

Creating Metabolic Vulnerabilities in patients with EGFR activated recurrent Glioblastoma by inhibiting EGFR with Osimertinib

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CREATING METABOLIC VULNERABILITIES IN PATIENTS WITH EGFR ACTIVATED RECURRENT GLIOBLASTOMA BY INHIBITING EGFR WITH OSIMERTINIB

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VERSION HISTORY

Version 7.0, April 03, 2020		
Amendment 6		
Summary of changes		
The changes made to protocol version 7.0 dated April 03, 2020 were detailed as below:		
Modified section	Modification	Rationale
Cover page and header	Protocol version and date has been updated to version 7.0, dated April 03, 2020	Administrative update
Section 1.1.2	Clinical data The context and Table 1 were updated per newly released IB version 13	Clinical information were updated per newly released IB version 13.
Section 1.1.2.1	Clinical pharmacokinetics <i>Removed:</i> As patients with CL _{Cr} less than 15 mL/min, patients on dialysis, or patients with severe hepatic dysfunction were not included in the clinical trials, the appropriate dose of osimertinib has not been established in these patients. <i>Added:</i> No dose adjustment for osimertinib is required when treating patients with severe renal impairment; however, as patients with severe renal failure have a higher osimertinib mean exposure compared to normal renal function patients, caution should be exercised when treating patients with severe and end-stage renal impairment.	Clinical information were updated per newly released IB version 13.
Section 1.1.2.2	Clinical efficacy <i>From:</i>	Clinical information were updated per newly

	A total of 673 patients with locally-advanced or metastatic EGFRm NSCLC have been dosed with first-line treatment in the FLAURA study. Of these, 117 remain blinded to treatment. Of the 556 patients who have been unblinded, 279 received osimertinib 80 mg QD and 277 received the standard of care (SoC). The data provided strong evidence for the clinical benefit of osimertinib for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR with Exon19 Deletion activating mutation (EGFR[Ex19del]) or EGFR with L858R activating mutation (EGFR[L858R]) mutations: <i>To:</i> A total of 673 patients with locally-advanced or metastatic EGFRm NSCLC have been dosed with first-line treatment in the FLAURA study (in both the Global cohort and the China cohort). Of the 556 patients who have been unblinded, 279 received osimertinib 80 mg QD and 277 received the standard of care (SoC). At DCO1 (12 June 2017), the data provided strong evidence for the clinical benefit of osimertinib for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR with Exon19 Deletion activating mutation (EGFR[Ex19del]) or EGFR with L858R activating mutation (EGFR[L858R]) mutations: <i>Added:</i> At the DCO2 (25 June 2019) final OS analysis, 321/556 patients had died (55.6% in the osimertinib arm and 59.9% in the SoC arm; 57.7% maturity overall). The HR for OS was 0.799 (adjusted 95.05% CI: 0.6406, 0.9968), signifying a 20% lower risk of death in the osimertinib arm compared with the SoC arm. The difference between treatment arms in favour of osimertinib was statistically significant, as the p-value of 0.0462 was below the predefined level of 0.0495 required at this analysis. Median OS was 38.6 (95% CI: 34.5, 41.8) months in the osimertinib arm, and 31.8 (95% CI: 26.6, 36.0) months in the SoC arm, a difference of 6.8 months. Post-progression outcomes showed a clinically relevant	released IB version 13.
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	longer time from randomisation to TFST or death for patients on osimertinib compared to patients on SoC (HR: 0.478 [95% CI: 0.3927, 0.5810; 2-sided p-value <0.0001). There was also a clinically relevant longer time to TSST for patients on osimertinib compared to patients on SoC (HR: 0.687 [95% CI: 0.5610, 0.8424; 2-sided p-value = 0.0003). Additionally, at DCO2, the improvement in CNS PFS was determined to be statistically significant and clinically relevant for patients on osimertinib compared to patients on SoC (HR: 0.48 [95% CI: 0.26, 0.86]; p-value = 0.014). The median CNS PFS was not reached in the osimertinib arm (95% CI: 16.5, NC) compared to 13.9 months in the SoC arm (95% CI: 8.3, NC). These data demonstrate that most of the benefit of osimertinib seen in the PFS analysis at DCO1 was preserved in the final OS analysis at DCO2. The OS benefit of osimertinib over SoC was consistent across all predefined subgroups, with variation in the magnitude of benefit in the subgroups of race (Asian/non-Asian) and EGFR mutation type (Ex19del/L858R). The OS data from DCO2 also adds further evidence that osimertinib offers clinically meaningful CNS efficacy to patients with CNS metastases at baseline, a subgroup of patients for whom no EGFR-TKIs other than osimertinib have demonstrated efficacy. The FLAURA China cohort (DCO1c: 10 January 2018) included 136 patients; 19 of whom were randomised prior to the end of global recruitment and were also included in the global analysis. Of the 136 patients randomised in the China cohort, 71 received osimertinib 80 mg once daily and 65 received the SoC (all gefitinib). The PFS (investigator assessed) efficacy of osimertinib compared to SoC was consistent with the overall global study population: • There was a clinically meaningful improvement in PFS for patients on osimertinib compared with patients on SoC based on investigator assessment (HR: 0.56 [95% CI: 0.37, 0.85; p=0.0065]). There was an 8.0-month improvement in median PFS compared to SoC (median PFS: 17.8 months [95% CI: 13.6, 20.7] in the osimertinib arm vs 9.8 months [95% CI: 8.3, 13.8] in the SoC arm).	
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	• The results from the interim OS analysis showed a HR of 0.68 (95% CI: 0.38, 1.22). Visual assessment of the Kaplan-Meier (KM) curves suggest that the proportionality assumption does not hold, therefore caution is required in interpretation of the OS effect via the HR. There were encouraging OS data for patients in the osimertinib arm compared to patients in the SoC arm: the OS curves separate after 12 months and a greater proportion of patients treated with osimertinib were alive at 18 months compared to patients in the SoC arm. The low maturity of the OS data (33.1%) and small number of events in this analysis should be taken into consideration. • High response rates (>75%) were seen in the China cohort and were as expected, with all responses being partial responses (PRs). • There was a clinically meaningful improvement in median DoR for patients on osimertinib (16.4 months [95% CI: 12.3, not calculable]) compared with patients on SoC (10.9 months [95% CI: 8.3, 13.8]). At the final OS analysis of the FLAURA China cohort (DCO2c: 25 June 2019), 89/136 patients had died, comprising 45 patients (63.4%) in the osimertinib arm, and 44 patients (67.7%) in the SoC arm. The maturity of the OS analysis was therefore calculated to be 65.4%, with a median follow-up for overall survival time of 31.0 months for osimertinib-treated patients and 24.9 months for patients receiving SoC. The final OS analysis HR was 0.848 (95% CI: 0.5568, 1.2910; p=0.4416), indicating a clinically meaningful 15% reduction in the risk of death in the osimertinib arm compared to the SoC arm. The median OS was 33.1 months (95% CI: 26.0, 35.9) in the osimertinib arm, and 25.7 months (95% CI: 19.6, 32.8) in the SoC arm. This represents a clinically meaningful 7.4 month extended OS benefit for patients in the osimertinib arm versus SoC. At DCO2c, the final OS analysis of the China cohort was generally consistent with the overall OS data for the global population. <i>Removed:</i> The overall ORR was 77% (95% CI: 64, 87) and the overall disease control rate (DCR) was 98% (95% CI: 89, 100). The median PFS was 19.3 months, with	
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	maximum duration of response (DoR) at 22.1 months. The percentage of patients remaining progression-free at 12 months was 72% (95% CI: 59, 82) and at 18 months 55% (95% CI: 41, 67). <i>Added:</i> In first-line (treatment-naïve) NSCLC patients, a total of 60 patients received PO treatment with osimertinib in the AURA Phase I study (30 patients each at 80 mg and 160 mg respectively). The overall ORR was 77% (95% CI: 64, 87) and the overall DCR was 98% (95% CI: 89, 100). The median PFS was 20.5 months (95% CI: 13.7, 26.1), with median DoR at 18.0 months (95% CI: 12.5, 24.7). The percentage of patients remaining progression-free at 12 months was 72% (95% CI: 59, 82) and at 18 months 56% (95% CI: 42, 68). Section AURA3 study: 2nd line or greater, T790M mutation positive, advanced NSCLC patient population was revised <i>From:</i> , assessment, at 59.7% maturity, there was a statistically significant and clinically meaningful improvement in PFS for patients on osimertinib 80 mg PO once-daily vs. those on chemotherapy based on investigator assessment (hazard ratio [HR]: 0.30, 95% CI: 0.23, 0.41; p-value: <0.001), indicating a 70% reduction in risk of disease progression or death (in the absence of a Response Evaluation Criteria In Solid Tumours [RECIST] progression) in the osimertinib arm. <i>To:</i> At the time of the primary efficacy analysis (DCO1: 15 April 2016), there was a statistically significant and clinically meaningful improvement in PFS (investigator assessed) for patients on osimertinib 80 mg PO once-daily vs. those on chemotherapy (HR: 0.30, 95% CI: 0.23, 0.41; p-value: <0.001), indicating a 70% reduction in risk of disease progression or death (in the absence of a Response Evaluation Criteria In Solid Tumours [RECIST] progression) in the osimertinib arm.	
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	<i>Removed:</i> The analysis of OS was immature (26.0%) but a numerical advantage for patients on osimertinib compared to patients on chemotherapy was observed, which did not reach statistical significance. <i>Added:</i> At the final OS analysis in AURA3 (DCO4 of 15 March 2019; 67.1% maturity for OS overall), osimertinib demonstrated a numerical advantage in OS compared to chemotherapy, which did not reach statistical significance (HR=0.87 [95.564% CI: 0.67, 1.13]; p=0.277). The median OS was 26.8 months (95% CI: 23.49, 31.54) in the osimertinib arm and 22.5 months (95% CI: 20.17, 28.81) in the chemotherapy arm. Patients initially randomised to the chemotherapy arm were allowed per protocol to cross-over to treatment with osimertinib following RECIST progression. The interpretation of the OS results from this study are thus confounded by the fact that a large proportion of patients in the chemotherapy arm crossed over to receive treatment with osimertinib after RECIST progression (99/140 [70.7%] patients in the chemotherapy arm overall. The protocol assumption for the median OS for the chemotherapy arm was 16 months, so this arm performed better than expected, meaning the KM curves were closer together than expected, and these data confirm that in patients with previously treated EGFR T790M mutation-positive NSCLC, responses to osimertinib were durable. <i>Removed:</i> Investigator's Brochure Drug Product AZD9291, Osimertinib, TAGRISSO™ Project Code D5160000000 Edition Number 9 Date 25 January 2018 25 (137)	
Section 1.1.2.3	Clinical safety <i>Replaced:</i>	Clinical information were updated per newly

	- Phase I Clinical Pharmacology studies in healthy volunteers osimertinib was generally well tolerated without any significant safety concerns. The healthy volunteer dose limit is set to 80 mg as a single oral dose. <i>With:</i> - An increased incidence in the ILD reporting rate has been reported for the combination of durvalumab and osimertinib in Study D5160C00006 (TATTON). This study showed an incidence rate of 32.4% for pneumonitis/ILD-like events, at a data cut-off of 12 July 2017, compared with an overall frequency of pneumonitis (including both non serious and serious cases) of around 5% for durvalumab 10 mg/kg monotherapy and an overall frequency of pneumonitis/ILD of 3.5% for osimertinib monotherapy. These findings were not subsequently replicated in Study D5165C00001 (CAURAL)	released IB version 13.
Section 4.1	Table 2 Study Visit ScheduleFootnote 13 Added: Cycle 1 Day 1 PK blood may be collected only when the visit is scheduled on week days.	Clarification was added for better study management.
Section 6.7	Management of IP related toxicities <i>The following adverse event management guideline were added:</i> 6.7.4 Haematological events Early reductions in the median laboratory counts of leukocytes, lymphocytes, neutrophils and platelets have been observed in patients treated with osimertinib, which stabilised over time and then remained above the lower limit of normal. AEs of leukopenia, lymphopenia,	Updated clinical information per IB version 13.

	neutropenia and thrombocytopenia have been reported, most of which were mild or moderate in severity and did not lead to dose interruptions. 6.7.5 Erythema multiforme and Stevens-Johnson syndrome Case reports of erythema multiforme (EM) and Stevens-Johnson syndrome (SJS) have been uncommonly and rarely reported, respectively, in association with osimertinib treatment. Before initiating treatment, patients should be advised of signs and symptoms of EM and SJS. If signs and symptoms suggestive of EM develop, close patient monitoring and drug interruption or discontinuation of osimertinib should be considered. If signs and symptoms suggestive of SJS appear, osimertinib should be interrupted or discontinued immediately.	
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Version 6.0, November 11, 2019
Amendment 5
Version 5.0, September 06, 2019
Amendment 4
Version 4.0, January 28, 2019
Amendment 3
Version 3.0, September 20, 2018
Amendment 2
Version 2.0, July 19, 2018
Amendment 1
Version 1.0, June 17, 2018
Initial creation

PROTOCOL SYNOPSIS

CREATING METABOLIC VULNERABILITIES IN PATIENTS WITH EGFR ACTIVATED RECURRENT GLIOBLASTOMA BY INHIBITING EGFR WITH OSIMERTINIB

Principle Investigator: Timothy Cloughesy, M.D.

Coordinating center: UCLA Neuro-Oncology Program, Clinical Trial Office

710 Westwood Plaza, RNRC1-230, Los Angeles, CA 90095

Study site(s) and number of subjects planned

Approximately 12 subjects will be enrolled at University of California Los Angeles

Study period		Phase of development
Estimated date of first subject enrolled	April 2019	Phase 2
Estimated date of last subject completed	April 2021	

Study design

This is a phase 2 study to validate 18F-FDG PET imaging as a non-invasive, repeatable early response biomarker to measure a change in glucose utilization in recurrent glioblastoma as a way to provide a proof of concept evaluation of osimertinib in this patient population. Recurrent Glioblastomas (GBM) patients with EGFR amplification and/or mutation and p53 wild type will have double baseline 18F-FDG PET scans (18 to 54 hours apart) prior to osimertinib dosing and one 18F-FDG PET scan early, post dosing (24-72 hour) to retest variance of tumor FDG uptake and evaluate the osimertinib-induced attenuation in tumor glucose uptake. All subjects will continue with the osimertinib treatment until disease progression, intolerable toxicity or consent withdrawal.

Objectives

Primary Objective:	Outcome Measure:
1. Define the test - retest variance of tumor FDG uptake using double baseline 18F-FDG PET imaging (18 to 54 hours apart) in patients with recurrent EGFR activated glioblastoma.	Inpatient Variance of tumor FDG uptake as determined by a double baseline FDG PET prior to osimertinib exposure.
2. After defining #1, evaluate whether osimertinib can create a statistically significant decrease in glucose utilization as determined using early, post dosing (24-72 hour) FDG-PET imaging in patients with recurrent EGFR activated glioblastoma.	Change in FDG uptake in tumor after short course exposure to osimertinib.
Secondary Objective:	Outcome Measure :
1. Safety and tolerability of osimertinib in this patient population	The AEs, SAEs, and AEs leading to discontinuation. The severity of AEs will be assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03. Safety laboratory parameters, physical examination findings, vital signs, and Karnofsky Performance Status (KPS). Duration of subject on study treatment. Dose modification.
2. Determine clinical effect of osimertinib in this patient population, as determined by 6 months progression-free survival	Percentage of participants surviving six months from the start of study treatment without progression of disease. PFS was defined as the time from the date of study treatment initiation to the date of the first documented progression according to Response Assessment in Neuro-oncology (RANO) criteria, or to death due to any cause.
3. Correlated clinical effect of osimertinib with FDG-PET results in this patient population, to define by ROC analysis a clinically meaningful decrease in glucose utilization, which correlates with the clinical effect	To correlate the reduction in glucose uptake with clinical outcomes (6 months progression-free survival), ROC analyses of simple thresholding strategies will be performed using leave one out cross validation.
4. Evaluate PK in this patient population using spot PK during imaging and at set time points during the study	Concentrations of osimertinib, and metabolites AZ5104 and AZ7550 in post-dosing plasma samples. PK Parameters.

Target subject population

Subjects who have histologically proven recurrent WHO grade IV glioblastoma with evidence of EGFR activation and/or EGFR mutations and wildtype p53.

