Clinical Study Report	
Drug Substance	[^{11}C]osimertinib, osimertinib
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An Open-label Positron Emission Tomography (PET) Study to Determine Brain Exposure of Osimertinib after Intravenous Microdose Administration of [^{11}C]osimertinib and Therapeutic Oral Doses of Osimertinib to Patients with EGFR Mutated Non-Small Cell Lung Cancer and Brain Metastases

Study dates: First subject enrolled: 12 October 2018
Last subject last visit: 19 March 2020
The analyses presented in this report are based on a database lock date of 19 October 2020

Phase of development: Clinical pharmacology (I)

International Co-ordinating Investigator:
PPD

Sponsor's Responsible Medical Officer:
PPD
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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

2. SYNOPSIS

Study centre

The study was conducted in Sweden. Recruitment and screening took place at PPD and PPD. The study procedures were conducted at the PPD, main study centre, in Stockholm.

Publications

1. Ekman S, Varrone A, Jucaite A, Vishwanathan K, Brown A, Cselényi Z, Martin H, Lewensohn R, Schou M, Laus G, Van Der Aart J, Johnström P, Singh N, Farde, L. **An Open-Label PET-MRI Study to Determine Brain Exposure of Osimertinib in Patients with EGFR Mutant NSCLC and CNS Metastases.** Poster presented at World Conference on Lung cancer, September 7-10, 2019, Barcelona. P2.14-33. *J Thorac Onco* 2019;14(10S):S842. DOI: https://doi.org/10.1016/j.jtho.2019.08.1818

2. Ekman S, Cselényi Z, Varrone A, Jucaite A, Martin H, Schou M, Johnström P, Laus G, Lewensohn R, Brown A, Van Der Aart J, Vishwanathan K, Farde L. **A PET and MRI study exploring osimertinib brain exposure and efficacy in EGFRm NSCLC CNS metastases.** Poster presented at the World Lung Conference on Lung Cancer, January 28-31, 2021, Singapore. Virtual Poster P76.72

3. Ekman S, Cselényi Z, Varrone A, Jucaite A, Martin H, Schou M, Johnström P, Laus G, Lewensohn R, Brown A, Van Der Aart J, Vishwanathan K, Farde L **Clinical exploration of osimertinib brain exposure in patients with EGFRm NSCLC and brain metastases using PET and MRI.** Submitted Manuscript, January 2021.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Pharmacokinetics	To determine the brain exposure of carbon-11 radiolabelled osimertinib ([^{11}C]osimertinib) in tumour regions of interest, (brain metastases [BM], including leptomeningeal metastases) in patients with epidermal growth factor receptor mutated (EGFRm) non-small cell lung cancer after a single IV microdose and after single and multiple therapeutic administrations of osimertinib.	The percentage of injected dose in the whole brain (%ID) and brain standard uptake value, to describe maximal radioactivity concentration in the brain, ($C_{max,\ \%ID\ brain}$; $C_{max,\ SUV\ brain}$). The time of the maximum radioactivity concentration in the brain, ($T_{max\ brain}$). The brain to plasma partition coefficient (concentration brain/plasma ratio) as the area under the concentration-time curve (AUC), ($Kp = AUC_{brain\ 0\text{-}90\ min}/AUC_{blood\ 0\text{-}90\ min}$). All parameters of exposure included the tumour region, whole brain, and anatomical regions.
Secondary	Pharmacokinetics	To determine the pharmacokinetics of osimertinib and its metabolite (AZ5104) after multiple administrations of osimertinib.	The following variables were calculated where the data allowed: maximum plasma concentration at steady state, ($C_{ss,max}$), time to reach maximum plasma concentration at steady state, ($t_{ss,max}$), area under the plasma concentration-time curve at steady state (AUC_{ss}). Also, the metabolite to parent ratio of the AUC_{ss} and $C_{ss,max}$ after multiple administrations were calculated, as appropriate.
	Safety	To examine the safety and tolerability of [^{11}C]osimertinib IV administration and multiple oral administrations of osimertinib in non-small cell lung cancer patients with BM.	Assessment of AEs graded by the Common Terminology Criteria for Adverse Events (version 4.03), standard 12-lead electrocardiograms, physical examination, vital signs (including blood pressure, pulse) and evaluation of laboratory parameters (clinical chemistry, haematology, and urine analysis).
CCI			

