Bioavailability in the Fed State

Geometric mean (geometric CV%) plasma PK parameters for AZD9833 following single oral doses of AZD9833 to healthy post-menopausal female subjects, as a late phase tablet, in the fed and fasted state are summarised in the following table.

Regimen Treatment Dose (mg) N	D Late phase tablet (fasted) 75 mg N= 15	E Late phase tablet (fed) 75 mg N=16	G Late phase tablet (fasted) 300 mg N=16	H Late phase tablet (fed) 300 mg N=15
Parameter				
t_{max}[a] (h)	4.000 (2.00-6.04)	4.001 (1.00-10.00)	4.000 (2.02-6.00)	3.016 (2.00-6.00)
C_{max} (ng/mL)	30.6 (44.1)	33.7 (39.6)	182 (18.4)	208 (19.0)
AUC_{0-t} (ng.h/mL)	568 (34.0)	655 (36.3)	2950 (18.6) [n=15]	3070 (18.7)
AUC (ng h/mL)	636 (35.1)	699 (35.1) [n=15]	3190 (19.2) [n=15]	3280 (19.8)
$t_{1/2}$ (h)	23.335 (18.3)	23.215 (25.1)	21.111 (17.6) [n=15]	19.614 (17.9)
λ_z (1/h)	0.02970 (18.3)	0.02986 (25.1)	0.03283 (17.6) [n=15]	0.03534 (17.9)
CL/F (L/h)	118 (35.1)	107 (35.1) [n=15]	94.1 (19.2) [n=15]	91.6 (19.8)
V_z/F (L)	3970 (34.5)	3430 (36.4) [n=15]	2870 (21.1) [n=15]	2590 (24.3)
MRT_{0-t} (h)	21.208 (6.7)	21.110 (6.5)	18.807 (8.9) [n=15]	18.365 (9.5)
MRT (h)	29.977 (15.0)	29.000 (11.9) [n=15]	24.894 (14.9) [n=15]	23.557 (14.0)
$F_{rel}C_{max}$ (%)	NA	104.677 (20.9) [n=15]	NA	115.895 (21.8)
F_{rel} AUC_{0-t} (%)	NA	110.198 (10.1) [n=15]	NA	103.939 (12.2)
F_{rel} AUC(%)	NA	109.099 (9.7) [n=14]	NA	102.800 (10.8)

%CV = coefficient of variation; F_{rel} = relative bioavailability based on AZD9833 late phase tablet (fed) vs late phase tablet (fasted); N = number of subjects in the dataset, unless otherwise stated; n = number of subjects with an observation; NA = not applicable

[a] Median (range)

Following administration of the late phase tablet in the fed state at 75 mg and 300 mg (Regimen E and Regimen H), median t_{max} were similar, ranging from 3.016 to 4.001 h. Terminal elimination $t_{1/2}$ estimates were similar in fed and fasted states, with geometric mean values of 23.215 h and 19.614 h for the 75 mg and 300 mg doses in the fed state, respectively, and 23.335 h and 21.111 h for the 75 mg and 300 mg doses, respectively, in the fasted state.

Statistical Analysis

Geometric mean and 90% confidence intervals (CIs) for the ratio of each pairwise comparison for AZD9833 are presented in the following table.