Duration of treatment

Osimertinib will be taken by subjects until disease progression or unacceptable toxicity, whichever occurs first.

Investigational product, dosage and mode of administration

Osimertinib 240 mg QD (on Days -3, -2 and -1) and 160 mg QD (28-day cycle) will be administered orally as 80 mg tablets.

Statistical methods

Intra-subject variability will be estimated as the variance of the difference between the first and second baseline F-DG PET scans. The primary objective of the study is focused on estimation. Using a sample of 12 measurements, targeting a Bayesian average coverage of 80%, we expect HPD lengths of 0.7 or less for the standard deviation, with probability 95%. After treatment, the effect of Osimertinib on glucose uptake will be quantified as a standardized effect, in relation to the baseline PET standard deviation. We will explore how a reduction in glucose uptake correlates with clinical outcomes (6 months progression free survival) via a Cox proportional hazard model. ROC analyses of simple thresholding strategies will be carried out using leave one out cross validation. Furthermore, unsupervised techniques, based on mixture models, will be used to determine if composite subpopulations of responders/non-responders represent a viable sampling model for the general population.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event
CRF	Case Report Form (electronic/paper)
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
DNA	Deoxyribonucleic acid
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
ECHO	Echocardiography
EGFR	Epidermal growth factor receptor
FDG	Fluorodeoxyglucose
GBM	Glioblastoma
GCP	Good Clinical Practice
HPD	High Posterior Density
ICH	International Conference on Harmonisation
IP	Investigational Product
KM	Kaplan-Meier
LVEF	Left ventricular ejection fraction
OAE	Other Significant Adverse Event
ORR	Objective response rate
OS	Overall survival
PET	Positron Emission Tomography
PFS	Progression-free survival
PI	Principal Investigator
RA	Research Agreement
ROC	Receiver operating characteristics
SAE	Serious adverse event
WoCBP	Women of childbearing potential

1. INTRODUCTION

1.1 Background and rationale

Malignant gliomas, including the universally lethal glioblastoma (GBM), are the most common primary brain tumors and the most deadly. GBM display heightened rates of glucose metabolism to satisfy the biosynthetic and energetic demands for tumor growth, proliferation, and survival. Conventional treatment for these highly metabolic tumors only minimally increases survival and, despite extensive molecular characterization, effective molecularly-guided therapies have yet to be identified. Recent work from our group and others demonstrated that the epidermal growth factor receptor (EGFR) – altered in ~60% of patients – drives glucose consumption [1]. We've presented compelling new evidence showing that targeting EGFR, using EGFR tyrosine kinase inhibitors, rapidly attenuates glucose metabolism in a subset of EGFR-altered GBMs [2]. As a consequence of this altered metabolic state, the tumor suppressor p53 engages the apoptotic machinery, thereby stimulating cell kill. Accordingly, inhibition of EGFR-driven glucose metabolism in tumors with a functional p53 is efficacious in preclinical GBM models. We demonstrate that rapid changes (within hours) in tumor glucose uptake using non-invasive [¹⁸F] FDG and positron emission tomography (PET) is an effective predictive biomarker of therapeutic response. Given that majority of GBMs with genetic alterations in EGFR are p53 wild-type, this new approach to manipulate GBM metabolism could be applicable to a significant number of GBM patients. Using clinical ¹⁸F-FDG PET imaging to detect changes in tumor glucose utilization allows investigators to obtain an early read out on the impact of EGFR inhibitors on glioblastoma patients whose tumors have EGFR activation. If the clinical translation of this approach is successful, it will speed clinical development of EGFR inhibitors in glioblastoma including exploration of dose and schedule.

This study will explore above concept using osimertinib in recurrent glioblastoma patients with EGFR amplification/mutation and wild type *p53*. Osimertinib (TAGRISSOTM, AZD9291) is an oral, potent, selective, central nervous system (CNS) active, irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), effective against both EGFR-TKI-sensitising mutations (EGFRm) as well as T790M mutation positive ([T790M mutation positive] TKI resistance conferring mutation) forms of EGFR.

1.1.1 Osimertinib[3]

Osimertinib is an established agent for the treatment of patients with non-small cell lung cancer (NSCLC). Osimertinib received marketing approval under the trade name TAGRISSOTM from the United States Food and Drug Administration (US FDA) on 13 November 2015. Osimertinib 80 mg once-daily tablets were approved for “the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy”. Osimertinib received marketing approval from the EU on 2nd February 2016.

1.1.1.1 Non-clinical studies

1.1.1.2 Non-clinical pharmacology

Non-clinical *in vitro* studies have demonstrated potent inhibition of mutant EGFR activity in biochemical enzyme assays and across NSCLC cell lines harbouring clinically relevant EGFR mutations (T790M, L858R and exon 19 deletion), with lower activity against wild-type EGFR. Moreover, osimertinib has caused profound tumour regression across representative mutant EGFR xenograft and transgenic disease models *in vivo* at clinically relevant concentrations, which was accompanied by dose and time dependent pharmacodynamic target effects. Osimertinib is also active against tumour models carrying rarer EGFR activating mutations, in exon 20 and at G719.

Taken together, *in vitro* and *in vivo* non-clinical studies have provided strong support that osimertinib is more potent towards mutant EGFR compared with wild-type EGFR. Osimertinib has two active metabolites, AZ5104 and AZ7550. The geometric mean exposure area under the plasma concentration time curve (AUC) of each metabolite (AZ5104 and AZ7550) was approximately 10% of the exposure of osimertinib at steady-state. AZ7550 displays near identical pharmacology properties *in vitro* to osimertinib. In contrast, AZ5104 has greater potency against mutant and wild-type EGFR *in vitro* than osimertinib, which suggests this metabolite may have a smaller selectivity margin for mutant EGFR than osimertinib.

Osimertinib is a highly selective inhibitor of mutant EGFR, showing minimal off-target kinase activity when tested in a broad biochemical kinome panel, only showing significant potency against 18 other kinases (including ACK1, BLK, ErbB2, ErbB4, BRK, MLK1, MNK2), although the clinical significance of this biochemical activity remains unclear. Osimertinib, AZ5104 and AZ7550 inhibited the hERG-encoded potassium channel with IC₅₀ values of 0.69 µM, 17.48 µM and >33 µM, respectively. There were no notable effects on the respiratory, visual, central nervous or cardiovascular systems in safety pharmacology studies. Reductions in gastric emptying and small intestinal transit were observed in rats.

1.1.1.3 Pharmacokinetics and drug metabolism in animals

Osimertinib is a moderately permeable compound in Caco-2 cells and has good absorption properties in rats and dogs. Osimertinib plasma protein binding is high (>94%) across mouse, rat, dog, monkey and in human plasma (94.7%). [¹⁴C]Osimertinib related material was shown to distribute to all tissues in a rat quantitative whole-body autoradiography (QWBA) study and there was also evidence that [¹¹C]osimertinib and its active metabolite [¹¹C]AZ5104 penetrated the blood-brain barrier (BBB) in a cynomolgus monkey PET study. In mouse, rat, dog and human hepatocytes, osimertinib metabolism was primarily to hydroxylated and dealkylated products with conjugation to a range of glutathione, cysteinylglycine, glucuronide and sulphate conjugates with all human metabolites also produced by rat and dog hepatocytes.

The major route of osimertinib excretion in rats and dogs was via the faeces with only minor elimination observed in urine. *In vitro* data supports CYP3A4/5 as the major enzyme responsible for the metabolism of osimertinib and its two active metabolites, AZ5104 and AZ7550. These data led to the conduct of clinical drug-drug interaction (DDI) studies with itraconazole (strong CYP3A4 inhibitor) and rifampicin (strong CYP3A4 inducer). *In vitro*, osimertinib showed potential to inhibit intestinal breast cancer resistance protein (BCRP) and

CYP3A4 that led to the conduct of clinical DDI studies with rosuvastatin (BCRP substrate) and simvastatin (CYP3A4 substrate).

1.1.1.4 Toxicology

The principal histopathological findings following daily oral dosing of osimertinib in rats and dogs were consistent with inhibition of wild-type EGFR. In a rat female fertility study osimertinib was associated with a reversible increase in post-implantation loss. Osimertinib had marked adverse effects on embryonic survival plus early postnatal viability and growth when administered to pregnant or lactating rats. Osimertinib has shown no genotoxic or phototoxic potential. The integrated non-clinical safety data supports the continued clinical development of osimertinib in the patient populations studied in the ongoing clinical studies.

1.1.2 Clinical data

As of 12 November 2019, a total of 3862 subjects (3744 NSCLC patients and 118 healthy volunteers) have been included in the osimertinib clinical development programme (not including those patients enrolled in NPS, EAP or RWE studies). Of these 3862 subjects, 2607 subjects received osimertinib monotherapy (2489 patients and 118 healthy volunteers), 381 patients received osimertinib in combination with another treatment, and 874 patients were exposed to comparator treatment (including placebo). Of the 874 patients exposed to comparator treatment, 190 patients subsequently crossed-over from comparator treatment to osimertinib monotherapy during their respective studies, and 684 patients were exposed to comparator treatment only (including placebo). An additional 4055 patients have participated in the osimertinib ESPs and NPS, and 3014 patients participated in the ASTRIS RWE study (D5160C00022).

A summary of the clinical programme for osimertinib is listed below, but further information can be found in the Investigator's Brochure (IB).

Table 1 Osimertinib Clinical programme as of 12 November 2019

Study Number (Study name; NCT number) [Status]	Study DCO (for safety and efficacy reporting)	Study design and dosage ^a	Total number of subjects dosed
Study D5160C00001 (AURA Phase I component; NCT01802632) [Phase I CSR available. Pts continued in follow up]	Latest DCO: 01 November 2016 Latest DCO for the first-line expansion cohort of EGFR TKI treatment-naïve patients: 01 May 2018	A Phase I/II, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Anti-tumour Activity of Ascending Doses of AZD9291 in Patients with Advanced Non-Small Cell Lung Cancer who have Progressed Following Prior Therapy with an Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Agent The AURA Phase I component was an open label, multi centre, dose escalation (Part A, n=31; rolling 6 design) and dose expansion (Part B, n=271) study. <u>Dosage:</u> 5 cohorts with daily oral dosing starting at 20 mg capsule formulation once daily for Cohort 1, escalating to 40 mg, 80 mg, 160 mg, and 240 mg once daily for Cohorts 2 to 5, respectively AURA Phase I also included: • A first-line expansion cohort of treatment-naïve patients (n=60) who received 80 mg once daily (n=30) or 160 mg once daily (n=30) osimertinib in the capsule formulation; • A cohort of pre-treated (2nd-line or greater) patients (n=12) who received 80 mg osimertinib once daily in the tablet formulation • A Japan-only cytology cohort (n=28) whose EGFR T790M mutational status was determined by cytology samples, who received 80 mg osimertinib once daily in the tablet formulation.	402 patients in total
Study D5160C00001 (AURA Phase II component; NCT01802632) [Phase II CSR available. Pts continued in follow up]	Pooled Phase II data DCO: 01 November 2015 Latest DCO: 01 May 2018	The AURA Phase II component was an open label, single-arm, non-randomised extension study (also referred to as AURA Part C and/or AURA extension).	201 patients

Study Number (Study name; NCT number) [Status]	Study DCO (for safety and efficacy reporting)	Study design and dosage ^a	Total number of subjects dosed
Study D5160C00002 (AURA2; NCT02094261) [CSR available. Pts continued in follow up]	Pooled Phase II data DCO: 01 November 2015 Latest DCO: 01 May 2018	A Phase II, Open Label, Single-arm Study to Assess the Safety and Efficacy of AZD9291 in Patients with Locally Advanced/Metastatic Non-Small Cell Lung Cancer whose Disease has Progressed with Previous Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy and whose Tumours are Epidermal Growth Factor Receptor Mutation and T790M Mutation Positive	210 patients
Study D5160C00003 (AURA3; NCT02151981) [CSR available. Pts continued in follow up]	Primary analysis (DCO1): 15 April 2016 Latest DCO (DCO4): 15 March 2019	A Phase III, Open Label, Randomized Study of AZD9291 versus Platinum-Based Doublet Chemotherapy for Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer whose Disease has Progressed with Previous Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy and whose Tumours harbour a T790M mutation within the Epidermal Growth Factor Receptor Gene	279 patients dosed in osimertinib arm, 136 patients dosed in chemotherapy arm (140 patients randomised and included in the FAS for efficacy analysis)
Study D5160C00005 (NCT01951599) [Study completed. CSR available.]	Last subject last visit (LSLV): 04 June 2014	A Phase I, Open-label, Single-centre, Sequential Design Study in Healthy Volunteers to Determine the Relative Bioavailability of Different Oral Formulations of AZD9291 and the Effect of Food <u>Dosage (Part A)</u> : Single 20 mg doses of osimertinib administered as a capsule in Period 1, as a solution in Period 2, and as a tablet in Period 3, all in the fasted state. <u>Dosage (Part B)</u> : Single 20 mg dose of osimertinib (tablet formulation) administered under fasted conditions in Period 1, and under fed conditions (following a high fat breakfast) in Period 2	32 healthy male volunteers (16 in the relative bioavailability part of the study and 16 in the food effect part of the study)

Study Number (Study name; NCT number) [Status]	Study DCO (for safety and efficacy reporting)	Study design and dosage ^a	Total number of subjects dosed
Study D5160C00006 (TATTON; NCT02143466) [Part A completed – CSR in production; Part B Ongoing]	Part A: 28 June 2019 (study analysis is ongoing at the DCO of this IB)	A Multi-arm, Phase Ib, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of AZD9291 in Combination with Ascending Doses of Novel Therapeutics in Patients with EGFRm+ Advanced NSCLC who have progressed following therapy with an EGFR TKI <u>Dosage (Part A; Combination dose finding):</u> Osimertinib 80 mg tablet, once daily, administered orally in the fasted state; durvalumab administered intravenously every 2 weeks; savolitinib, once daily, administered orally; selumetinib, oral dose twice daily. <u>Dosage (Part B; Dose-expansion):</u> Daily oral doses of osimertinib and savolitinib, or osimertinib and selumetinib, the dose determined from Part A will be used for Part B	315 patients exposed to a study treatment: 34 to osimertinib and durvalumab, 83 to osimertinib and selumetinib, 198 to osimertinib and savolitinib.
Study D5160C00007 (FLAURA; NCT02296125) [Study completed. CSR available]	Primary analysis (DCO1): 12 June 2017 (Global) 10 January 2018 (China Cohort) Latest DCO (DCO2): 25 June 2019 (Global and China Cohort)	A Phase III, Double-blind, Randomised Study to Assess the Efficacy and Safety of AZD9291 versus a Standard of Care Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor as First-line Treatment in Patients with Epidermal Growth Factor Receptor Mutation-positive, Locally-advanced or Metastatic Non-small cell Lung Cancer <u>Dosage:</u> Osimertinib: 80 mg tablet or matching placebo once daily, administered orally versus a standard of care EGFR TKI (either gefitinib 250 mg or erlotinib 150 mg) single daily dose, administered orally	338 patients dosed in the osimertinib arms of both the Global and China cohorts

