Clinical Study Report Synopsis	
Drug Substance	Osimertinib
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An Open-label, Non-randomised, Multicentre, Phase I Study to Assess the Pharmacokinetics, Safety and Tolerability of Osimertinib (TAGRISSO™)[1] Following a Single Oral 80 mg Dose to Patients with Advanced Solid Tumours and Normal Renal Function or Severe Renal Impairment

Study dates: First patient enrolled: 04 May 2017
Last patient last visit (Part A): 20 September 2018
Last patient last visit (Part B): 10 May 2018

Phase of development: Clinical pharmacology (I)

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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

[1] TAGRISSO is a trade name of the AstraZeneca group of companies.

Study centre(s)

This study was conducted at 10 sites in 2 countries in Europe (6 sites in France [1 site did not screen any patients] and 4 sites in Spain) and at 2 sites in 1 country in Asia (2 sites in South Korea).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	PK (Part A)	To investigate the PK of osimertinib after a single oral dose of 80 mg in patients with advanced solid tumours and normal renal function or severe renal impairment.	C_{max} and AUC for osimertinib
Secondary	PK (Part A)	To investigate the PK of osimertinib and metabolites (AZ5104 and AZ7550) after a single oral dose of 80 mg in patients with advanced solid tumours and normal renal function or severe renal impairment.	AUC_{0-t}, AUC_{0-24}, t_{max}, CL/F, Vz/F, λz, $t_{½λz}$, A_{e0-24} and CL_R for osimertinib. C_{max}, t_{max}, AUC, AUC_{0-t}, AUC_{0-24}, λz, $t_{½λz}$, A_{e0-24} and CL_R for AZ5104 and AZ7550 as well as metabolite to parent ratios for C_{max} and AUC.
Secondary	Safety (Part A)	To investigate the safety and tolerability of a single oral dose of osimertinib in patients with advanced solid tumours and normal renal function or severe renal impairment.	Adverse events, graded by the National Cancer Institute CTCAE v4.0, physical examination, vital signs (blood pressure, pulse, temperature, height, weight), standard 12-lead ECG and evaluation of laboratory parameters (haematology, coagulation, clinical chemistry and urinalysis), ophthalmology, ECHO/MUGA.

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Secondary	Safety (Part B)	To investigate the safety and tolerability of multiple oral doses of osimertinib in patients with advanced solid tumours and severe renal impairment.	Adverse events, graded by CTCAE v4.0, physical examination, vital signs (blood pressure, pulse, temperature, height, weight), standard 12-lead ECG and evaluation of laboratory parameters (haematology, clinical chemistry and urinalysis) ophthalmology, ECHO/MUGA.
Exploratory	PK (Part A)	To explore changes in protein binding of osimertinib (and metabolites AZ5104 and AZ7550) and the subsequent effects on its PK in patients with severe renal impairment.	f_u, $C_{max,u}$, and AUC_u (and/or $AUC_{0-t,u}$) for osimertinib, AZ5104 and AZ7550; CL/F_u for osimertinib.[a]
Exploratory	PK (Part A)	To provide data to allow analysis using population PK approaches.	None defined. The results of any exploratory research will be reported separately and are not included in this CSR.
Exploratory	Pharmacogenetic (Part A)[b]	To collect and store a pharmacogenetics blood sample for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to osimertinib.	None defined. The results of any exploratory research will be reported separately and are not included in this CSR.

[a] Since concentrations of osimertinib and its metabolites (AZ5104 and AZ7550) were not quantifiable in any of plasma ultrafiltrate samples, the unbound parameters described above could not be calculated.

[b] Participation in the pharmacogenetic part of the study was optional.

A_{e0-24}, amount excreted in urine from time zero to 24 hours postdose; AUC area under the plasma concentration-time curve from zero to infinity; AUC_{0-24}, area under the plasma concentration-time curve from zero to 24 hours; AUC_{0-t} area under the plasma concentration-time curve from zero to the last quantifiable time point; AUC_u AUC of unbound analytes; CL/F apparent clearance following oral administration; CL/F_u apparent plasma clearance of unbound osimertinib following oral administration; CL_R renal clearance; C_{max} maximum plasma drugconcentration; $C_{max,u}$ maximum unbound plasma drugconcentration; CSP Clinical study protocol; CSR Clinical study report; CTCAE Common Terminology Criteria for Adverse Events; ECHO echocardiogram; ECG electrocardiogram; f_u fraction of analyte unbound; PK pharmacokinetic; SAP statistical analysis plan; $t_{½\lambda z}$ terminal half-life; t_{max} time to reach maximum plasma concentration; Vz/F apparent volume of distribution; λ_z terminal rate constant.