		Test			Reference				
PK Parameter	**Comparison (Test vs Reference)**	**n**	**Adj Geo Mean**	**90% CI of Adj Geo Mean**	**n**	**Adj Geo Mean**	**90% CI of Adj Geo Mean**	**Point Estimate of geometric mean ratio of Test vs Reference**	**90% CI of geometric mean ratio of Test vs Reference**
C_{max} (ng/mL)	75 mg late phase fasted vs 75 mg Phase 1 fasted	15	31.7	(27.2, 37.0)	15	32.1	(27.5, 37.5)	98.74	(87.42, 111.53)
AUC_{0-t} (ng h/mL)		15	591	(514, 680)	15	617	(537, 710)	95.71	(90.93, 100.73)
AUC (ng h/mL)		15	662	(571, 768)	15	680	(586, 788)	97.41	(92.59, 102.48)
C_{max} (ng/mL)	75 mg Phase 1 fasted vs 75 mg solution fasted	15	32.1	(27.5, 37.5)	15	33.0	(28.3, 38.4)	97.47	(86.30, 110.09)
AUC_{0-t} (ng h/mL)		15	617	(537, 710)	15	599	(521, 690)	103.02	(97.88, 108.43)
AUC (ng h/mL)		15	680	(586, 788)	15	666	(574, 772)	102.11	(97.05, 107.42)
C_{max} (ng/mL)	75 mg late phase fasted vs 75 mg solution fasted	15	31.7	(27.2, 37.0)	15	33.0	(28.3, 38.4)	96.24	(85.25, 108.65)
AUC_{0-t} (ng h/mL)		15	591	(514, 680)	15	599	(521, 690)	98.59	(93.69, 103.75)
AUC (ng h/mL)		15	662	(571, 768)	15	666	(574, 772)	99.46	(94.56, 104.61)
C_{max} (ng/mL)	75 mg late phase fed vs 75 mg late phase fasted	16	33.7	(28.9, 39.2)	15	31.7	(27.2, 37.0)	106.24	(94.33, 119.65)
AUC_{0-t} (ng h/mL)		16	655	(569, 754)	15	591	(514, 680)	110.86	(105.46, 116.54)
AUC (ng h/mL)		15	727	(627, 843)	15	662	(571, 768)	109.79	(104.36, 115.50)
C_{max} (ng/mL)	300 mg late phase fasted vs 300 mg Phase 1 fasted	15	182	(165, 200)	15	188	(171, 207)	96.64	(86.88, 107.50)
AUC_{0-t} (ng h/mL)		15	3000	(2660, 3380)	15	3020	(2680, 3400)	99.33	(94.80, 104.08)
AUC (ng h/mL)		15	3240	(2860, 3670)	15	3230	(2850, 3650)	100.42	(96.16, 104.88)
C_{max} (ng/mL)	300 mg late phase fed vs 300 mg late phase fasted	15	211	(192, 231)	15	182	(165, 200)	115.89	(104.33, 128.72)
AUC_{0-t} (ng h/mL)		15	3100	(2750, 3490)	15	3000	(2660, 3380)	103.39	(98.74, 108.27)
AUC (ng h/mL)		15	3320	(2930, 3750)	15	3240	(2860, 3670)	102.29	(98.00, 106.76)

Adj geo mean = adjusted geometric mean from model; CI = confidence interval; PK = pharmacokinetic

At both 75 mg and 300 mg the exposures were similar between the fed and fasted treatments. The fed to fasted geometric mean ratios (GMRs; 90% CI) for C_{max}, AUC_{0-t} and AUC were 106.24% (94.33%, 119.65%), 110.86% (105.46%, 116.54%) and 109.79% (104.36%, 115.50%), respectively, for 75 mg. At 300 mg the fed to fasted GMRs (90% CI) for C_{max},

AUC_{0-t} and AUC were 115.89% (90% CI; 104.33%, 128.72%), 103.39% (98.74%, 108.27%) and 102.29% (98.00%, 106.76%), respectively.

Absolute Bioavailability

Geometric mean (geometric CV%) plasma PK parameters for AZD9833 following single IV doses of [^{14}C]AZD9833 co-administered with a single oral dose of AZD9833 to healthy post-menopausal female subjects are shown in the following table.

Regimen **Treatment** **Dose** **N**	**A** **100 µg [^{14}C] IV fasted** **(+ Regimen D)** **100 µg** **N=6**	**D** **Late Phase tablet (fasted)** **75 mg** **N= 15**	**A** **100 µg [^{14}C] IV fasted** **(+Regimen G)** **100 µg** **N=7**	**G** **Late Phase tablet (fasted)** **300 mg** **N=16**
Parameter				
t_{max}[a] (h)	0.253 (0.10-0.33)	4.000 (2.00-6.04)	0.250 (0.08-0.25)	4.000 (2.02-6.00)
C_{max} (pg*/mL)	866 (54.2)	30.6 (44.1)	863 (45.8)	182 (18.4)
AUC_{0-t} (pg* h/mL)	1740 (29.0)	568 (34.0)	1700 (19.2) [n=6]	2950 (18.6) [n=15]
AUC (pg*.h/mL)	1950 (29.2)	636 (35.1)	1900 (18.3) [n=6]	3190 (19.2) [n=15]
$t_{1/2}$ (h)	19.332 (24.9)	23.335 (18.3)	16.275 (38.7) [n=6]	21.111 (17.6) [n=15]
λ_z (1/h)	0.03586 (24.9)	0.02970 (18.3)	0.04259 (38.7) [n=6]	0.03283 (17.6) [n=15]
CL[1] (L/h)	51.4 (29.2)	118 (35.1)	52.6 (18.3) [n=6]	94.1 (19.2) [n=15]
V_z[2] (L)	1430 (15.6)	3970 (34.5)	1240 (40.2) [n=6]	2870 (21.1) [n=15]
MRT_{0-t} (h)	15.8 (21.8)	21.208 (6.7)	13.9 (20.6) [n=6]	18.807 (8.9) [n=15]
MRT (h)	23.6 (18.4)	29.977 (15.0)	20.5 (28.9) [n=6]	24.894 (14.9) [n=15]
F AUC_{0-t} (%) [b]	NA	42.680 (37.7, 48.3) [n=6]	NA	56.891 (50.9, 63.6) [n=6]
F AUC(%) [b]	NA	42.5 (36.8, 49.0) [n=6]	NA	55.1 (48.5, 62.5) [n=6]