Study Number (Study name; NCT number) [Status]	Study DCO (for safety and efficacy reporting)	Study design and dosage ^a	Total number of subjects dosed
Study D5160C00008 (Hepatic Impairment Study; NCT02161770) [Study completed. CSR available.]	Part A: 24 October 2016 LSLV (Part B): 16 May 2017	An Open-label, Non-randomised, Multicentre, Comparative, Phase I Study to Determine the Pharmacokinetics, Safety and Tolerability of AZD9291 following a Single Oral Dose to Patients with Advanced Solid Tumours and Normal Hepatic Function or Mild or Moderate Hepatic Impairment <u>Dosage (Part A):</u> osimertinib 40 mg and 80 mg tablets, 80 mg administered orally in the fasted state on Day 1. <u>Dosage (Part B):</u> osimertinib 40 mg and 80 mg tablets, 80 mg administered orally in the fasted state once daily for the duration of their participation	30 patients with advanced solid tumours and normal hepatic function or mild or moderate hepatic impairment
Study D5160C00009 (Food effect study; NCT02163733) [Study completed. CSR available]	Part A: 22 April 2015 Part B: 10 August 2016	An Open-label, Randomised, Phase I Study to Determine the Effect of Food on the Pharmacokinetics of Single Oral Doses of AZD9291 in Patients with EGFRm Positive NSCLC whose Disease has Progressed on an EGFR TKI <u>Dosage (Part A):</u> osimertinib 80 mg tablet, administered orally, once in the fasted state and once following a high-fat meal. <u>Dosage (Part B):</u> Continuous daily dosing of osimertinib 80 mg tablet, administered orally in the fasted state for 1 year from the date the last patient entered Part B.	38 patients
Study D5160C00010 (Gastric pH study; NCT02224053) [Study completed. CSR available.]	LSLV: 05 January 2015	A Phase I, Fixed Sequence, Open-label, Study to Assess the Pharmacokinetics of AZD9291 in Healthy Male Volunteers when a Single Oral Dose of AZD9291 80 mg is Administered Alone and in Combination with Omeprazole <u>Dosage:</u> Osimertinib 80 mg tablet; omeprazole 40 mg capsule; administered orally in the fasted state	68 healthy male adult volunteers
Study D5160C00011 (Radiolabelled mass balance study; NCT02096679) [Study completed. CSR available.]	LSLV: 29 August 2014	A Phase I, Single-centre, Non-randomised, Open-label, Pharmacokinetic and Mass Balance Study of Orally Administered [¹⁴ C]-AZD9291 in Healthy Male Volunteers <u>Dosage:</u> [¹⁴ C]osimertinib 20 mg solution formulation; administered orally in the fasted state	8 healthy volunteers

Study Number (Study name; NCT number) [Status]	Study DCO (for safety and efficacy reporting)	Study design and dosage ^a	Total number of subjects dosed
Study D5160C00012 (DDI Inhibitor Study; NCT02157883) [Study completed. CSR available]	Part A: 04 May 2015 Part B: 09 September 2016	A Phase I, Open-label, Non-randomised Study to Assess the Effect of Itraconazole (a CYP3A4 Inhibitor) on the Pharmacokinetics of a Single Oral Dose of AZD9291 in Patients with EGFRm Positive NSCLC Whose Disease has Progressed on an EGFR TKI <u>Dosage (Part A):</u> 80 mg single oral dose osimertinib administered in the morning 1 hour after completion of the breakfast; itraconazole capsules (200 mg twice daily). <u>Dosage (Part B):</u> 80 mg osimertinib administered orally, once daily	38 patients
Study D5160C00013 (DDI Inducer Study; NCT02197247) [Study completed. CSR available]	Part A: 03 August 2015 Part B: 10 October 2016	A Phase I, Open-Label, Non-Randomised, Multicentre Study to Assess the Effect of Rifampicin (a CYP3A4 Inducer) on the Pharmacokinetics of AZD9291 in Patients with EGFRm Positive NSCLC Whose Disease has Progressed on an EGFR TKI <u>Dosage (Part A):</u> 80 mg osimertinib administered orally once daily in the fasted state; rifampicin capsules (600 mg), administered orally once daily <u>Dosage (Part B):</u> 80 mg osimertinib administered orally, once daily	41 patients
Study D5160C00014 (DDI Substrate Study; NCT02197234) [Study completed. CSR available.]	Part A: 24 June 2015 Part B: 05 October 2016	A Phase I, Open-Label, Non-Randomised, Multicentre Study to Assess the Effect of AZD9291 on the Pharmacokinetics of Simvastatin (a Sensitive CYP3A4 Substrate) in Patients with EGFRm Positive NSCLC whose disease has Progressed on an EGFR TKI <u>Dosage:</u> 80 mg osimertinib administered orally once daily in the fasted state; simvastatin 20 mg and 40 mg tablets, administered orally	52 patients
Study D5160C00017 (NCT02442349) [CSR available. Pts continued in follow-up]	Primary analysis DCO (DCO1): 04 March 2016 Latest DCO (DCO3): 20 March 2018	A Phase II, Open Label, Single-arm Study to Assess the Safety and Efficacy of osimertinib in Asia Pacific Patients with Locally Advanced/Metastatic NSCLC whose Disease has Progressed with Previous EGFR TKI Therapy and whose Tumours harbour a T790M mutation within the EGFR Gene	171 patients Asian patients only were enrolled.

Study Number (Study name; NCT number) [Status]	Study DCO (for safety and efficacy reporting)	Study design and dosage ^a	Total number of subjects dosed
Study D5160C00018 (NCT02529995) [Part A completed. CSR available. Part B ongoing]	Part A DCO: 28 January 2016	A Phase I, Open-Label, Two Parts Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of osimertinib in Chinese Patients with Advanced NSCLC who have Progressed Following Prior Therapy with an EGFR TKI <u>Dosage:</u> 40 mg or 80 mg osimertinib administered orally once daily in the fasted state	31 patients (15 patients received 40 mg dose level; 16 patients received 80 mg dose level)
Study D5160C00019 (DDI Substrate Study; NCT02317016) [Study completed. CSR available.]	Part A: 12 August 2015 Part B: 28 October 2016	A Phase I, Open-Label, Non-Randomised, Multicentre Study to Assess the Effect of AZD9291 on the Pharmacokinetics of Rosuvastatin (a Sensitive BCRP Substrate) in Patients with EGFRm Positive NSCLC whose disease has Progressed on an EGFR TKI <u>Dosage:</u> 80 mg osimertinib administered orally once daily in the fasted state; rosuvastatin 20 mg tablets, administered orally	44 patients
Study D5160C00020 (Absolute Bioavailability; NCT02491944) [Study completed. CSR available]	LSLV: 26 August 2015	A Phase I, Open-label, Single Dose, Single-Centre Study to Assess the Absolute Bioavailability of a Single Oral Dose of AZD9291 with Respect to an Intravenous Microdose of [¹⁴ C]AZD9291 in Healthy Male Subjects <u>Dosage:</u> 80 mg osimertinib administered orally plus 100 µg [¹⁴ C] osimertinib	10 healthy volunteers
Study D5160C00021 (Expanded Access Program; NCT02451852) [Ongoing]	N/A	A Multicentre, AZD9291 Expanded Access Program for the Treatment of Patients with Advanced/Metastatic EGFR T790M Mutation-Positive NSCLC Who Have Received Prior EGFR TKI Therapy	4055 patients
Study D5160C00022 (ASTRIS real world treatment study; NCT02474355) [Ongoing]	N/A	Open Label, Multinational, Multicentre, Real World Treatment Study of Single Agent osimertinib for Patients with Advanced/Metastatic EGFR T790M Mutation-Positive NSCLC Who Have Received Prior Therapy with an EGFR-TKI	3014 patients

Study Number (Study name; NCT number) [Status]	Study DCO (for safety and efficacy reporting)	Study design and dosage ^a	Total number of subjects dosed
Study D5160C00035 (Severe renal impairment study; NCT02923947) [Study completed. CSR available]	Part A (LSLV): 20 September 2018 Part B (LSLV): 10 May 2018	An Open-label, Non-randomised, Multicentre, Phase I study to assess the Pharmacokinetics, Safety and Tolerability of Osimertinib Following a Single Oral 80 mg Dose to Patients with Advanced Solid Tumours and Normal Renal Function or Severe Renal Impairment	16 patients with advanced solid tumours
Study D5160C00036 (P-gp interaction study; NCT02908750) [Study completed. CSR available]	PK Phase (LSLV): 30 July 2017	An Open-label, Non-randomised, Phase I Study to Assess the Effect of Single and Multiple Oral Doses of Osimertinib on the Pharmacokinetics of a P-glycoprotein Probe Drug (Fexofenadine) in Patients with Advanced EGFRm NSCLC that have Progressed on a Prior EGFR-TKI Regimen	24 patients
Study D5160C00043 (ODIN-BM; NCT03463525) [Ongoing]	N/A	A Phase I open-label 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 NSCLC and brain metastases.	3 patients
Study D5160C00048 (LAURA; NCT03521154) [Ongoing]	N/A	A Phase III, randomised, double-blind, placebo-controlled, multicentre, international study of osimertinib as maintenance therapy in patients with locally advanced, unresectable EGFR mutation-positive NSCLC (Stage III) whose disease has not progressed following definitive platinum-based chemoradiation therapy. Dosage: 40 to 80 mg osimertinib administered orally once daily.	26 patients were randomised at the DCO of this IB, due to blinding and randomised ratio of 2:1, 18 patients are assumed to have been treated with osimertinib
Study D5161C00003 (ELIOS; NCT03239340) [Ongoing]	N/A	A Phase II multicentre, open-label, single-arm, molecular profiling study of patients with EGFR mutation-positive locally advanced or metastatic NSCLC treated with osimertinib.	154 patients

Study Number (Study name; NCT number) [Status]	Study DCO (for safety and efficacy reporting)	Study design and dosage ^a	Total number of subjects dosed
Study D5164C00001 (Adjuvant study ADAURA; NCT02511106) [Ongoing]	N/A	A Phase III, Double-blind, Randomized, Placebo-Controlled Multi-centre, study to assess the efficacy and safety of osimertinib versus Placebo, in Patients with Epidermal Growth Factor Receptor Mutation Positive Stage IB-IIIA NSCLC, following Complete Tumour Resection with or Without Adjuvant Chemotherapy	682 patients were randomised at the DCO of this IB, due to blinding and randomised ratio of 1:1, 341 patients are assumed to have been treated with osimertinib
Study D5165C00001 (CAURAL; NCT02454933) [Study completed. CSR available]	Primary analysis (DCO1): 21 August 2017 Latest DCO: 21 March 2018	A Phase III, Multi-Centre, Open Label, Randomized Study to Assess the Efficacy and Safety of AZD9291 in Combination with durvalumab versus AZD9291 Monotherapy in Patients with Locally Advanced or Metastatic Epidermal Growth Factor Receptor T790M mutation-positive NSCLC who have received Prior EGFR TKI Therapy <u>Dosage:</u> 80 mg AZD9291 administered orally once daily in the fasted state with or without 10 mg/kg durvalumab administered by IV infusion once every 2 weeks	29 patients: 12 patients received osimertinib + durvalumab; 17 patients received osimertinib monotherapy. Original intention was to recruit 350 patients; however, recruitment was terminated as of 30 September 2015.

Study Number (Study name; NCT number) [Status]	Study DCO (for safety and efficacy reporting)	Study design and dosage ^a	Total number of subjects dosed
Study D5169C00001 (FLAURA2; NCT04035486) [Ongoing]	N/A	A Phase III, Open-label, Randomized Study of Osimertinib with or without Platinum Plus Pemetrexed Chemotherapy, as First-line Treatment in Patients with Epidermal Growth Factor Receptor (EGFR) Mutation-Positive, Locally Advanced or Metastatic NSCLC <u>Dosage (safety run-in period)</u>: osimertinib 1 tablet of 80 mg once daily with pemetrexed (500 mg/m²) plus cisplatin (75 mg/m²) on Day 1 of 21-day cycles (every 3 weeks) for 4 cycles, followed by osimertinib 80 mg once daily plus pemetrexed maintenance (500 mg/m²) every 3 weeks; or osimertinib 1 tablet of 80 mg once daily with pemetrexed (500 mg/m²) plus carboplatin (AUC5) on Day 1 of 21-day cycles (every 3 weeks) for 4 cycles, followed by osimertinib 80 mg once daily plus pemetrexed maintenance (500 mg/m²) every 3 weeks <u>Dosage (randomized period)</u>: osimertinib 1 tablet of 80 mg once daily; or osimertinib 1 tablet of 80 mg once daily with pemetrexed (500 mg/m²) plus either cisplatin (75 mg/m²) or carboplatin (AUC5) on Day 1 of 21-day cycles (every 3 weeks) for 4 cycles, followed by osimertinib 80 mg once daily plus pemetrexed maintenance (500 mg/m²) every 3 weeks.	13 patients in the safety run-in period
Study D6186C00001 (ORCHARD; NCT03944772) [Ongoing]	N/A	A Phase II biomarker-directed platform study in patients with advanced NSCLC whose disease has progressed on first-line osimertinib therapy.	2 patients in total, of which 1 patient has received osimertinib (in combination with AZD6094)
Study D5084C00007 (SAVANNAH; NCT03778229) [Ongoing]	N/A	A Phase II, single arm study assessing the efficacy of osimertinib in combination with savolitinib in patients with EGFRm+ and MET+, locally advanced or metastatic non-small cell lung cancer who have progressed following treatment with osimertinib. <u>Dosage</u>: Osimertinib 80 mg once daily plus savolitinib (initially 600 mg/day, subsequently 300 mg/day)	25 patients

Study Number (Study name; NCT number) [Status]	Study DCO (for safety and efficacy reporting)	Study design and dosage ^a	Total number of subjects dosed
Study D6030C00001 (BLOOM) [Study completed. CSR available]	15 October 2017	A Phase I, Open-label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-Tumour Activity of AZD3759 or osimertinib in Patients with EGFR Mutation Positive Advanced Stage NSCLC <u>Dosage:</u> 160 mg osimertinib administered orally once daily	41 patients with locally advanced or metastatic NSCLC (EGFR T790M mutation-positive) with LM
Study D6070C00004 (Umbrella) [Ongoing]	N/A	A Phase Ib/II multi-arm, open-label, multicentre, study to evaluate novel combination therapies in subjects with previously treated advanced EGFRm NSCLC. <u>Dosage:</u> MEDI9447 3000 mg IV every 2 weeks in combination with osimertinib 80 mg administered orally once daily	15 patients receiving osimertinib plus MEDI9447

^a Osimertinib 80 mg tablets administered orally, once daily, in a fasted state unless noted otherwise.

Abbreviations: AUC, Area under the plasma concentration-time curve; BCRP, breast cancer resistance protein; CSR, Clinical Study Report; CYP, Cytochrome p450; DCO, Data cut-off date; DDI, Drug-drug interaction; EGFR, Epidermal growth factor receptor; EGFRm/EGFRm+, Epidermal growth factor receptor mutation positive; FAS, Full analysis set; IB, Investigator's Brochure; IV, intravenous; LM, Leptomeningeal metastases; LSLV, Last subject last visit; N/A, not applicable; NSCLC, non-small cell lung cancer; P-gp, P-glycoprotein; PK, pharmacokinetics; TKI, tyrosine kinase inhibitor.

The key findings from the clinical programme to date are summarised below:

1.1.2.1 Clinical pharmacokinetics

Osimertinib pharmacokinetic parameters have been characterised in healthy subjects and NSCLC patients. Based on population pharmacokinetic analysis, osimertinib apparent plasma clearance is 14.2 L/h, apparent volume of distribution is 997 L and terminal half-life is approximately 48 hours. The area under the plasma concentration-time curve (AUC) and maximal plasma concentration (C_{max}) of osimertinib increased dose proportionally over 20 mg to 240 mg dose range (i.e, 0.25 to 3 times the recommended dosage) after oral administration and exhibited linear pharmacokinetics (PK). Administration of osimertinib orally once daily resulted in approximately 3-fold accumulation with steady state exposures achieved after 15 days of dosing. At steady state, the C_{max} to C_{min} (minimal concentration) ratio was 1.6-fold.

The median time to C_{max} of osimertinib was 6 hours (range 3 to 24 hours). The absolute bioavailability of TAGRISSO is 70% (90% CI 67, 73). Neither food nor gastric pH affects the exposure of osimertinib. In vitro, plasma protein binding of osimertinib is 94.7% (5.3% free). Osimertinib has also been demonstrated to bind covalently to rat and human plasma proteins, human serum albumin and rat and human hepatocytes. In vitro studies indicate that osimertinib is metabolised predominantly by CYP3A4/5. Two pharmacologically active metabolites (AZ7550 and AZ5104) have been identified in the plasma after oral administration. The geometric mean exposure (AUC) of each metabolite (AZ5104 and AZ7550) was approximately 10% of the exposure of osimertinib at steady-state. Osimertinib is primarily eliminated in the faeces (67.8%) and to a lesser extent in the urine (14.2%). Unchanged osimertinib accounted for approximately 2% of the elimination.

Based on in vitro studies, osimertinib is a competitive inhibitor of CYP 3A4/5 but not YP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1 at clinically relevant concentrations. In vitro, osimertinib is not a substrate of OATP1B1 and OATP1B3 and does not inhibit P-gp, OAT1, OAT3, OATP1B1, OATP1B3, OCT2, MATE1 and MATE2K at clinically relevant concentrations. Based on in vitro studies, osimertinib is a substrate of P-glycoprotein and BCRP, but is unlikely to result in clinically relevant drug interactions. Osimertinib is an in vitro inhibitor of BCRP.