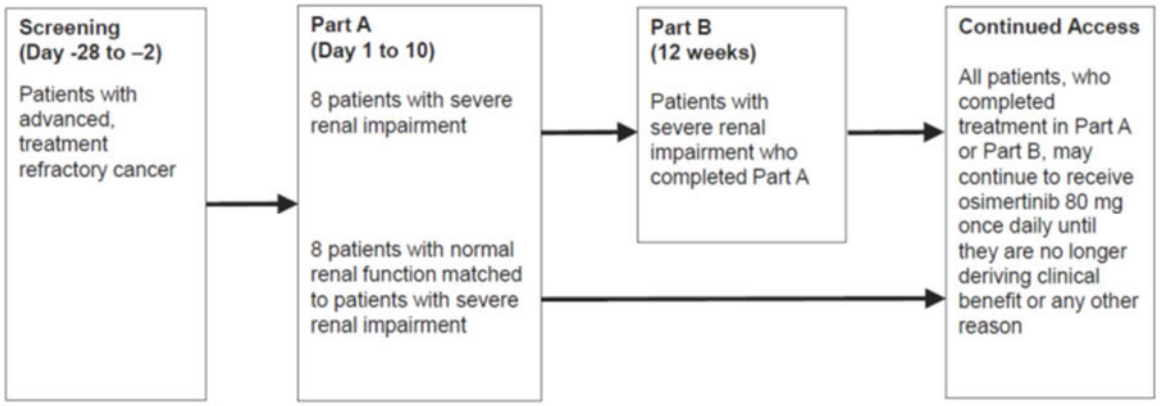
Study design

This was a Phase I, open-label, non-randomised 3-part study (Part A, Part B and continued access) in patients with advanced solid tumours. Part A investigated the pharmacokinetics

(PK) of a single 80 mg oral dose of osimertinib in patients with severe renal impairment compared with patients with normal renal function. Patients with severe renal impairment who completed Part A entered Part B where they received osimertinib 80 mg oral once daily for 12 weeks. Part B allowed patients to continue to receive osimertinib after the PK phase (Part A) and provided additional safety data. At the end of Part B, those patients with severe renal impairment who were deemed to have gained clinical benefit from osimertinib, as per the Investigator, entered the continued access phase. Patients with normal renal function could enter the continued access phase immediately after completing Part A. During the continued access phase, patients could continue to take osimertinib 80 mg once daily, if they and the Investigator deemed it appropriate, until the Investigator believed they were no longer deriving clinical benefit or they stopped taking osimertinib for any other reason. Data from the continued access phase of the study are not reported in this Clinical Study Report.

Figure S1 shows the design of the study and the sequence of treatment periods.

Figure S1 Flow chart of study design



Target patient population and sample size

The target population was adult patients with advanced solid tumours that were refractory to standard therapies or for which no standard therapies exist, and either severe renal impairment (creatinine clearance [CrCl] <30 mL/min at screening) or normal renal function (CrCl ≥90 mL/min at screening). To allow for completion of at least 6 evaluable patients per renal function group (severe impairment and normal), a total of 8 patients per renal function group were planned to be enrolled.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Osimertinib 80 mg oral tablets CCI and 40 mg oral tablets CCI A 40 mg tablet was provided if dose reduction was necessary in Part B.

Duration of treatment

In Part A, patients were to receive a single oral dose of osimertinib 80 mg on Day 1. Patients participating in Part B and the continued access phase were to receive continuous oral dosing of osimertinib 80 mg once daily for the duration of their participation, until the Investigator believed they were no longer deriving clinical benefit or they stopped taking osimertinib for any other reason.

Statistical methods

Pharmacokinetic: To assess the effect of renal impairment on the PK of osimertinib (primary) and metabolites (AZ5104 and AZ7550: secondary), natural log-transformed maximum plasma drug concentration (C_{max}), area under plasma concentration-time curve from zero to infinity (AUC), and area under the plasma concentration-time curve from zero to the last quantifiable time point (AUC_{0-t}) were compared between renal function groups (severe versus normal) separately for osimertinib and each metabolite using an analysis of variance (ANOVA) model, with renal function group as a fixed effect.