%CV = coefficient of variation; F = absolute bioavailability; N = number of subjects in the dataset, unless otherwise stated; n = number of subjects with an observation; NA = not applicable

[a] Median (range)

[b] Geometric mean (90% CI)

[*]ng for the oral doses (Regimen D and Regimen G); [1]CL/F for oral doses; [2]V_z/F for oral doses

Following a single 15 minute IV infusion of 100 µg [^{14}C]-AZD9833 (Regimen A), concentrations were evident from the first sampling time point in all subjects. Median t_{max} was noted at the end of infusion (0.253 h and 0.250 h) for Regimen D+A and Regimen G+A; with individual values ranging from 0.08 to 0.33 h post-start of infusion.

The geometric mean $t_{1/2}$ following IV infusion for Regimen A+D was 19.332 h, for Regimen G+A, the geometric mean $t_{1/2}$ was 16.275 h. The $t_{1/2}$ was slightly shorter when dosed as an IV infusion (19.332 h and 16.275 h) compared with the oral dose (23.335 h and 21.111 h) at the 75 mg and 300 mg dose levels, respectively.

Absolute bioavailability of AZD9833, based on AUC_{0-t} and AUC, following the 75 mg oral late phase tablet dose was 43%. When the dose increased to 300 mg the bioavailability increased to 57% and 55% based on AUC_{0-t} and AUC, respectively.

Safety Results

Single oral 75 mg and 300 mg doses of AZD9833, with or without a radiolabelled IV microdose of [^{14}C]AZD9833, were well tolerated in healthy female subjects and there were no severe or serious AEs or deaths.

Two subjects experienced AEs which led to discontinuation of IMP, both following 75 mg AZD9833 administration; neither of these AEs were considered related to IMP.

Overall, more subjects reported AEs that were assessed as possibly related to IMP for the 300 mg dose compared with the 75 mg dose (13 [81.3%] and 7 [43.8%] subjects, respectively). The possibly related AE with the highest incidence was PPD, reported in 7 (43.8%) subjects in the 300 mg dosing group overall (compared with 2 [12.5%] subjects in the 75 mg dosing group overall). This was followed by PPD, reported in 5 (31.3%) subjects in the 75 mg dosing group overall (compared with 1 [6.3%] subject in the 300 mg dose group overall), and by PPD, reported in 4 (25.0%) subjects in the 300 mg dose group overall (compared with 1 [6.3%] subject in the 75 mg dose group overall). All other possibly related AEs were reported by 1 (6.3%) subject in each dose group PPD, or 1 subject overall (PPD [75 mg dose group overall], PPD and PPD [300 mg dose group overall]). There were no clinically important clinical laboratory, vital signs, ECGs or physical examination findings considered possibly related to IMP.

Conclusions

- At the 75 mg dose, the median t_{max} for the late phase tablet (4 h) occurred slightly earlier than for the Phase 1 tablet (6 h) and oral solution (6 h).
- At the 300 mg dose level, the median t_{max} occurred later for the late phase tablet (4 h) compared to Phase 1 tablet (2 h)
- Systemic exposure to AZD9833 was similar for the late phase tablet and the Phase 1 tablet at the 75 mg and 300 mg dose
- At 75 mg dose, the C_{max} and AUC values for AZD9833 for the late phase tablet and the Phase 1 tablet were similar to those for the oral solution.
- At both 75 mg and 300 mg the exposures were similar between the fed and fasted treatments. The fed to fasted point estimates of the GMRs (90% CI) for C_{max}, AUC_{0-t} and AUC were 106.24% (94.33%, 119.65%), 110.86% (105.46%, 116.54%) and 109.79% (104.36%, 115.50%), respectively, for 75 mg. At 300 mg the fed to fasted point estimates of the GMRs (90% CI) for C_{max}, AUC_{0-t} and AUC were 115.89% (90% CI; 104.33%, 128.72%), 103.39% (98.74%, 108.27%) and 102.29% (98.00%, 106.76%), respectively.
- AZD9833 was well tolerated by healthy subjects; no new safety concerns were identified in this trial.
- There were no severe or serious AEs or deaths and no early withdrawals due to IMP related AEs
- Overall, 11 (68.8%) and 14 (87.5%) subjects reported AEs in the 75 mg AZD9833 and 300 mg AZD9833 dose groups, of which 7 (43.8%) and 13 (81.3%) subjects reported AEs that were assessed as possibly related to the IMP, respectively.

- All AEs assessed as possibly related to IMP were mild in intensity.
- There were no clinically important clinical laboratory, vital signs, ECG or physical examination findings considered possibly related to IMP.

Date of Report: 09 Aug 2021