Based on clinical DDI studies, interactions with strong CYP3A4 inhibitors are unlikely but strong CYP3A4 inducers can decrease the exposure of osimertinib. Osimertinib may also increase the exposure of co-administered BCRP substrates or P-gp substrates. Clinical PK interactions with co-administered CYP3A4 substrates are unlikely.

No clinically significant differences in the pharmacokinetics of osimertinib were observed based on age, sex, ethnicity, body weight, smoking status, mild or moderate or severe renal impairment (creatinine clearance [CL_{cr}] >15 mL/min by Cockcroft-Gault) or mild or moderate hepatic impairment (mild: total bilirubin less than or equal to the upper limit of normal [ULN] and aspartate aminotransferase [AST] greater than ULN or total bilirubin between 1 to 1.5 times ULN and any AST; moderate: total bilirubin between 1.5 to 3 times ULN and any AST). No dose adjustment for osimertinib is required when treating patients with severe renal impairment;

however, as patients with severe renal failure have a higher osimertinib mean exposure compared to normal renal function patients, caution should be exercised when treating patients with severe and end-stage renal impairment.

Based on an analysis of dose-exposure response relationships over the dose range of 20 mg (0.25 times the recommended dose) to 240 mg (3 times the recommended dose), no apparent relationship between osimertinib exposure and objective response rate, duration of response and progression-free survival was identified. Over the same dose range, increased exposure led to increased probability of adverse reactions, specifically rash, diarrhoea and interstitial lung disease (ILD). A pharmacokinetic/pharmacodynamic analysis in AURA2 suggested a concentration-dependent QTc interval prolongation of 14 msec (upper bound of two-sided 90% confidence interval [CI]: 16 msec) at a dose of 80 mg orally (PO). In summary, the clinical pharmacology package provides characterization of the key PK and ADME characteristics of osimertinib and provides confirmatory data in support of the 80 mg dose and adequate labelling for special populations. From a clinical PK perspective, these data support a once daily fixed 80 mg PO dose for this advanced NSCLC population.

1.1.2.2 Clinical efficacy

FLAURA study: First-line locally advanced or metastatic NSCLC patient population

A total of 673 patients with locally-advanced or metastatic EGFRm NSCLC have been dosed with first-line treatment in the FLAURA study (in both the Global cohort and the China cohort). Of the 556 patients who have been unblinded, 279 received osimertinib 80 mg QD and 277 received the standard of care (SoC). At DCO1 (12 June 2017), the data provided strong evidence for the clinical benefit of osimertinib for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR with Exon19 Deletion activating mutation (EGFR[Ex19del]) or EGFR with L858R activating mutation (EGFR[L858R]) mutations:

- Median PFS was 18.9 months with osimertinib and 10.2 months with SoC, representing an 8.7-month improvement for osimertinib compared with SoC (p-value <0.0001; hazard ratio [HR] 0.46; 95% CI 0.37, 0.57).
- The results from the interim overall survival (OS) analysis showed a clinically meaningful improvement in OS in the osimertinib arm (HR: 0.63 [95% CI: 0.45, 0.88]) compared with SoC, which did not reach formal statistical significance (maturity: 25.4% overall).
- The ORR was 79.9% (95% CI: 74.7, 84.5) in the osimertinib arm and 75.8% (95% CI: 70.3, 80.7) with SoC (odds ratio [OR] 1.27; 95% CI 0.85, 1.90; p = 0.2421).
- There was a doubling of the median DoR for osimertinib (17.2 months [95% CI: 13.8, 22.0]) compared with SoC (8.5 months [95% CI: 7.3, 9.8]).

- The disease control rate (DCR) was similar and >90% in both arms: 97.1% (95% CI: 94.4, 98.8) in the osimertinib arm and 92.4% (95% CI: 88.6, 95.2) with SoC (OR 2.78; 95% CI 1.25, 6.78; $p = 0.0110$).
- Patients who received osimertinib as first-line treatment also had clinically meaningful improvements in time to second progression (PFS2), time to first subsequent therapy (TFST) and time to second subsequent therapy (TSST) compared with patients randomised to SoC. The analysis of these post-progression endpoints demonstrated that PFS benefit was largely preserved through subsequent lines of therapy.

Data from the FLAURA study confirmed the superior CNS efficacy results in first-line setting that have been reported in later lines of therapy with osimertinib:

- There was a statistically significant (p -value=0.014) and clinically meaningful improvement in PFS in the osimertinib arm compared with the SoC arm in the CNS Full Analysis Set (cFAS) based on CNS Blinded Independent Central Review (BICR; HR: 0.48 [95% CI: 0.26, 0.86]), indicating a 52% reduction in the risk of CNS disease progression or death in the osimertinib arm compared to the SoC arm. Median PFS could not be calculated for osimertinib and was 13.9 months for SoC.
- A numerically greater proportion of patients had CNS objective response in the osimertinib arm (66%) compared with the SoC arm (43%).
- The median CNS DoR could not be calculated for the osimertinib arm and was 14 months in the SoC arm.

At the DCO2 (25 June 2019) final OS analysis, 321/556 patients had died (55.6% in the osimertinib arm and 59.9% in the SoC arm; 57.7% maturity overall). The HR for OS was 0.799 (adjusted 95.05% CI: 0.6406, 0.9968), signifying a 20% lower risk of death in the osimertinib arm compared with the SoC arm. The difference between treatment arms in favour of osimertinib was statistically significant, as the p -value of 0.0462 was below the predefined level of 0.0495 required at this analysis. Median OS was 38.6 (95% CI: 34.5, 41.8) months in the osimertinib arm, and 31.8 (95% CI: 26.6, 36.0) months in the SoC arm, a difference of 6.8 months. Post-progression outcomes showed a clinically relevant longer time from randomisation to TFST or death for patients on osimertinib compared to patients on SoC (HR: 0.478 [95% CI: 0.3927, 0.5810; 2-sided p -value <0.0001). There was also a clinically relevant longer time to TSST for patients on osimertinib compared to patients on SoC (HR: 0.687 [95% CI: 0.5610, 0.8424; 2-sided p -value = 0.0003).

Additionally, at DCO2, the improvement in CNS PFS was determined to be statistically significant and clinically relevant for patients on osimertinib compared to patients on SoC (HR: 0.48 [95% CI: 0.26, 0.86]; p -value = 0.014). The median CNS PFS was not reached in the osimertinib arm (95% CI: 16.5, NC) compared to 13.9 months in the SoC arm (95% CI: 8.3, NC).

These data demonstrate that most of the benefit of osimertinib seen in the PFS analysis at DCO1 was preserved in the final OS analysis at DCO2. The OS benefit of osimertinib over SoC was consistent across all predefined subgroups, with variation in the magnitude of benefit in the subgroups of race (Asian/non-Asian) and EGFR mutation type (Ex19del/L858R). The OS data from DCO2 also adds further evidence that osimertinib offers clinically meaningful CNS efficacy to patients with CNS metastases at baseline, a subgroup of patients for whom no EGFR-TKIs other than osimertinib have demonstrated efficacy.

The FLAURA China cohort (DCO1c: 10 January 2018) included 136 patients; 19 of whom were randomised prior to the end of global recruitment and were also included in the global analysis. Of the 136 patients randomised in the China cohort, 71 received osimertinib 80 mg once daily and 65 received the SoC (all gefitinib). The PFS (investigator assessed) efficacy of osimertinib compared to SoC was consistent with the overall global study population:

- There was a clinically meaningful improvement in PFS for patients on osimertinib compared with patients on SoC based on investigator assessment (HR: 0.56 [95% CI: 0.37, 0.85; p=0.0065]). There was an 8.0-month improvement in median PFS compared to SoC (median PFS: 17.8 months [95% CI: 13.6, 20.7] in the osimertinib arm vs 9.8 months [95% CI: 8.3, 13.8] in the SoC arm).
- The results from the interim OS analysis showed a HR of 0.68 (95% CI: 0.38, 1.22). Visual assessment of the Kaplan-Meier (KM) curves suggest that the proportionality assumption does not hold, therefore caution is required in interpretation of the OS effect via the HR. There were encouraging OS data for patients in the osimertinib arm compared to patients in the SoC arm: the OS curves separate after 12 months and a greater proportion of patients treated with osimertinib were alive at 18 months compared to patients in the SoC arm. The low maturity of the OS data (33.1%) and small number of events in this analysis should be taken into consideration.
- High response rates (>75%) were seen in the China cohort and were as expected, with all responses being partial responses (PRs). □ There was a clinically meaningful improvement in median DoR for patients on osimertinib (16.4 months [95% CI: 12.3, not calculable]) compared with patients on SoC (10.9 months [95% CI: 8.3, 13.8]).

At the final OS analysis of the FLAURA China cohort (DCO2c: 25 June 2019), 89/136 patients had died, comprising 45 patients (63.4%) in the osimertinib arm, and 44 patients (67.7%) in the SoC arm. The maturity of the OS analysis was therefore calculated to be 65.4%, with a median follow-up for overall survival time of 31.0 months for osimertinib-treated patients and 24.9 months for patients receiving SoC. The final OS analysis HR was 0.848 (95% CI: 0.5568, 1.2910; p=0.4416), indicating a clinically meaningful 15% reduction in the risk of death in the osimertinib arm compared to the SoC arm. The median OS was 33.1 months (95% CI: 26.0, 35.9) in the osimertinib arm, and 25.7 months (95% CI: 19.6, 32.8) in the SoC arm. This represents a clinically meaningful 7.4 month extended OS benefit for patients in the osimertinib arm versus SoC. At DCO2c, the final OS analysis of the China cohort was generally consistent with the overall OS data for the global population.

In first-line (treatment-naïve) NSCLC patients, a total of 60 patients received PO treatment with osimertinib in the AURA Phase I study (30 patients each at 80 mg and 160 mg respectively).

In first-line (treatment-naïve) NSCLC patients, a total of 60 patients received PO treatment with osimertinib in the AURA Phase I study (30 patients each at 80 mg and 160 mg respectively). The overall ORR was 77% (95% CI: 64, 87) and the overall DCR was 98% (95% CI: 89, 100). The median PFS was 20.5 months (95% CI: 13.7, 26.1), with median DoR at 18.0 months (95% CI: 12.5, 24.7). The percentage of patients remaining progression-free at 12 months was 72% (95% CI: 59, 82) and at 18 months 56% (95% CI: 42, 68).

AURA3 study: 2nd line or greater, T790M mutation positive, advanced NSCLC patient population

The AURA3 study demonstrated superior efficacy of osimertinib compared to chemotherapy in patients with advanced EGFR T790M mutation positive NSCLC, whose disease has progressed on or after EGFR TKI therapy. At the time of the primary efficacy analysis (DCO1: 15 April 2016), there was a statistically significant and clinically meaningful improvement in PFS (investigator assessed) for patients on osimertinib 80 mg PO once-daily vs. those on chemotherapy (HR: 0.30, 95% CI: 0.23, 0.41; p-value: <0.001), indicating a 70% reduction in risk of disease progression or death (in the absence of a Response Evaluation Criteria In Solid Tumours [RECIST] progression) in the osimertinib arm. Treatment with osimertinib resulted in a 5.7-month improvement in median PFS compared to chemotherapy (10.1 months [95% CI: 8.3, 12.3] vs. 4.4 months [95% CI: 4.2, 5.6]). Similar results were seen with the BICR assessment of PFS.

There was also a clinically meaningful and statistically significant improvement in ORR in the osimertinib arm (70.6%) compared with the chemotherapy arm (31.4%), with an OR of 5.39 (95% CI: 3.47, 8.48) (p-value: <0.001). The median DoR (51.9% maturity; investigator assessed) was 9.7 months (95% CI: 8.3, 11.6) in the osimertinib arm vs. 4.1 months (95% CI: 3.0, 5.6) in the chemotherapy arm. There was a statistically significant improvement in expected DoR (EDoR) for patients on osimertinib compared with those on chemotherapy (ratio of EDoR: 6.22; 95% CI: 4.04, 9.57; p-value: <0.001). Furthermore, a statistically significant difference ($p \leq 0.001$) in mean change from baseline (from randomisation to 6 months) between osimertinib and chemotherapy was also observed for all 5 pre-specified key lung cancer symptoms of the patient-reported outcomes (PRO) (cough, dyspnoea, pain in chest, fatigue, and appetite loss); with prolonged time to deterioration for dyspnoea and cough.

A BICR assessment of CNS efficacy in patients with CNS metastases at baseline showed a clinically meaningful improvement for patients randomised to receive osimertinib vs. chemotherapy. The improvements in CNS efficacy outcomes were consistent across multiple analyses (ORR of 70% vs 31.3%, OR of 5.13 with a p-value of 0.015; DoR 8.9 months vs 5.7 months; PFS 11.7 months vs 5.6 months, for osimertinib vs. chemotherapy, respectively).

At the final OS analysis in AURA3 (DCO4 of 15 March 2019; 67.1% maturity for OS overall), osimertinib demonstrated a numerical advantage in OS compared to chemotherapy, which did not reach statistical significance (HR=0.87 [95.564% CI: 0.67, 1.13]; $p=0.277$). The median OS was 26.8 months (95% CI: 23.49, 31.54) in the osimertinib arm and 22.5 months (95% CI: 20.17, 28.81) in the chemotherapy arm. Patients initially randomised to the chemotherapy arm were allowed per protocol to cross-over to treatment with osimertinib following RECIST progression. The interpretation of the OS results from this study are thus confounded by the fact

that a large proportion of patients in the chemotherapy arm crossed over to receive treatment with osimertinib after RECIST progression (99/140 [70.7%] patients in the chemotherapy arm overall. The protocol assumption for the median OS for the chemotherapy arm was 16 months, so this arm performed better than expected, meaning the KM curves were closer together than expected, and these data confirm that in patients with previously treated EGFR T790M mutation-positive NSCLC, responses to osimertinib were durable.

Efficacy findings in the osimertinib arm of the AURA3 study were consistent with those in the pooled Phase II studies.

The pooled single arm Phase II studies (AURA extension and AURA2) support the consistency and durability of effect of osimertinib 80 mg PO once-daily in a broader population of patients (including second [2nd] line and $\geq$ third [3rd] line therapy) with advanced EGFR T790M mutation positive NSCLC with longer follow up. Confirmed ORR (BICR) was 66.0% (95% CI: 61.1, 70.7) and median DoR (BICR) (44.3% maturity) was 12.5 months (95% CI: 11.1, not calculable [NC]). The estimated percentage of patients remaining in response at 9 months was 65.0% (95% CI: 58.5, 70.6) and at 12 months was 52.9% (95% CI: 45.9, 59.4). The median PFS (BICR) in the Full Analysis Set (FAS) was 11.0 months (95% CI: 9.6, 12.4). The median follow-up for OS was 13.4 months, however OS data were still immature. Overall, the efficacy variables determined by both BICR and investigator assessment showed similar results.

A BICR assessment of CNS efficacy in a subgroup of patients with CNS metastases from the pooled Phase II studies showed consistent results with the AURA3 analysis. ORR in patients was 54.0% (95% CI: 39.32, 68.19); 80.4% of patients remained in response at 6 months and 75.4% at 9 months. The Kaplan-Meier (KM) estimated percentage of patients alive and CNS progression-free at 6 and 12.

In summary, the Phase III AURA3 study demonstrated clear evidence of overall favourable efficacy of osimertinib compared with the standard of care, chemotherapy. The CNS metastases efficacy analysis results in AURA3 also demonstrated the superior efficacy of osimertinib compared to chemotherapy in patients with CNS metastases. The overall efficacy and CNS efficacy findings from the pooled single arm Phase II studies support the consistency and durability of effect of osimertinib in a broader population of patients (including 2nd-line and $\geq$ 3rd-line therapy) with advanced EGFR T790M mutation-positive NSCLC with longer follow-up and are consistent with the efficacy observed with osimertinib in AURA3.

1.1.2.3 Clinical safety

Osimertinib 80 mg PO once-daily has an acceptable safety profile for the intended advanced NSCLC population.

- In the osimertinib clinical program,
 - ILD or ILD-like adverse reactions (eg, pneumonitis) were reported in 3.9% and were fatal in 0.4% (5 patients) of the 1142 patients who received osimertinib in AURA and FLAURA studies. The incidence of ILD was 10.4% in patients of Japanese ethnicity, 1.8% in patients of non-Japanese Asian ethnicity and 2.8% in non-Asian patients. The median time to onset of ILD or ILD-like adverse reactions was 2.8 months.