Estimates of the mean difference between renal function groups (severe – normal) and corresponding 90% confidence intervals (CIs) were calculated. The mean differences and the CIs were back-transformed to the original scale in order to give estimates of the ratios (severe versus normal) and the associated 90% CIs. Additionally, back-transformed geometric means together with 95% CIs for AUC and C_{max} were estimated and presented for each renal function group.

For osimertinib and its metabolites, the relationships between CrCl collected on Day -1 and natural log-transformed PK parameters AUC and C_{max}, were assessed using a regression model with CrCl value included as the independent variable and PK parameter as the dependent variable. Slopes, intercepts and the associated 90% CIs were presented along with the coefficient of determination.

Safety: Safety data were listed and summarised using descriptive statistics.

Patient population

Overall, 26 patients were consented for screening. Of these, 16 patients were assigned to treatment from centres in Spain (8 patients from 4 centres), France (6 patients from 4 centres) and Korea (2 patients from 1 centre): 9 patients were assigned to the normal renal function group and 7 assigned to the severe renal impairment group based on their screening CrCl. Of the 9 patients assigned to the normal renal function group, 1 patient had an 80 mL/min CrCl at screening (site calculated CrCl with corrected Cockcroft-Cault formula instead of the Cockcroft-Gault formula specified in the clinical study protocol).

The safety analysis set for Part A included all 16 patients who received at least 1 dose of osimertinib. As mild renal impairment has no effect on osimertinib, the patient with mild renal impairment has been included in the normal group for summaries of demographics and safety results.

The PK analysis set in Part A included 15 patients who received at least 1 dose of osimertinib and had at least 1 postdose quantifiable plasma osimertinib or metabolite concentration without important protocol deviations/violations or events thought to significantly affect the PK of osimertinib. The patient with mild renal impairment was excluded from all categorical (ie, by renal function group) statistical analyses.

The safety analysis set for Part B included all 6 patients who received at least 1 dose of osimertinib in Part B.

All 16 patients completed Part A. The 9 patients in the normal renal function group terminated the study at the end of Part A, as per protocol: 7 patients entered continued access, 1 patient died due to disease under investigation and 1 patient had progressive disease. One patient in the severe renal impairment group terminated the study at the end of Part A due to physician decision; the remaining 6 patients were ongoing into Part B.

All 6 patients in the severe renal impairment group who entered Part B received treatment. Three patients completed treatment and entered continued access. The remaining 3 patients discontinued treatment due to an adverse event (1 patient), condition under investigation worsened (1 patient) and subjective disease progression (1 patient).

The demographics of patients with normal renal function were to be matched as closely as possible to the age, sex and body mass index of patients with severe renal impairment. All patients in the normal renal function group were appropriate matched controls.

Demographics, disease characteristics and concomitant medications of the patients were representative of the intended patient population for this study, within the protocol eligibility criteria.

Summary of pharmacokinetic results

Osimertinib

Statistical comparisons of osimertinib exposure parameters (C_{max} and AUC) in patients in the PK analysis set are summarised in Table S2.

Osimertinib exposure, based on C_{max} and AUC, was 1.19-fold and 1.85-fold, respectively, for severe renal impaired patients relative to patients with normal renal function. However, the 90% CIs were wide and included unity.

Table S2 Statistical comparison of key osimertinib pharmacokinetic parameters (Pharmacokinetic analysis set)

Parameter (unit)	Renal Function Group[a]			Comparison of patients with severe renal impairment vs normal patients		
		n	Geometric LS mean	Pair	Ratio (%)	90% CI
AUC (nM*h)	Normal	8	11070			
	Severe	6	20460	Severe vs Normal	184.78	(93.85, 363.80)
C_{max} (nM)	Normal	8	195.5			
	Severe	7	233.4	Severe vs Normal	119.36	(68.88, 206.85)

[a] Normal renal function creatinine clearance (CrCl) ≥90 mL/min at screening; Severe renal impairment CrCl <30 mL/min at screening.

Note: Patient PPD had a CrCl of 80 mL/min at screening and is excluded from this analysis.

Results based on an ANOVA model with a fixed effect for renal function group.

ANOVA analysis of variance; AUC area under plasma concentration-time curve from zero to infinity; C_{max} maximum plasma drug concentration; CI confidence interval; LS least-squares.