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
		CCI	

AE: adverse event; AUC_{ss}: area under the concentration curve at steady state; BM: brain metastases; C_{max}: maximum concentration after single administration; CNS: central nervous system; CSF: cerebrospinal fluid; $C_{ss,max}$: maximum concentration at steady state; CT: computed tomography; ctDNA: circulating tumour DNA; CTCAE: Common Terminology Criteria for Adverse Events; ECG: electrocardiogram; CCI IV: intravenous; LM: leptomeningeal metastases; MRI: magnetic resonance imaging; NSCLC: non-small cell lung cancer; PK: pharmacokinetics; CCI ROI: region of interest; SUV: standardised uptake value; T_{max}: time of maximum drug concentration after single administration; $t_{ss,max}$: time of maximum drug concentration at steady state.

Study design

The study design included 2 phases, the Imaging Phase, and the Continued Access Phase (CAP). High resolution positron emission tomography (PET) was used to examine brain distribution and retention of a microdose of carbon-11 radiolabelled osimertinib

([^{11}C]osimertinib) in patients with epidermal growth factor receptor mutated (EGFRm) non-small cell lung cancer (NSCLC) with BM. The imaging data analysis included quantification of the maximum radioactivity concentration of [^{11}C]osimertinib in the brain after injection (percent of injected dose entering the brain).

The Imaging Phase of the study included an intravenous microdose administrations of [^{11}C]osimertinib at the start of each of the 3 PET scans. Oral administration of osimertinib tablets (80 mg once daily) to patients began from the day of the second PET for at least 21 days before the third PET examination. The second phase, the CAP, allowed patients to continue to take osimertinib tablets (80 mg once daily) as a single agent after the third PET scan, depending on the agreement between the patient and the Principal Investigator (PI). Osimertinib administration continued until, in the opinion of the PI, the patients were no longer deriving clinical benefit, or the patients stopped taking osimertinib for any other reason, including tolerability, or withdrawal of consent.

Target subject population and sample size

The target population for this study was patients who had EGFRm NSCLC with BM. Approximately 12 patients were planned to be enrolled to obtain 8 evaluable patients with EGFRm NSCLC with BM in the study. A total of 8 patients were successfully enrolled of whom 4 were dosed, when the COVID-19 pandemic resulted in recruitment being put on hold due to the PET centre closing. The study team reviewed available data from these 4 patients and recommended to complete the study due to consistency of results across the 4 patients, and the view that data from additional 4 patients was unlikely to change the study result pertaining to the primary objective: assessment of brain exposure of [^{11}C]osimertinib. The Global Study Team endorsed this decision on 17 June 2020, as was allowed per protocol. The remainder of the study continued as planned.

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

Osimertinib

Osimertinib 40 mg and 80 mg oral, film-coated tablets, manufactured by AstraZeneca were provided for the study. Osimertinib 40 mg tablets were provided for use only in the cases where dose reduction was necessary.
Batch numbers for Osimertinib 80 mg: CCI [redacted]
Batch numbers for Osimertinib 40 mg: CCI [redacted]

[^{11}C]osimertinib

[^{11}C]osimertinib was manufactured ex tempore by the PET centre, Radiochemistry Laboratory at the Karolinska Institute, PPD [redacted], Solna, Sweden, from a precursor 'AZ13774738' supplied by PharmaSynth AS (Tartu, Estonia) and close to the time of each PET measurement. After synthesis, the [^{11}C]osimertinib was dissolved in a sterile buffer

solution and sterile filtered and the final product underwent quality control prior to release for human administration.

Duration of treatment

The study consisted of 2 phases, an Imaging Phase, and a CAP. The patient's participation in the Imaging Phase of the study was approximately 32 days. Osimertinib 80 mg tablets were taken once a day by the patient from the day of the second PET for at least 21 days before the third PET examination. During the CAP patients could continue to take osimertinib tablets (80 mg once daily) as a single agent depending on the agreement between the patient and the PI.

Statistical methods

All 4 patients underwent 3 PET examinations using IV administration of [^{11}C]osimertinib as well as oral doses of osimertinib and both were included in the assessment of safety. All 4 patients completed all 3 PET examinations and were included in the Complete PET Analysis Set and evaluation of [^{11}C]osimertinib brain distribution. Pharmacokinetic parameters were summarised for all 4 patients as they had postdose pharmacokinetic assessments without any clinical study protocol deviations or dosing deviations that might have affected the pharmacokinetic analysis. The statistical analyses were descriptive. Demographic and baseline characteristics, imaging outcomes, safety outcomes, and treatment duration were summarised using descriptive statistics, as appropriate.