- Osimertinib leads to a predicted drug-related QTc interval prolongation at the 80 mg dose of 14.2 msec with an upper bound (90% CI) of 15.8 msec, but with no evidence that this is associated with an increased risk of cardiac arrhythmias or Torsades de Point (TdP). In safety dataset of 1142 patients in AURA studies treated with osimertinib 80 mg, 0.9% (n=10) were found to have a QTc greater than 500 msec, and 3.6% (n=41) had an increase from baseline QTc greater than 60 msec.
- Based on the available clinical trial data, a causal relationship between changes in cardiac contractility and osimertinib has not been established.
- Osimertinib has not been associated with gastrointestinal perforations or haemorrhagic diarrhoea and no events leading to dehydration or renal failure have been reported. No severe bullous, blistering or exfoliative skin conditions were observed.
- AstraZeneca considers there to be a reasonable possibility of a causal relationship between osimertinib, keratitis and related corneal disorders.
- Decreases from baseline in median values for platelets, neutrophils and leucocytes were observed early in treatment with osimertinib. Median values appear to stabilise after the initial drop with the majority of patients experiencing a single grade change or no change in CTCAE grade. As would be expected with the small magnitude of these changes, no clinically significant sequelae in the population have been observed.
- Evaluation for potential liver toxicity has shown no apparent association of osimertinib with drug induced liver injury.
- There is no apparent association of osimertinib with renal toxicity.
- An increased incidence in the ILD reporting rate has been reported for the combination of durvalumab and osimertinib in Study D5160C00006 (TATTON). This study showed an incidence rate of 32.4% for pneumonitis/ILD-like events, at a data cut-off of 12 July 2017, compared with an overall frequency of pneumonitis (including both non serious and serious cases) of around 5% for durvalumab 10 mg/kg monotherapy and an overall frequency of pneumonitis/ILD of 3.5% for osimertinib monotherapy. These findings were not subsequently replicated in Study D5165C00001 (CAURAL)

1.2 Rationale for study design and doses selection

Glioblastomas, the highly metabolic tumor, are still known to represent a therapeutic challenge characterized by inevitable disease recurrence. The high medical need in this indication has driven the development of new therapeutic approaches targeting cancer metabolism over the last several years.

In the current study, we will use clinical 18F-FDG PET imaging to detect changes in tumor glucose utilization, which allows investigators to obtain an early read out on the impact of EGFR inhibitor osimertinib on glioblastoma patients whose tumors have EGFR activation. If the

clinical translation of this approach is successful, it will speed clinical development of EGFR inhibitors in glioblastoma including exploration of dose and schedule.

Glioblastomas (GBM) patients enrolled to the study will have two baseline 18F-FDG PET scans (18 to 54 hours apart) prior to osimertinib dosing. Patients will then be given osimertinib at 240 mg (QD) for 3 days and the 3rd 18F-FDG PET scan will be taken early post dosing (between 24-72 hours). We will assess the osimertinib-induced attenuation in tumor glucose uptake by the three 18F-FDG PET scans. The dosing with osimertinib at 240 mg (QD) will increase speed to steady state in the CNS and optimise the possibility of identifying a signal on 18F-FDG PET scan.

After the completion of the 3-day treatment period, the patients will start osimertinib treatment cycles (28-day cycle) at dose of 160 mg (QD) with dose reduction (80 mg QD) as clinically indicated. Although the recommended dose in advanced NSCLC patients is 80 mg PO once a day. The Phase I AURA study demonstrated clinical activity in all doses studied (20 mg to 240 mg), with no maximum tolerated dose (MTD) reached at the 240 mg dose. Therefore, 160 mg with dose reductions was chosen for this study in order to achieve the highest concentrations safely achievable of osimertinib for this study. The recommended dose is 80 mg in EGFRm NSCLC. It is acknowledged that in glioblastoma, the receptor may be wild type rather than mutant, and there may be receptor amplification. Therefore, an increased dose of 160mg is proposed for the study to optimize the potential of identifying a signal in the patient population. Use of 160mg has been demonstrated to be tolerated in patients (BLOOM study).

1.3 Benefit/risk and ethical assessment

Gliomas are the most common primary brain tumors in adults and glioblastomas are classified as the most malignant subtype. Median survival in glioblastoma patients is restricted to approximately 16 months in clinical trial populations [4]. There is clearly a need for more effective therapies based on novel mechanisms of action.

EGFR is one of four closely related subfamily members: EGFR (ErbB-1), HER-2/neu (ErbB-2), HER-3 (ErbB-3), and HER-4 (ErbB-4). Ligand activation of the monomeric receptor leads to homo- or heterodimerization with activation of the tyrosine kinase intracellular domain, leading in turn to activation of cell signaling pathways. Activation of EGFR is associated with signaling via PLC-gamma-1, Ras-Raf-MEK-MAPKs, phosphatidylinositol-3 kinase (PI3K) and Akt, Src, the stress-activated protein kinases (SAPKs), PAK-JNKK-JNK, and the signal transducers and activators of transcription (STATs) [5]. Activation of such cell-signaling pathways directly modulates tumor cell division, invasion and apoptosis. In addition, EGFR activation also indirectly affects factors that play an important role in tumor cell survival and growth such as vascular endothelial growth factor (VEGF) directed angiogenesis [6].

Activation of EGFR via overexpression, amplification, and mutation affects the majority of GBM tumors [7-9]. There are two different types of mutations to the EGFR gene in GBM that have been discovered [10]. One mutation with deletion of several exons in the gene, EGFRvIII, leads to constitutive activation of the receptor. Several other missense mutations in the extracellular domains also lead to increase activation of the receptor [11]. Recently, The Cancer Genome Atlas project confirmed that about 45% of GBM tumors harbor either focal amplification, mutations, or both of the EGFR gene [12], confirming that EGFR is a critical

mediator of GBM pathogenesis and therefore represents a potentially important therapeutic target.

There have been multiple trials of EGFR inhibitors in GBM, mainly using small molecular ATP-competitive tyrosine kinase inhibitors (TKIs). However, several phase II trials of First- and second-generation EGFR TKIs inhibitors such as erlotinib or gefitinib have demonstrated limited effectiveness of these agents for gliomas due to limited blood brain barrier penetration [13-15], with afatinib having the highest efficacy despite its incomplete penetration [16].

Osimertinib, the third-generation *EGFR* TKI, is a mono-anilino-pyrimidine compound that acts as a covalent *EGFR* TKI. In *EGFR*-recombinant enzyme assays, osimertinib showed potent activity against diverse *EGFR* mutations (L858R, L858R/T790M, exon 19 deletion, and exon 19 deletion/T790M) and exhibited nearly 200 times greater potency against L858R/T790M than wild-type *EGFR*. There has been evidence supporting osimertinib having good blood brain barrier penetrating properties.

- Osimertinib was shown to distribute into mouse brain and H1975 lung tumour xenografts, with higher concentrations in these tissues than in plasma. In the cynomolgus monkey PET study, the data clearly showed that [¹¹C]osimertinib penetrated the blood-brain barrier of the cynomolgus monkey and to a superior extent to that of its active metabolite [¹¹C]AZ5104.
- Osimertinib induced sustained tumor regression in an EGFR-mutated PC9 mouse BM model and human pharmacokinetics and mouse pharmacokinetics/pharmacodynamics models suggest that doses of 80 mg and 160 mg could be active in human central nervous system (CNS) disease.
- Preliminary PK data from the BLOOM study (ClinicalTrials.gov identifier: NCT02228369) showed that osimertinib penetrated the blood brain barrier (BBB) with decreases in EGFRm DNA copies indicating exposure in cerebrospinal fluid (CSF) of approximately 15% of the osimertinib concentration in free plasma.
- Clinical activity of osimertinib in CNS disease was observed in the phase I AURA trial and an analysis from AURA phase II trials [17] demonstrated the consistent activity of osimertinib in patients with EGFR-mutant T790M NSCLC with and without brain metastases, suggesting its activity in the brain.
- In the CNS full analysis set ($N = 128$) from FLAURA trial, osimertinib reported improved CNS RR (66 vs. 43%) and longer CNS PFS (NR vs. 13.9 months, HR 0.48, 95% CI: 0.26–0.86, $p = 0.014$) and reduced the risk of CNS progression compared with the standard of care. Among evaluable CNS evaluable patients ($N = 41$), osimertinib improved the CNS RR (91 vs. 68%) with similar DOR compared with the standard of care (15.4 vs. 18.7 months) [18].

Thus, osimertinib has great clinical potential in treating glioblastoma and not been investigated in clinical studies yet.

Osimertinib was relatively well tolerated in the phase I AURA trial. No DLT was observed at any dose level up to 240 mg daily. In the combined cohort of 253 patients, the most common adverse events (usually grade 1–2) were diarrhea (47%), skin toxicity (rash/acne, 40%), nausea

(22%), and anorexia (21%). Diarrhea and skin toxicity increased with escalating doses of osimertinib. Overall, however, osimertinib was associated with less dermatologic and gastrointestinal toxicity compared with historic data and clinical experience with other approved *EGFR* TKIs. Only 13% of patients experienced a grade 3 or higher drug-related adverse event. Serious adverse events were observed in 22% of patients (pneumonitis-like events, pulmonary embolism, and pleural effusion), with 6% of patients experiencing a serious drug-related adverse event. Adverse events prompted drug reductions in 7% of patients and drug discontinuation in 6% of patients. The frequency and severity of adverse events were similar between Asian and non-Asian patients. The six cases of potential pneumonitis-like events resolved after treatment discontinuation. Hyperglycemia and QT prolongation were reported in 6 (2%) and 11 (4%) patients, respectively. Among the seven fatal adverse events reported, only one (pneumonia) was considered as possibly drug related.

In the ongoing phase I BLOOM study for NSCLC patients with leptomeningeal metastases, 160 mg daily osimertinib has been investigated for safety. At the study DCO, a total of 13 NSCLC patients with leptomeningeal metastases LM had been dosed with 160 mg daily osimertinib. The most frequent AEs were diarrhoea (7 [54%] patients, all CTCAE Grade ≤ 2) and rash (grouped terms; 6 [46%] patients, all CTCAE Grade ≤ 2). There were 4 AEs of CTCAE Grade ≥ 3 occurring in one patient each; anaemia; neutropenia; hyponatraemia and aspiration pneumonia. The event of neutropenia resolved after a 3-day dose interruption and the patient continued to receive osimertinib at a dose of 80 mg once daily. Two patients withdrew because of AEs (dysphagia and aspiration pneumonia). There had been no events of ILD or QT prolongation[19].

Osimertinib appeared less tolerable at doses above 80 mg; an approximate doubling in the incidence of skin disorders, nail effects and diarrhoea were observed at doses higher than 80 mg, with severe CTCAE Grade ≥ 3 instances of these events occurring more frequently at the 160 mg and 240 mg doses.

Taking consideration of the risk/benefit and ethical assessment, osimertinib 240 mg QD (on Days -3, -2 and -1) and 160 mg QD (28-day cycle) with dose reduction (80 mg QD) as clinical indicated will be administered orally in glioblastoma patient population in this study. Patients will be monitored closely for AE during the treatment as outlined in table.

Please refer the latest investigator brochure for updated clinical information details.

1.4 18-FDG- Positron Emission Tomography (PET)

Positron emission tomography (PET) is a powerful non-invasive imaging technique for studying and quantifying biochemistry in vivo[20]. The glycolytic phenotype of tumors, including malignant gliomas, can be measured by PET using the fluorinated glucose derivative [^{18}F]-2-fluoro-2-deoxyglucose ([^{18}F]-FDG), a glucose analog that is used to monitor glucose utilization of cancer. It serves a highly sensitive early intermediate endpoint biomarker for therapy response for many cancers. Although not a specific biomarker, FDG-PET detects meaningful changes in tumor and organ glucose metabolism (i.e. lymph nodes, spleen, etc.) Given the critical role of glucose metabolism in GBM, [^{18}F]-FDG PET may have a tremendous value for assessing the metabolic phenotype in GBM and early response evaluation to glycolytic interventions [21, 22]. [^{18}F]-FDG PET is not widely used in GBM as the normal brain has high avidity for [^{18}F]-FDG, which can make the detection of brain tumors with [^{18}F]-FDG challenging. However, the use of combined PET and magnetic resonance imaging (MRI) and/or delayed imaging techniques can improve the delineation between brain tumor and surrounding benign neural tissue [23].

The rationale for employing FDG-PET is based on the premise that malignant nodules will exhibit increased glucose uptake and metabolism compared to benign nodules. This phenomenon is the well-known “Warburg Effect”, which is a consequence of genetic alterations in oncogenes and/or tumor suppressors, is often visualized non-invasively in cancer patients using 18F-fluorodeoxyglucose (18F-FDG) and positron emission tomography (PET)[24].

In our recent pre-clinical study, it has been shown that the detection of rapid inhibitory effects on [^{18}F] fluorodeoxyglucose uptake, assessed through noninvasive positron emission tomography, was an effective predictive biomarker of response in vivo (Figure 1)[2].