Median osimertinib time to reach maximum plasma concentration (t_{max}) was 6.00 hours (range 4.00 to 10.07) hours and 5.03 hours (range 2.00 to 6.05 hours) for patients with severe renal impairment and normal renal function, respectively. Arithmetic mean and standard deviation (SD) osimertinib terminal half-life ($t_{1/2\lambda z}$) was 71.38 (14.81) hours and 49.29 (13.02) hours for patients with severe renal impairment and normal renal function, respectively.

The arithmetic mean (SD) osimertinib apparent plasma clearance (CL/F) was 9.241 (6.079) L/h and 17.87 (10.60) L/h for patients with severe renal impairment and normal renal function, respectively. The arithmetic mean (SD) osimertinib apparent volume of distribution (V_z/F) was 951.3 (581.8) L and 1159 (573.9) L for patients with severe renal impairment and normal renal function, respectively.

The arithmetic mean (SD) renal clearance (CL_R) for osimertinib was low in all patients, 0.09421 (0.07079) L/h and 0.1223 (0.1053) L/h for patients with severe renal impairment and normal renal function, respectively, and represented approximately 1% or less of CL/F. Osimertinib was not quantifiable (NQ) in plasma ultrafiltrate (PUF) (lower limit of quantitation [LLOQ] 0.0500 nM).

Creatinine clearance accounted for less than 18% of the between-patient variability in osimertinib exposure and the slope of the linear regressions of the log-transformed osimertinib exposure parameters versus CrCl were not statistically different from zero (C_{max} p=0.5574, AUC p=0.1151) showing no relationship between osimertinib exposure and CrCl.

AZ5104

Statistical comparisons of AZ5104 exposure parameters (C_{max} and AUC) in patients in the PK analysis set are summarised in Table S3.

AZ5104 exposure based on C_{max} and AUC was approximately 0.86-fold and 1.62-fold, respectively, for severe renal impaired patients relative to patients with normal renal function. However, the 90% CIs were wide and included unity.

Table S3 Statistical comparison of key AZ5104 pharmacokinetic parameters (Pharmacokinetic analysis set)

Parameter (unit)	Renal Function Group[a]	n	Geometric LS mean	Comparison of patients with severe renal impairment vs normal patients		
				Pair	Ratio (%)	90% CI
AUC (nM*h)	Normal	8	1202			
	Severe	5	1953	Severe vs Normal	162.46	(81.51, 323.77)
C_{max} (nM)	Normal	8	10.15			
	Severe	7	8.763	Severe vs Normal	86.32	(49.29, 151.16)

[a] Normal renal function creatinine clearance (CrCl) ≥90 mL/min; Severe renal impairment CrCl <30 mL/min.
Note: Patient PPD had a CrCl of 80 mL/min at screening and is excluded from this analysis.
Results based on an ANOVA model with a fixed effect for renal function group.
ANOVA analysis of variance; AUC area under plasma concentration-time curve from zero to infinity; C_{max} maximum plasma drug concentration; CI confidence interval; LS least-squares.

Geometric mean metabolite to parent ratios for C_{max} and AUC were comparable for patients with severe renal impairment and patients with normal renal function and amounted to less than 11% of exposure to osimertinib.

The arithmetic mean (SD) CL_R for AZ5104 was low in all patients, 0.1408 (0.01780) L/h and 0.5159 (0.4248) L/h for patients with severe renal impairment and normal renal function, respectively. AZ5104 was NQ in PUF (LLOQ 0.0515 nM).

AZ7550

Statistical comparisons of AZ7550 exposure parameters (C_{max} and AUC) in patients in the PK analysis set are summarised in AZ7550 exposure, based on C_{max} and AUC, was approximately 0.57-fold and 0.74-fold, respectively, for severe renal impaired patients relative to patients with normal renal function. The 90% CIs were wide and included unity for AUC but not for C_{max}.

Table S4.

AZ7550 exposure, based on C_{max} and AUC, was approximately 0.57-fold and 0.74-fold, respectively, for severe renal impaired patients relative to patients with normal renal function. The 90% CIs were wide and included unity for AUC but not for C_{max}.