Subject population

A total of 8 patients consented to participate in the study and were enrolled, of which 4 patients were dosed and all 4 patients completed the study. No important protocol deviations were noted. All 4 patients completed the planned 3 [^{11}C]osimertinib PET scans. The site reported a consistent 100% compliance rate for all patients after oral osimertinib administration during the Imaging Phase, without dose reduction or interruption..

Summary of PET evaluation

- [^{11}C]Osimertinib crossed the blood-brain barrier (BBB) and rapidly entered the brain and BMs in patients with EGFRm NSCLC.

- [^{11}C]Osimertinib brain exposure at PET1 was homogenous throughout the whole brain grey matter, with a maximum injected dose of 1.4% to 1.6%, with median time to reach maximum drug concentration after single administration (median T_{max}) of 22.160 minutes). The percent of radioactive drug injected (%ID) following single or repeat dosing with 80 mg osimertinib was comparable at 1.6% and 1.5% ID, respectively.

Summary of osimertinib treatment effect on CNS and extra-cranial tumours

- After approximately 4 weeks of oral osimertinib 80 mg QD treatment, CNS RECIST 1.1 tumour assessments showed responses of unconfirmed PR (2 patients), stable disease (2 patients).
- After approximately 4 weeks of oral osimertinib 80 mg QD treatment, extra-cranial (thorax and abdomen) RECIST 1.1 tumour assessments showed responses of unconfirmed PR (3 patients) and stable disease (1 patient).

Summary of pharmacokinetic results

- Osimertinib was steadily absorbed and slowly eliminated; median $t_{ss,max}$ was 4.0 hours, with a flat PK profile across the dosing interval at steady state.
- Plasma concentrations at steady state were higher than those after single dose for both osimertinib and metabolite AZ5104, indicating accumulations in plasma following daily dosing.
- Steady state geometric mean metabolite to parent exposure ratio for AZD5104 was 0.118 and 0.127 based on maximum plasma concentration at steady state ($C_{ss,max}$) and area under the plasma concentration-time curve at steady state (AUC_{ss}), respectively.
- Inter-patient variability in osimertinib and AZ5104 PK exposure ($C_{ss,max}$ and AUC_{ss}) ranged from 29.6% to 64.1%.
- At steady-state, systemic mean exposure of metabolite AZ5104 was approximately 13% of osimertinib.

Summary of safety results

- Three of the 4 patients reported at least one adverse event (AE) that was considered as causally related to oral osimertinib, one patient reported at least one AE that was considered as causally related to [^{11}C]osimertinib.
- All AEs were of Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2; there were no AEs of CTCAE Grade 3 or higher.
- There were no SAEs, deaths or AEs leading to discontinuation of the investigational product (IP) reported in this study.
- No clinically meaningful changes or trends were noted in laboratory evaluations, vital signs, electrocardiogram, or physical examination assessments.
- The AEs observed in this study were in line with expected risks of PET examinations (eg, haematoma) and no new safety signals were noted.

Conclusion(s)

- Radiolabelled osimertinib crossed the BBB and distributed uniformly across the brain regions in all 4 patients with EGFRm NSCLC with BMs. Approximately 1.5% of injected radioactivity (range 1.4% to 1.6%) was observed in the brain at T_{max} (median T_{max} of 22.160 minutes) after an IV microdose of [^{11}C]osimertinib.
- The radioactivity level of [^{11}C]osimertinib in the brain was similar when administered alone or after single and repeat dosing with oral 80 mg osimertinib.
- Osimertinib was steadily absorbed and slowly eliminated with a flat PK profile across the dosing interval at steady state. At steady-state mean systemic exposure to metabolite AZ5104 was approximately 13% of that to parent osimertinib.
- After approximately 4 weeks of oral osimertinib 80 mg QD treatment, CNS RECIST 1.1 tumour assessments showed responses of unconfirmed PR (2 patients), stable disease (2 patients).
- After approximately 4 weeks of oral osimertinib 80 mg QD treatment, extra-cranial (thorax and abdomen) RECIST 1.1 tumour assessments showed responses of unconfirmed PR (3 patients) and stable disease (1 patient).
- Overall, oral osimertinib and [^{11}C]osimertinib were well tolerated in this study and no new safety concerns were observed.