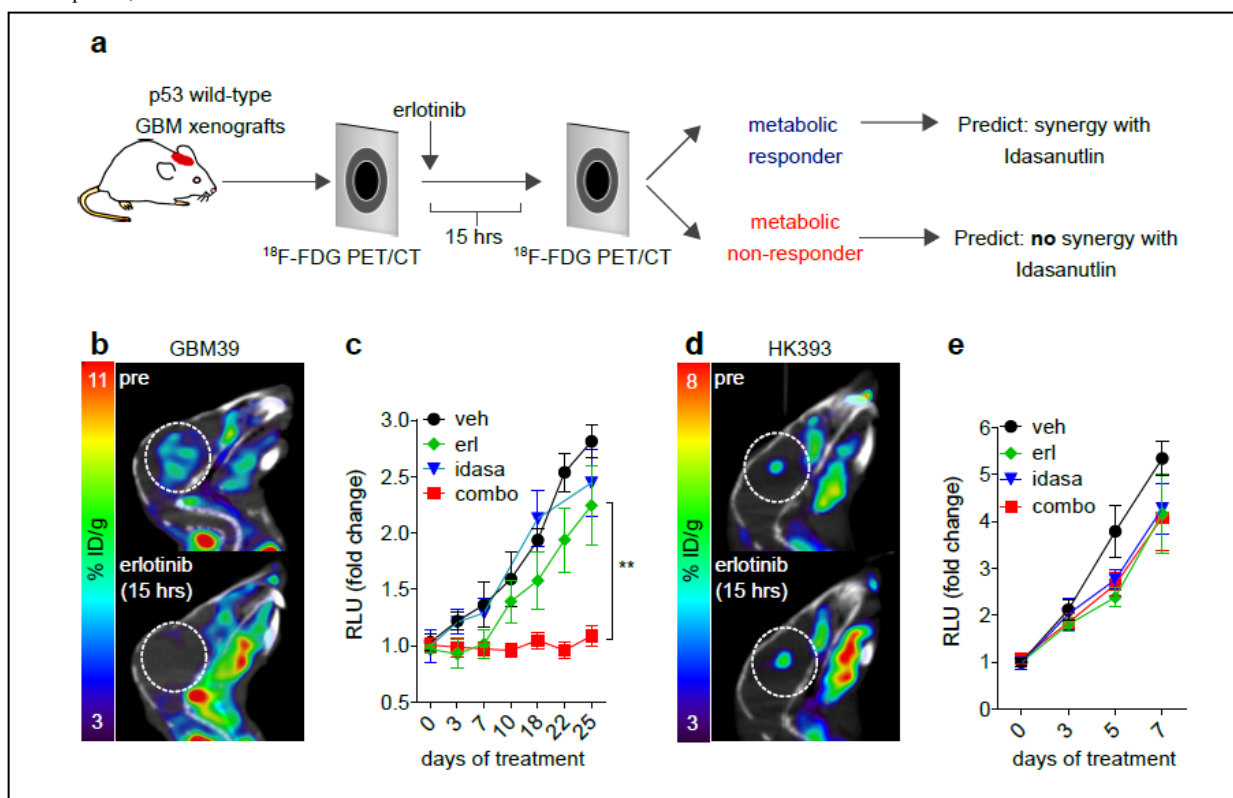
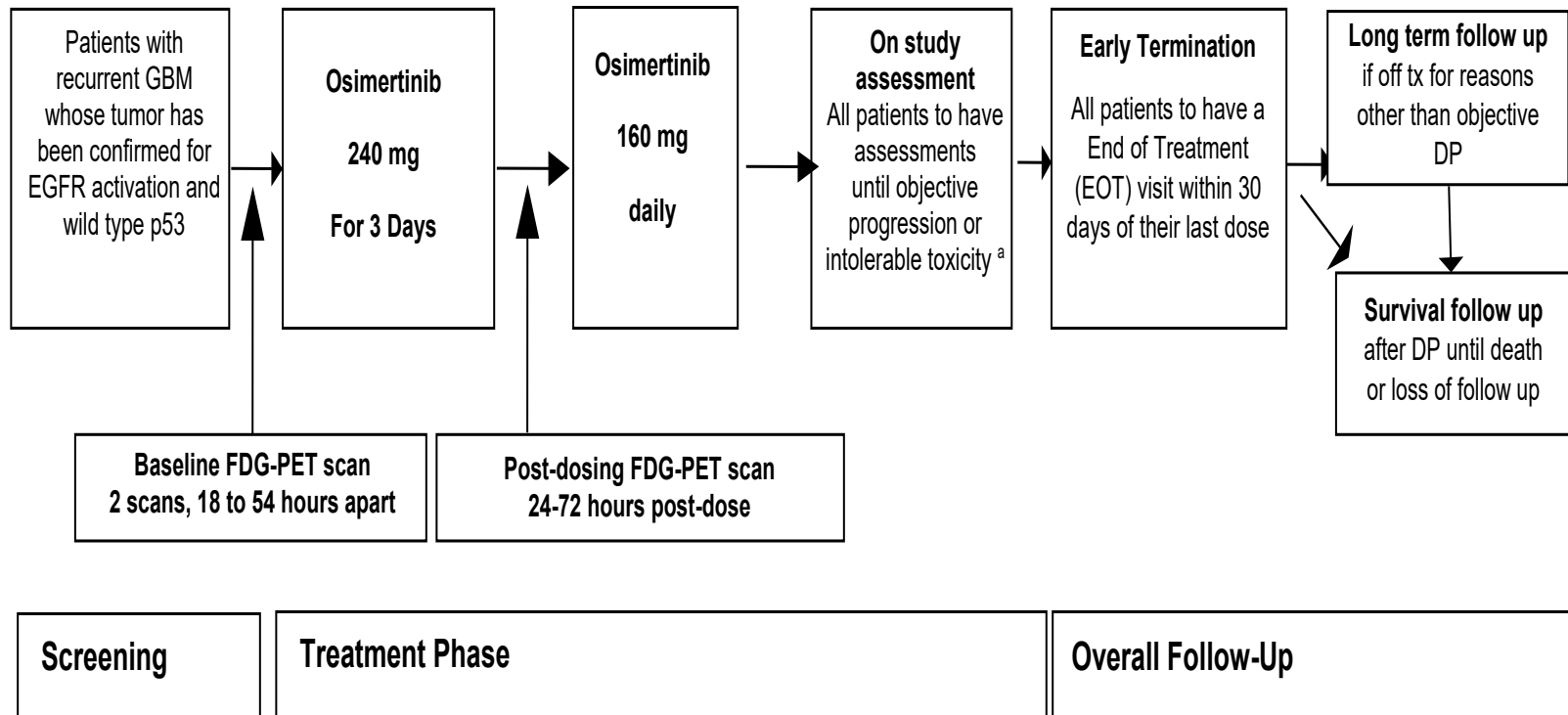


Figure 1. Combined targeting of EGFR-driven glucose uptake and p53 suppresses tumor growth in vivo. (a) Schematic of approach using [18F]FDG PET to rapidly predict changes in glucose uptake after EGFR-inhibitor treatment and consequent sensitivity to p53 stabilization with idasanutlin. (b) Representative [18F]FDG PET/CT images of GBM39 intracranial xenografts scanned before (pre) and after 15 h of 75 mg/kg erlotinib treatment (n = 3 mice). ID/g, injected dose per g. (c) GBM39 intracranial xenografts were treated daily with vehicle (veh; n = 6 mice), 75 mg/kg erlotinib (erl; n = 9 mice), 50 mg/kg idasanutlin (idasa; n = 7 mice), or both erlotinib and idasanutlin (combo; n = 8 mice), and tumor burden was assessed on the indicated days on the basis of secreted Gaussia luciferase activity (mean $\pm$ s.d.; measurements in Online Methods). RLU, relative light units. (d) As in b, but for HK393 intracranial xenografts. (e) As in c, but for HK393 intracranial xenografts (mean $\pm$ s.d., n = 7 mice for all groups). (f) Percentage survival of c (after 25-d treatment, then release). Tx, treatment.

Although heightened glycolysis is typically synonymous with cancer metabolism, recent technological advances to quantify cellular metabolites (e.g., ^{13}C -glucose metabolic tracing with liquid chromatography-mass spectrometry) has revealed numerous other metabolic pathways that may also be aberrantly activated in cancer. These include, but certainly not limited to, elevated flux into amino acid, nucleotide and lipid biosynthetic pathways, as well as increased oxidative phosphorylation for synthesis of ATP and NADH. Accordingly, there is now significant interest in precisely identifying which metabolic pathways are utilized in certain malignancies, and whether they stratify within a specific genetic context. This may ultimately lead to novel therapeutic strategies to target tumor metabolism for anti-cancer therapy[4].

1.5 Study Design

Figure 2 Study Design



^a Patients will continue to receive treatment until objective disease progression or for as long as they are receiving clinical benefit in the opinion of the Investigator unless any of the criteria for treatment discontinuation are met first.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
1. Define the test - retest variance of tumor FDG uptake using double baseline 18F-FDG PET imaging (18 to 54 hours apart) in patients with recurrent EGFR activated glioblastoma.	Inpatient Variance of tumor FDG uptake as determined by a double baseline 18F-FDG PET prior to osimertinib exposure.
2. After defining #1, evaluate whether osimertinib can create a statistically significant decrease in glucose utilization as determined using early, post dosing (24-72 hour) FDG-PET imaging in patients with recurrent EGFR activated glioblastoma.	Change in FDG uptake in tumor after short course exposure to osimertinib.

2.2 Secondary objectives

Secondary Objective:	Outcome Measure :
1. Safety and tolerability of osimertinib in this patient population	The AEs, SAEs, and AEs leading to discontinuation. The severity of AEs will be assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03. Safety laboratory parameters, physical examination findings, vital signs, and Karnofsky Performance Status (KPS). Duration of subject on study treatment. Dose modification.
2. Determine clinical effect of osimertinib in this patient population, as determined by 6 months progression-free survival	Percentage of participants surviving six months from the start of study treatment without progression of disease. PFS was defined as the time from the date of study treatment initiation to the date of the first documented progression according to Response Assessment in Neuro-oncology (RANO) criteria, or to death due to any cause.

3. Correlated clinical effect of osimertinib with FDG-PET results in this patient population, to define by ROC analysis a clinically meaningful decrease in glucose utilization, which correlates with the clinical effect	To correlate the reduction in glucose uptake with clinical outcomes (6 months progression-free survival), ROC analyses of simple thresholding strategies will be performed using leave one out cross validation.
4. Evaluate PK in this patient population using spot PK during imaging and at set time points during the study	Concentrations of osimertinib, and metabolites AZ5104 and AZ7550 in post-dosing plasma samples. PK Parameters (CLss/F, C _{ss} , min and C _{ss} , max AUC _{ss}) will be derived using population PK analysis and reported separately to the CSR.

3. SUBJECT SELECTION, ENROLMENT, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Approximately 12 evaluable subjects will be enrolled in the study at UCLA.

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study, subjects should fulfil the following criteria based on local regulations:

1. Patients must be able to provide written informed consent.
2. Patients must have histologically proven WHO grade IV glioblastoma who have supratentorial contrast enhancing progressive or recurrent tumor by MRI imaging following standard or experimental treatment
3. Patients must have measurable contrast enhancing disease with a measurement of at least 1x1x1 cm³ using MRI contrast imaging
4. Patients must have recovered from severe toxicity of prior therapy. The following intervals from previous treatments are required to be eligible:
 - 12 weeks from the completion of radiation
 - 6 weeks from a nitrosourea chemotherapy
 - 3 weeks from a non-nitrosourea chemotherapy
 - 4 weeks from any FDA approved agents
 - 5 half-lives or 4 weeks, whichever is greater, from any investigational (not FDA-approved) agents

- 4 weeks from the last treatment with bevacizumab
 - 2 weeks from administration of a non-cytotoxic, FDA-approved agent other than bevacizumab (e.g., hydroxychloroquine, etc.)
5. Patient tumor sample must have evidence of EGFR activation as determined by EGFR amplification and/or EGFR mutations by FISH or sequencing approaches.
6. Patient tumor sample must be *p53* wild type

Note: Patients will be enrolled based on the documented EGFR/p53 status from the previous assays completed locally. If post enrollment evaluation of the archival tissue revealed that neither EGFR amplification nor EGFR mutations were present by using FISH or next generation sequencing, or mutant p53 by exon sequencing, the patients may continue their participation in the study. The investigator should discuss with patients regarding their willingness of continuation of participation in the study.

7. Patient must be adult male or female who is 18 years of age or older
8. Patient must have a KPS ≥ 60
9. Patients must have a life expectancy ≥ 12 weeks.
10. Patients must be able to swallow medication by mouth
11. Women of childbearing potential must have a negative serum pregnancy test prior to study entry. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

Female subjects should be using highly effective contraceptive measures, and must have a negative pregnancy test and not be breast-feeding prior to start of dosing if of child-bearing potential or must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:

- Post-menopausal defined as aged more than 50 years and amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments
 - Women under 50 years old would be consider postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range for the institution
 - Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation
12. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and for 4 months after completion of osimertinib administration.
13. Provision of informed consent for genetic research.

3.2 Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1. Involvement in the planning and/or conduct of the study
2. Previous enrolment in the present study or previous treatment with osimertinib
3. Prior exposure to osimertinib. Note: prior exposure to EGFR targeted therapy including EGFR TKIs, but excluding osimertinib, is allowed if the patient has subsequently undergone craniotomy and the tumour is proven to be EGFR amplified.
4. Currently receiving any other investigational agents
5. Currently receiving (or unable to stop use prior to receiving the first dose of study treatment) medications or herbal supplements known to be potent inducers of CYP3A4 (at least 3 week prior) (Appendix A). However, corticosteroids are allowed for symptom management related to mass effect or brain edema.
6. Any unresolved toxicities from prior therapy greater than CTCAE grade 1 at the time of starting study treatment, with the exception of alopecia and grade 2, prior platinum-therapy-related neuropathy.
7. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardise compliance with the protocol, or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV).
8. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of osimertinib.
9. Any of the following cardiac criteria:
 - Mean resting corrected QT interval (QTc) > 470 msec obtained from an electrocardiogram (ECG), using the screening clinic ECG machine derived QTc value.
 - Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG e.g. complete left bundle branch block, third degree heart block and second degree heart block.
 - Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, electrolyte abnormalities (including: Serum/plasma potassium < LLN; Serum/plasma magnesium < LLN; Serum/plasma calcium < LLN), congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age in first degree relatives or any concomitant medication known to prolong the QT interval.

10. Inadequate bone marrow reserve or organ function (as demonstrated by any of the following laboratory values: absolute neutrophil count $<1.5 \times 10^9/L$; platelet count $<100 \times 10^9/L$; haemoglobin $<9.0 \text{ g/L}$; alanine aminotransferase >2.5 times ULN if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases; aspartate aminotransferase >2.5 times ULN if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases; total bilirubin >1.5 times ULN if no liver metastases or >3 times ULN in the presence of documented Gilbert's Syndrome [unconjugated hyperbilirubinaemia] or liver metastases; serum creatinine >1.5 times ULN concurrent with creatinine clearance $<50 \text{ mL/min}$ [measured or calculated by Cockcroft and Gault equation]—confirmation of creatinine clearance is only required when creatinine is >1.5 times ULN.
14. History of hypersensitivity active or inactive excipients of osimertinib or drugs with a similar chemical structure or class to osimertinib.
15. Past medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease.
16. Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.

3.3 Subject enrolment

Before subjects begin participation in any study-specific activities/procedures, a copy of the UCLA Institutional Review Board (IRB) approval of the protocol, informed consent form, and all other subject information and/or recruitment material must be filed in study regulatory binder. Investigator(s) should keep a record, the subject screening log, of subjects who entered study screening.

The Investigator(s) will:

1. Obtain signed informed consent from the potential subject before any study specific procedures including screening are performed.
2. Assign potential subject a unique enrolment number. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. The unique subject identification number will consist of 3 digits and be assigned in sequential order as subjects are screened (eg, 001, 002, or 003). For example, the first subject to enter screening at UCLA will receive the number 001, and the second subject at the same site will receive the number 002. The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened. If a subject withdraws from participation in the study, then his/her enrolment number cannot be reused.
3. Determine subject eligibility. See Section 3.

4. The Investigator must document the enrolment decision and date, in the subject's medical record and in/on the enrolment case report form (CRF).

3.3.1 Informed Consent

Investigators should always use the most current, approved versions of informed consent documents for obtaining and documenting informed consent. After explaining the research and assessing participant comprehension, investigators must document the informed consent process. At minimum, it involves obtaining the signature of the participant as well as the person obtaining consent. The participant must sign and date the consent form at the time of the consenting process and only after all questions are answered and s/he agree to participate in the study. The person who has oriented and obtained consent from the participant must also sign and date the consent form. This signature cannot pre-date the participant's signature.

3.4 Procedures for handling incorrectly enrolled subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be initiated on treatment, and must be withdrawn from the study.

Where a subject does not meet all the eligibility criteria but incorrectly started on treatment, the Investigator should inform the Sponsor-investigator immediately, and a discussion should occur between the Sponsor-investigator and the Investigator regarding whether to continue or discontinue the patient from treatment. Sponsor-investigator must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

Not applicable

3.6 Methods for ensuring blinding

Not applicable

3.7 Restrictions

1. Female patients of child-bearing potential should use reliable methods of contraception from the time of screening until 6 weeks after discontinuing osimertinib. Acceptable methods are provided in Appendix E.
2. Male patients should be asked to use barrier contraceptives (i.e., by use of condoms) during sex with all partners during the trial and for a washout period of months. Male

patients should avoid procreation four months after completion of trial treatment. Patients should refrain from donating sperm from the start of dosing until 4 months after discontinuing study treatment.

3. Once enrolled all patients must try to avoid concomitant use of medications, herbal supplements and/or ingestion of foods that are known to be potent inducers of CYP3A4 whenever feasible, but patients may receive any medication that is clinically indicated for treatment of adverse events. Such drugs must have been discontinued for an appropriate period before they enter screening and for a period of 3 months after the last dose of osimertinib. All concomitant medications should be captured on the CRF. Guidance on medicines to avoid, medications that require close monitoring and on washout periods is provided (see Appendix A).
4. If medically feasible, patients taking regular medication, with the exception of potent inducers of CYP3A4 (see above), should be maintained on it throughout the study period. Patients taking concomitant medications whose disposition is dependent upon BCRP or *Pgp* and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving osimertinib. Guidance on medications to avoid, medications that require close monitoring and on washout periods is provided (see Appendix A).

Patients taking rosuvastatin should have creatine phosphokinase levels monitored (due to BCRP-mediated increase in exposure). If the patient experiences any potentially relevant AEs suggestive of muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, rosuvastatin must be stopped and any appropriate further management should be taken.

3.8 Discontinuation of investigational product

Subjects may be discontinued from investigational product (IP) in the following situations:

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Pregnancy
- Patients incorrectly initiated on treatment
- Objective disease progression or patient is no longer receiving clinical benefit, lost to follow up
- Patient starts receiving an additional anticancer therapy
- Severe non-compliance with the study protocol

Patients experiencing any of the following adverse events will not be permitted to restart study treatment:

- Interstitial Lung Disease (ILD)
- QTc interval prolongation with signs/symptoms of serious arrhythmia

3.8.1 Procedures for discontinuation of a subject from investigational product

Any subject who discontinues study treatment for reasons other than objective disease progression will enter long term follow up (see Table 2) until objective disease progression is documented or death occurs, unless consent is withdrawn. Study procedures related to PROs, SAEs and anti-cancer treatment must be captured until permanent withdrawal from the study. Any subject who discontinues study treatment due to objective disease progression will be followed up for survival.