Table S4 Statistical comparison of key AZ7550 pharmacokinetic parameters (Pharmacokinetic analysis set)

Parameter (unit)	Renal Function Group[a]	n	Geometric LS mean	Comparison of patients with severe renal impairment vs normal patients		
				Pair	Ratio (%)	90% CI
AUC (nM*h)	Normal	6	563.0			
	Severe	3	417.7	Severe vs Normal	74.20	(52.98, 103.91)
C_{max} (nM)	Normal	8	4.556			
	Severe	7	2.618	Severe vs Normal	57.46	(36.38, 90.78)

[a] Normal renal function creatinine clearance (CrCl) ≥90 mL/min; Severe renal impairment CrCl <30 mL/min.
Note: Patient PPD had a CrCl of 80 mL/min at screening and is excluded from this analysis.
Results based on an ANOVA model with a fixed effect for renal function group.
ANOVA analysis of variance; AUC area under plasma concentration-time curve from zero to infinity; C_{max} maximum plasma drug concentration; CI confidence interval; LS least-squares.

Metabolite to parent ratios for AZ7550 C_{max} and AUC were lower for patients with severe renal impairment relative to patients with normal renal function; metabolite AUC amounted to less than 2.3% (severe renal impairment) or 8% (normal renal function) of the exposure to osimertinib.

The arithmetic mean (SD) CL_R for AZ7550 was low in all patients, 0.3266 (0.09460) L/h and 0.8580 (0.6490) L/h for patients with severe renal impairment and normal renal function, respectively. AZ7550 was NQ in PUF (LLOQ 0.0515 nM).

Summary of safety results

Part A

In Part A, 7 (43.8%) patients (3 patients in the normal group and 4 patients in the severe renal impairment group) had a total of 20 adverse events (AEs) and 4 (25.0%) patients (2 patients in each group) had at least 1 AE that the Investigator considered as related to osimertinib.

The AEs reported for the greatest number of patients overall were nausea, vomiting and weight decreased (2 patients [12.5%] each); all other AEs were reported singularly.

Two (12.5%) patients (1 patient in each group) had at least 1 AE of CTCAE Grade 3 or higher: hypotension, constipation and hypertension (all Grade 3). The events were all considered as unrelated to osimertinib per the Investigator's assessment.

A total of 2 (12.5%) patients, both in the severe renal impairment group, had an SAE during Part A of the study; both events (rib fracture and hypotension) were considered as unrelated to osimertinib by the Investigator.

There were no AEs resulting in death or discontinuation of osimertinib.

Adverse events of special interest (AESI) PTs were not reported more than once for patients in Part A: diarrhoea, lacrimation increased, eye irritation and nephrolithiasis.

There were no clinically significant findings for clinical laboratory evaluations, vital signs, electrocardiogram (ECGs), left ventricular ejection fraction (LVEF) measurements or physical findings.

Part B

In Part B, 6 (100%) patients had a total of 36 AEs and 3 (50.0%) patients had at least 1 AE that the Investigator considered possibly related to osimertinib.

The AEs reported for the greatest number of patients overall were anaemia (3 patients [50.0%]) and decreased appetite, depression and oedema peripheral (2 patients [33.3%] each).

A total of 4 (66.7%) patients had an AE of CTCAE Grade 3 or higher: asthenia (2 patients), anaemia (2 patients) and renal failure (1 patient). All events were CTCAE Grade 3 and were considered as unrelated to osimertinib by the Investigator.

No AEs resulted in death. One (16.7%) patient had an AE (PT: cardiomyopathy) that led to discontinuation of osimertinib.

A total of 2 (33.3%) patients had an SAE during Part B of the study; the events (dyspnoea and asthenia) were considered as unrelated to osimertinib by the Investigator

Adverse events of special interest (AESI) PTs were not reported more than once for patients in Part B: cardiomyopathy, diarrhoea, paronychia, conjunctivitis, eye irritation, renal failure and mucosal dryness.

There were no clinically significant findings for clinical laboratory evaluations, vital signs, ECGs, LVEF measurements or physical findings.

Conclusion(s)

Part A

- Osimertinib exposure for severe renal impaired patients, based on AUC, was 1.85-fold (90% CI: 0.9385; 3.6380) relative to that of patients with normal renal function with no clear correlation between CrCl and exposure.

- Based on the established exposure-response analysis for osimertinib, no dose adjustment is required when treating patients with severe renal impairment.
- Osimertinib 80 mg administered orally as a tablet was well tolerated in patients with both normal renal function and severe renal impairment.
- No new safety concerns were identified after a single dose of osimertinib 80 mg.
- The adverse event profile of osimertinib was similar between the 2 groups.

Part B

- No new safety signals were identified during and after 12 weeks of osimertinib 80 mg continuous dosing in patients with severe renal impairment