At any time, subjects are free to discontinue investigational product or withdraw from the study (i.e., investigational product and assessments – see Section 3.9), without prejudice to further treatment. A subject that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up (See Section 6); diary cards and all study drugs should be returned by the subject.

As a minimum, telephone contact should be made with the patient 30 days following the discontinuation of osimertinib to collect new AEs and follow up on any ongoing AEs and concomitant medications (including any subsequent cancer therapy). Refer to Section 6 for full details on AE recordings during follow-up.

3.9 Criteria for withdrawal

3.9.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be treated in the study. If any screening failure patients are accidentally enrolled, these patients should have the reason for study withdrawal recorded as ‘Incorrect Enrolment’ (i.e., patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures.

3.9.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment. All materials related to the study, including any unused medications, will be returned to the study investigator.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow up AEs outside of the clinical study.

If a subject withdraws from participation in the study, then his/her enrolment/ code cannot be reused. Withdrawn subjects will be replaced if they did not complete the minimum two 18-FDG-PET scans at baseline and one post high-dose osimertinib per protocol.

3.10 Discontinuation of the study

The study may be stopped if, in the judgment of the Sponsor-investigator, trial subjects are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug,
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor-investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

4.1 Study Plan

Table 2 Study Visit Schedule

Visit/ Cycle	Screening	Prior to Cycle 1		Cycle 1		Cycle 2 and thereafter			EOT	Follow up		
Study Day	-28 Days	Day -28 through Day -4	Day -3 through Day -1	Day 1*	Weekly	Day 1	Every 8 weeks from Cycle 3 Day 1	Every 12 weeks from Cycle 4 Day 1	Within 7 days after the last dose	Safety FU Within 30 days after last dose	Long term follow-up For DP (q2mo)	Survival follow-up After DP (q2mo)
Informed consent	X											
Demographics	X											
Medical/surgical history	X											
Inclusion/exclusion criteria	X											
Physical examination and weight	X			X		X			X			
height	X											
Vital signs	X			X		X			X			
KPS	X			X		X			X	X		
ECG ¹	X			X		X			X			
ECHO ²	X							X				
Brain MRI ³	X						X				X ³	

18-FDG-PET ⁴		X	X									
Hematology ⁵	X			X ¹¹	X	X			X			
Clinical chemistry ⁶	X			X ¹¹	X ⁶	X			X			
Coagulation ⁷	X											
Serum Pregnancy ⁸	X			X		X						
Urinalysis	X			X ¹¹		X						
Osimertinib Dispensation			X ¹²	X ¹²		X ¹²						
Diary review				X		X			X			
Concomitant medication	X		X	X		X			X	X	X	
Adverse event review ⁹	X			X		X			X	X	X	
Blood sampling for PK			X	X ¹³		X ¹³						
Archival tissue ¹⁰	X											
Survival status												X

Abbreviations: ECG= electrocardiogram; ECHO= echocardiography; LVEF= left ventricular ejection fraction; MRI= magnetic resonance imaging; 18-FDG-PET= 18-Fluorodeoxyglucose - Positron Emission Tomography

¹ Resting 12-lead ECG should be performed at Screening, prior to dosing on Day 1 of each treatment cycle and at EOT if the previous ECG assessment was abnormal. Subjects with a QT interval (QTc) > 470 msec at baseline will not be allowed to enrol. Repeat ECG if QTc was found > 500 msec during the treatment period. If QTc > 500 ms was found on at least 2 separate ECGs, study drug will be withheld until QTc <481 msac and dose should be reduced to 80 mg when restarted. Study drug will be permanently discontinued if QTc interval prolongation with sign/symptoms of serious arrhythmia occurs. Please refer section 6.7.

² ECHO for LVEF should be performed at Screening, every 12 ±1 weeks throughout the treatment period and as clinically indicated during the study treatment period. A 28-day follow-up assessment will be required if an on-treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality.

³ Radiological Assessment by MRI for tumor staging by modified RANO will be performed at screening (within 14 days of enrollment), on C3D1 and then repeated every 8 ±1 weeks. If available, data from a prior imaging evaluation (within 14 days of enrollment) will be used for screening. Brain imaging data will be collected during long term follow up if the subjects were off treatment for any reason other than disease progression.

⁴ Two 18-FDG-PET will be performed prior to dosing, 18 to 54 hours apart. One 18-FDG-PET scan will be performed 24 to 72 hours post initial dose of 240 mg osimertinib [on Day -2 or Day -1]. The scan should be performed 24 hours post initial dose of 240 mg osimertinib on Day -2 if there is immediate dosing interruption or reduction.

⁵ Hematology including CBC, Diff, Platelets will be performed at screening, within 2 days prior to Day 1 of each cycle, weekly (with ± 2 days window) during Cycle 1, and EOT visit.

⁶ Clinical chemistry including sodium, potassium, chloride, CO₂, glucose, creatinine, urea nitrogen (BUN), albumin, total bilirubin, calcium, alkaline phosphatase, total protein, AST (SGOT), ALT (SGPT), creatinine kinase and magnesium will be performed at screening, within 2 days prior to Day 1 of each cycle, Cycle 1 Day 15 (with ± 2 days window), and EOT visit. Electrolyte abnormalities (hypokalaemia, hypomagnesaemia, hypocalcaemia) must be corrected to be within normal ranges prior to first dose and electrolyte levels monitored during study treatment.

⁷ Coagulation includes APTT and PT.

⁸ Serum Pregnancy test will be performed for all female subject with child bearing potential at screening and prior to Day 1 of each cycle.

⁹ Subjects with eye inflammation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist for full assessment.

¹⁰ Archived tumor tissue, preferably from the most recent biopsy/resection, of at least 20 freshly-cut, unstained FFPE slides (4-5 µm each) will be obtained from all subjects within 60 days from the enrollment for retrospective central laboratory confirmation of EGFR amplification/mutation status and p53 mutation status. Corresponding pathology report is also required. Detailed instructions can be found in Lab manual. Patients will be enrolled based on the documented EGFR/p53 status from the previous assays completed locally. If post enrollment evaluation of the archival tissue revealed that neither EGFR amplification nor EGFR mutations were present by using FISH or next generation sequencing, or mutant p53 by exon sequencing, the patients may continue their participation in the study. The investigator should discuss with patients regarding their willingness of continuation of participation in the study.

¹¹ No need to repeat hematology and clinical chemistry if the previous lab assessment was done within 7 days.

¹² Osimertinib will be administrated orally at dose of 240 mg QD for three days on Day -3 through Day -1 prior to Cycle 1 and then at dose of 160mg QD for each cycle starting from Cycle 1 Day 1.

¹³ PK blood will be collected on Day 1 of each cycle prior to dosing. Cycle 1 Day 1 PK blood may be collected only when the visit is scheduled on week days. Additional PK blood may be collected if osimertinib was held or for treatment related toxicity if applicable.

* The study date of Day 1 may be delayed due to medical reason (e.g. hospitalization) per investigator's determination. Please discuss with PI regarding the delay of Day 1. There is no Day 0.

4.2 Enrolment/screening period

Procedures will be performed according to the Study Plan.

At screening, consenting subjects are assessed to ensure that they meet eligibility criteria within 28 days period. Subjects who do not meet these criteria must not be enrolled in the study. If dosing wasn't initiated within 28 days period, the screening procedures including physical exam, laboratory tests including pregnancy test, ECG, ECHO should be repeated in order to enrol the subject.

4.2.1 Informed consent

The purpose of the study, the procedures to be carried out, and the potential hazards will be described in non-technical terms and presented to each potential subject by the Investigator or his/her designee. Subjects will be required to read, sign, and date the informed consent form prior to undergoing any study assessments.

4.2.2 Demographics and Medical/surgical history

Subject demographic data including gender, date of birth, age, race, and ethnicity will be obtained during Screening. A complete medical and surgical history, including the type of underlying malignancy and the date of confirmation of the histologic diagnosis of the underlying malignancy, will be obtained during Screening. The medical history is to include all relevant prior medical history as well as all current medical conditions. All medications administered and procedures conducted within 28 days prior to the first dose should be reported in the paper CRF. In addition, all prior treatment regimens for the underlying malignancy will be reported.

4.2.3 Physical examination and Karnofsky performance status

A complete physical examination, including assessment of weight and height, will be obtained at Screening. The complete physical examination includes an assessment of the following: general appearance, skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems.

Determination of KPS will be performed at Screening. The KPS criteria for this protocol are further defined in Appendix B.

4.2.4 Vital signs

Vital signs, including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature, will be obtained at Screening.

4.2.5 Electrocardiogram

The 12-lead ECGs will be performed at Screening following 10 minutes of recumbency or semi-recumbency. Subjects with a QT interval (QTc) > 470 msec at baseline will not be allowed to enrol.

4.2.6 Echocardiogram

ECHO for assessment of Left Ventricular Ejection Fraction (LVEF) should be performed at Screening per institutional guideline.

4.2.7 Brain MRI

Radiological Assessment by MRI for tumor staging by RANO will be performed at screening (within 14 days of start of the treatment). Previous scans within 6 months prior to enrollment will be collected by investigator for further analysis.

4.2.8 Laboratory assessment

Blood samples will be collected for hematology, clinical chemistry, and coagulation testing. Urinalysis will be performed. A serum qualitative pregnancy test will be performed at UCLA lab or local lab on all females unless they are surgically sterile or ≥ 2 years postmenopausal. The subject cannot be enrolled if the test is positive.

4.2.9 Adverse Event

Adverse event and serious adverse event assessments will be made during the screening process and will be evaluated and recorded in the source documents and on the paper CRF. Determination of the severity of all adverse events will be consistent with the CTCAE, version 4.0 unless specified otherwise.

Adverse Events (AEs) for new malignant tumours (i.e., it is not the tumour for which entry into the study is a criterion and that is being treated by the IP under study and is not the development of new or progression of existing metastasis to the tumour under study) reported during a study should generally be assessed as Serious AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a Non-Serious AE. For example, if the tumour is included as medical history, and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfill the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

4.3 Treatment period

4.3.1 Descriptions of the procedures for this period are included in the Study Plan in Section 4. Electrocardiogram

The 12-lead ECGs will be performed prior to dosing on Day 1 of each treatment cycle. All ECGs should be obtained following 10 minutes of recumbency or semi-recumbency. A 12-lead ECG should also be obtained as clinically indicated.

4.3.2 Echocardiogram

ECHO assessment of Left Ventricular Ejection Fraction (LVEF) should be performed every 12 weeks per institution guideline and as clinically indicated during the study treatment period.

4.3.3 18-FDG-PET

Two 18-FDG-PET brain scan will be performed prior to the start of the treatment, 18 to 54 hours apart.

One 18-FDG-PET scan will be performed 24 to 72 hours post initial dose of 240 mg osimertinib [on Day -2 or Day -1]. The scan should be performed 24 hours post initial dose of 240 mg osimertinib on Day -2 if there is immediate dosing interruption or reduction.

4.3.4 Research blood collection for PK analysis

Blood samples will be collected from all subjects to determine circulating plasma concentrations of osimertinib and for the identification of osimertinib metabolites at the time points indicated in **Table 3**. Approximately 20 ml whole blood will be collected at each time point.

Table 3. PK blood sampling

Visit/Cycle	Prior to Cycle 1	Cycle 1 and subsequent Cycles
Visit/Day	At the time of 3 rd PET scan	Day 1 (pre-dosing)
Blood samples for PK	X	X

4.3.5 Research tissue collection

Archived tumor tissue, preferably from the most recent biopsy/resection, of at least 20 freshly-cut, unstained FFPE slides (4-5 μ m each) will be obtained at Screening from all subjects for retrospective central laboratory confirmation of EGFR amplification/mutation status and p53 mutation status. Corresponding pathology report is also required. Detailed instructions can be found in Lab manual.

Patients will be enrolled based on the documented EGFR/p53 status from the previous assays completed locally. If post enrollment evaluation of the archival tissue revealed that neither EGFR amplification nor EGFR mutations were present by using FISH or next generation

sequencing, or mutant p53 by exon sequencing, the patients may continue their participation in the study. The investigator should discuss with patients regarding their willingness of continuation of participation in the study.

4.3.6 Long term storage of Research blood

Plasma aliquot will be stored in Nathanson Lab for future studies which include the mutation analysis of cfDNA.

4.4 Follow-up period

Descriptions of the procedures for this period are included in the Study Plan in Section 4. All subjects will be followed up for safety within 30 days after their last study drug dosing. Subjects who were taken off study for reasons other than disease progression will be followed every 2 months until disease progression, death or withdrawal from follow up. Imaging scans will be collected during long term follow up. All subjects will be followed up for survival every 3 months after disease progression.

5. STUDY ASSESSMENTS

The Investigator will ensure that data are recorded on the paper Case Report Forms as specified in the study protocol and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, legibility and timeliness of the data recorded and of the provision of answers to data queries according to the Research Agreement. The Investigator will sign the completed paper Case Report Forms. A copy of the completed paper Case Report Forms will be archived at the study site.

5.1 Clinical Activity Assessments and Efficacy assessments

The clinical activity of osimertinib will be evaluated by Investigator assessment of response to treatment according to RANO criteria. For each subject, radiographic assessments (MRI) of the brain will first be conducted at Screening to confirm the presence of contrast enhancing tumor and for the measurement of tumor size for eligibility. And it will be used as the baseline assessment for on-treatment response assessments. The subsequent MRI scans will be done every 8 weeks starting from Cycle 3 Day 1 per patients' standard of care. Radiographic evidence of disease progression will be evaluated and corroborated Sponsor-investigator to determine disease status for this trial. Unscheduled MRI scans will be recorded in CRFs. The results will be documented on the CRF. If during unscheduled procedures, there is evidence of disease progression, such will be confirmed through central review. Evidence of disease progression requires removal from active study treatment per investigator discretion. Assessment of MRI includes T1 (with and without contrast), T2, and FLAIR sequences.

The central review of MRI Scans:

Dicom format CD of all MRI scans are required to be sent to Dr. Timothy Cloughesy, M.D. at 710 Westwood Plaza, Suite 1-230, Los Angeles, 90095

Efficacy assessments will include

- 6-month Progression-free survival (PFS) – the proportion of subjects surviving six months or longer from the start of the study treatment without progression of disease based on RANO criteria as assessed by central radiology review, in addition to clinical status and steroid use, or death due to any cause
- Durable response rate – the proportion of patients whose best response is either CR or PR lasting at least 24 weeks, according to RANO criteria as assessed by central radiology review, in addition to clinical status and steroid use
- Duration of durable response – time from documentation of durable response to disease progression or death due to disease progression
- Durable clinical benefit rate – the proportion of subjects whose best overall response is either CR or PR lasting at least 24 weeks, or stable disease (SD) lasting at least 18 months, according to RANO criteria as assessed by central radiology review, in addition to clinical status and steroid use
- Overall survival– time from the date of initial treatment to death due to any cause

Progression is defined as one of the following:

- In the case of incomplete resection during primary therapy: a 25% increase or greater in the residual tumor if the recurrent portion of the tumor is at least 1 cm or greater in its longest diameter, measured by MRI and confirmed by imagery as attributable to tumor growth.
- If resection is indicated for recurrent disease, while radiographic criteria for progression have not been met: surgical resection, subsequently confirmed as progressive GBM by pathology at the clinical site and confirmed by independent pathology.
- Appearance of any new lesion at least 1 cm x 1cm or greater in at least one dimension as measured by MRI and confirmed by imagery.
- Unequivocal progression of non-measurable disease (either non-enhancing disease seen only on T2/FLAIR images or enhancing disease not meeting size criteria for measurability), such that there is confidence that tumor growth has occurred.
- Death: all deaths are counted as events for the progression endpoint.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood samples for determination of Clinical chemistry, hematology, coagulation, serum pregnancy will be taken at the times indicated in the Study Plan (see Section 6.3).

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate CRF.

The Clinical chemistry, hematology coagulation, and serum pregnancy will be performed at UCLA Clinical laboratory, or at a local laboratory. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The following laboratory variables will be measured:

Table 4 Laboratory Safety Variables

Hematology (whole blood)	Clinical Chemistry (serum or plasma)	Coagulation (whole blood)	Urinalysis (dipstick)
Haemoglobin (Hgb)	Creatinine	APPT	Colour
WBC	Bilirubin, total	PT	Specific gravity
RBC	Alkaline phosphatase (ALP)		pH
Hct (hematocrit)	Aspartate transaminase (AST)		protein
MCV (mean corpuscular volume),	Alanine transaminase (ALT)		Glucose
MCH (mean corpuscular hemoglobin)	Albumin		Ketones
MCHC (mean corpuscular hemoglobin concentration)	Potassium		Bilirubin
RDW-SD (red cell distribution width standard deviation)	Chloride		Occult blood
RDW-CV (red cell distribution width coefficient of variation)	CO ₂		Nitrite
Platelet count	Glucose		Leukocyte esterase
MPV (mean platelet volume)	urea nitrogen (BUN)		
nucleated RBC % and absolute count	total protein		
neutrophil % and absolute count	Calcium, total		
lymphocyte % and absolute count	Sodium		
monocyte % and absolute count	Creatine Kinase		
eosinophil % and absolute count	Magnesium		
basophil % and absolute count			

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

In case a subject shows an AST **or** ALT $\geq 3 \times \text{ULN}$ **or** total bilirubin $\geq 2 \times \text{ULN}$ please refer to Appendix D ‘Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy’s Law’, for further instructions.

*In light of the potential for QT changes associated with osimertinib, electrolyte abnormalities (hypokalaemia, hypomagnesaemia, hypocalcaemia) must be corrected to be within normal ranges prior to first dose and electrolyte levels monitored during study treatment.

5.2.2 Serum pregnancy test

A serum qualitative pregnancy test will be performed at UCLA clinical laboratory or local laboratory on all females unless they are surgically sterile or ≥ 2 years postmenopausal. The serum pregnancy test must be performed at screening, prior to dosing with study drug on Day 1 of each cycle. If the pregnancy test is positive at day 1 of cycle 1, the subject should not be given study drug. If the pregnancy test is positive at any other visit, then study drug must be held and a confirmatory quantitative serum pregnancy test must be done. If the confirmatory quantitative serum pregnancy test is positive, the study drug must be discontinued. If the quantitative pregnancy test is negative the subject should restart study drug dosing.

5.2.3 Physical examination and Karnofsky Performance Status

A complete physical examination will be performed at screening. After Screening, a limited symptom-directed physical examination will be completed on Day 1 of each cycle, and at EOT. The complete physical examination includes an assessment of the following: general appearance, skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems.

Determination of KPS will be performed at Screening, on Day 1 of each cycle and at EOT. The KPS criteria for this protocol are further defined in Appendix B.

Weight will be recorded at screening, on Day 1 of each cycle and at EOT.

Height is to be obtained only at the Screening.

5.2.4 Vital signs

Vital signs will be collected at screening, Day 1 of each cycle and EOT. Vital signs include systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature. Assessments should be conducted while the subject is seated or supine.

5.2.5 Electrocardiogram

12-lead ECGs will be obtained after the patient has been resting semi-supine for at least 10 minutes prior to assessment. All ECGs should be recorded with the patient in the same physical position. A standardised ECG machine should be used and the patient should be examined using the same machine throughout the study if possible.

After paper ECGs have been recorded, the investigator or designated physician will review each of the ECGs and may refer to a local cardiologist if appropriate. Heart rate, PR, R-R, QRS and QT intervals will be determined. A paper copy should be filed in the patient's medical records. If an abnormal ECG finding at screening or baseline is considered to be clinically significant by

the investigator, it should be reported as a concurrent condition. For all ECGs details of rhythm, ECG intervals and an overall evaluation will be recorded.

If there is a clinically significant abnormal ECG finding during the Treatment period, this should be recorded on the AE CRF, according to standard adverse events collection and reporting processes. A 28-day follow-up assessment will be required if an on-treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality.

5.2.6 Echocardiogram

An echocardiogram (ECHO) to assess LVEF will be performed at screening and every 12 weeks throughout the study as shown in the Study Plan (Table 2). The screening echocardiogram to be considered as the baseline. A new echocardiogram will be performed if any clinical significant cardiological changes have occurred between the last ECHO exam and the initiation of the study at investigators discretion. The patients should also be examined using the same machine and operator whenever possible and quantitative measurements should be taken. A 28-day follow-up assessment will be required if an on-treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality.

ECHO for left ventricular ejection fraction assessment should be used throughout the study.

5.2.1 Ophthalmic examinations

Full ophthalmic assessment, including slit lamp examination, should be performed if a patient experiences any visual symptoms (including blurring of vision), and with additional tests if clinically indicated. Ophthalmology examination results should be collected in the CRF.

Any clinically significant findings, including those confirmed by the ophthalmologist must be reported as an AE.

5.2.2 Adverse Events

Adverse event and serious adverse event assessments will be made throughout the study and will be evaluated and recorded in the source documents and on the paper CRF. Determination of the severity of all adverse events will be consistent with the CTCAE, version 4.0 unless specified otherwise.

The NCI CTCAE, version 4.03, can be accessed using the following link:http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf)

5.3 18-FDG-PET

All subjects will be required to have two baseline 18-FDG-PET brain scan prior to dosing (18 to 54 hours apart), and one scan post dosing (24-72 hour) as indicated on the study visit schedule.

The Siemens Biograph 64 TrueV HI-REZ and the Siemens Biograph mCT are combined PET/CT systems. The time-of-flight capability and resolution recovery in the image reconstruction enable an improved image S/N and a uniform image resolution across the FOV of about 2 mm. The CT scanners of both systems are capable of acquiring all standard clinical CT protocols (64 detections). Together with the PET system the CT is used both for attenuation correction of the PET data as well as for localization of the biological information seen in the PET images.

Patients will be instructed to fast for at least 4 hours prior to injection. After an intravenous injection of 18F-FDG at 5 mCi and after an uptake period of 90 min, static 18F-FDG PET images will be acquired for 15 min. To minimize a patient's head motion, hypoallergenic medical tape will be applied across the forehead and head cushion before the PET acquisition. PET emission data are corrected for photon attenuation, photon scatter, and random coincidences will be reconstructed by use of iterative reconstruction with ordered-subset expectation maximization (16 iterations) and a gaussian filter with a full width at half maximum of 4 mm.

5.4 Pharmacokinetics

5.4.1 Collection of samples

Serial blood samples for determination of osimertinib and its metabolites in plasma will be taken at the times presented in the study visit schedule table 2.

Samples will be collected, labelled stored and shipped as detailed in the Laboratory Manual.

5.4.2 Determination of drug concentration

Samples for determination of drug concentration in plasma will be sent and stored at Nathanson lab, and analysed using an appropriate bioanalytical method.

5.4.3 Storage and destruction of pharmacokinetic samples

Pharmacokinetic (PK) samples will be disposed of after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the Clinical Study Report but separately in a Bioanalytical Report.

Any residual back-up PK samples may be used for additional exploratory biomarker research (in this case, residual back-up PK samples will be stored at Nathanson lab, see details in the Laboratory Manual).

5.5 Biomarker analysis

The subject's consent to the use of donated biological samples is mandatory.

Biological samples (research blood and archived tumour samples) will be collected and may be analysed for exploratory biomarkers to assess correlations with disease activity, effects of study drug, clinical outcomes and toxicity.

5.5.1 Storage, re-use and destruction of biological samples

Samples will be stored for an indefinite time from the date of the Last Subject's Last Visit. The results of this biomarker research will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication.

5.5.2 Labelling and shipment of biological samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual.

5.5.3 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

Sponsor-investigator keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for additional analysis are stored in Nathanson lab during the entire life cycle.

5.5.4 Withdrawal of Informed Consent for donated biological samples

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, Sponsor-investigator is not obliged to destroy the results of this research.

As collection of the biological samples is an integral part of the study, then the subject is withdrawn from further study participation.

The Principal Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to Sponsor-investigator
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject and Sponsor-investigator are informed about the sample disposal.

Sponsor-investigator ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.1 Definition of adverse events

An AE is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g., an abnormal laboratory finding), symptom (e.g., nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

6.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, and washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity

- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the Investigator(s) and communicated to Investigator-Sponsor.

For further guidance on the definition of a SAE, see Appendix C: Additional Safety Information to the Clinical Study Protocol.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse Events will be collected from the time of informed consent throughout the treatment period, and including the long term follow-up period for disease progression. The safety follow-up period is defined as 30 days after study drug is discontinued.

SAEs will be recorded from the time of informed consent. Following discontinuation of study treatment, SAEs considered related to study procedures should continue to be collected while patients are followed up for disease progression.

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF.

6.3.3 Variables

The following variables will be collected for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against Osimertinib (yes or no)
- Action taken with regard to osimertinib
- AE caused subject's withdrawal from the study treatment or overall study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE

- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Description of SAE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

The Investigator will assess causal relationship between osimertinib and each Adverse Event, and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by osimertinib?’

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as ‘yes’.

A guide to the interpretation of the causality question is found in Appendix C: Additional Safety Information to the Clinical Study Protocol.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or care provider or reported in response to the open question from the study personnel or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests and vital signs will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, etc. should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with osimertinib unless clearly due to disease progression under study.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign/etc. will be considered as additional information. Wherever possible, the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.3.7 Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq 3 \times \text{ULN}$ together with total bilirubin $\geq 2 \times \text{ULN}$ may need to be reported as SAEs. Please refer to Appendix D: Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.3.8 Disease progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

6.3.9 New cancers

The development of a new primary cancer should be regarded as a SAE and will generally meet at least one of the serious criteria (see Section 6.4.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

6.3.10 Lack of efficacy

When there is deterioration in the condition for which the study treatment(s) is being used glioblastoma, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the Sponsor or the reporting physician considers that the study treatment contributed to the deterioration of the condition, or local regulations state to the contrary, the deterioration should be considered to be a lack of efficacy and not an AE.

6.3.11 Deaths

All deaths that occur during the study, or within the protocol-defined 30-day post-study follow-up period after the administration of the last dose of study treatment, must be reported as follows:

- Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the CRF but should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as a SAE within **24 hours** (see Section 6.4.4 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as a SAE. A post mortem maybe helpful in the assessment of the cause of death, and if performed, the post-mortem results should be included to the SAE report.

6.4 Reporting of serious adverse events to the IRB and/or the Regulatory Authority

All SAEs have to be reported, whether or not considered causally related to the investigational product. The Sponsor-investigator is responsible for informing the UCLA IRB and JCCC DSMB of the SAE as per local requirements.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate Sponsor representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative works with the Investigator to ensure that all the necessary information is provided to the database **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform Sponsor-investigator or assigned representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

Sponsor-investigator and other site personnel must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32. It is the responsibility of the Sponsor-investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines.

Sponsor-investigator's contact information for study SAE reporting:

Timothy Cloughesy, M.D.
UCLA Neuro-Oncology Program
710 Westwood Plaza, Suite 1-230, Los Angeles, CA 90095
Phone: +1 310-825-5321
Fax: +1 310-825-0644

A copy of the MedWatch/AdEERs report must be emailed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the sponsor to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

* A cover page should accompany the MedWatch/AdEERs form indicating the following:

- "Notification from an Investigator Sponsored Study"
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number (ESR-17-13375)

* Sponsor-investigator must also indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal investigator.

* Send SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox: AEMailboxClinicalTrialTCS@astrazeneca.com

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the FDA.

Serious adverse events that do not require expedited reporting to the FDA still need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

6.5 Overdose

A maximum tolerated dose has not been established for osimertinib. In the context of a clinical study, an overdose is any dose which exceeds the daily dose that is defined in the clinical study protocol. Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration CRF.

There is no specific treatment in the event of osimertinib overdose, and symptoms of overdose are not established. In the event of an overdose, physicians should follow general supportive measures and should treat symptomatically.

If an overdose on osimertinib occurs in the course of the study, then the Investigator or other site personnel inform the appropriate Sponsor-investigator or Sponsor-investigator's representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative works with the Investigator to ensure that all relevant information is provided to the Sponsor-investigator data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

Any overdose of a study patient with osimertinib, with or without associated AEs/SAEs, will be reported to AstraZeneca Patient Safety by Sponsor-investigator or Sponsor-investigator's representatives within 24 hours of knowledge of the event using the designated Safety e-mailbox mentioned in the above.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the Sponsor-investigator and AstraZeneca during the course of the study and within 6 weeks of the last dose of osimertinib.

6.6.1 Maternal exposure

If a subject becomes pregnant during the course of the study osimertinib should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study or within 6 weeks of the final dose of the investigational product, then the Investigator or other site personnel informs the appropriate Sponsor-investigator/Sponsor-investigator representatives and AstraZeneca representatives within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor-investigator representative works with the Investigator to ensure that all relevant information is provided to the Sponsor data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

6.6.2 Paternal exposure

Pregnancy of the subject's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

To capture information about a pregnancy from the partner of a male subject, the male subject's partner consent must be obtained to collect information related to the pregnancy and outcome; the male subject should not be asked to provide this information. A consent form specific to this situation must be used. The outcome of any conception occurring from the date of the first dose until 4 months after dosing ends should be followed up and documented.

6.7 Management of IP related toxicities

IP related toxicities will be managed according to local/institutional guidelines. If a patient experiences a CTCAE grade 3 or higher and/or unacceptable toxicity (any grade), where the clinician considers the event of concern to be specifically associated with osimertinib (and not attributable to the disease or disease-related processes for which patient is being treated), dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines.

If a toxicity resolves or reverts to $\leq$ CTCAE grade 2 within 3 weeks of onset, treatment with osimertinib may be restarted at the same dose 160 mg or a lower dose 80 mg using the rules below for dose modifications (**Table 5 and Table 6**) and with discussion and agreement with the Sponsor-investigator Study Team Physician as needed. There will be no individual modifications to dosing schedule in response to toxicity, only potential dose reduction or dose interruption.

If the toxicity does not resolve to $\leq$ CTCAE grade 2 after 3 weeks, then the patient should be withdrawn from the study and observed until resolution of the toxicity.

Table 5 Dose interventions	
Intervention	Osimertinib Dose
Initial 3-day high dose	240 mg QD
Starting Dose	160 mg QD
Reduced Dose –1	80 mg QD

Dose adjustment for adverse events should be in accordance with the following table:

Table 6. Dose adjustment information for adverse reactions		
Target Organ	Adverse Reaction	Dose Modification
Pulmonary	ILD/Pneumonitis	Permanently discontinue osimertinib
Cardiac	QTc interval greater than 500 msec on at least 2 separate ECGs	Withhold osimertinib until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then restart at a reduced dose (80 mg)
	QTc interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue osimertinib
Other	Grade 3 or higher adverse reaction	Withhold osimertinib for up to 3 weeks

	If Grade 3 or higher adverse reaction improves to Grade 0-2 after withholding of osimertinib for up to 3 weeks	Osimertinib may be restarted at the same dose (160 mg) or a lower dose (80 mg)
	Grade 3 or higher adverse reaction that does not improve to Grade 0-2 after withholding for up to 3 weeks	Permanently discontinue osimertinib

On resolution of toxicity within 3 weeks:

- If an AE subsequently requires dose interruption, osimertinib may restart at the same dose or the reduced dose, on resolution/improvement of the AE at the discretion of the Investigator.

Patients experiencing any of the following adverse events will not be permitted to restart study treatment:

- Interstitial Lung Disease (ILD)
- QTc interval prolongation with signs/symptoms of serious arrhythmia

6.7.1 ILD/Pneumonitis-like toxicity

If new or worsening pulmonary symptoms (e.g., dyspnoea) or radiological abnormality suggestive of interstitial lung disease is observed, an interruption in study treatment dosing is recommended, and the Sponsor-investigator study team should be informed. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic oedema or pulmonary haemorrhage. The results of full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, haematological parameters) will be captured by CRF. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of interstitial lung disease should be considered and study treatment permanently discontinued.

In the absence of a diagnosis of interstitial lung disease study treatment may be restarted following consultation with the Sponsor-investigator Study Team Physician.

6.7.2 QTc prolongation

In light of the potential for QT changes associated with osimertinib, electrolyte abnormalities (hypokalaemia, hypomagnesaemia, hypocalcaemia) must be correct to be within normal ranges prior to first dose and electrolyte levels monitored during study treatment.

Patients with QTcF prolongation to >500 msec should have study treatment interrupted and regular ECGs performed until resolution to <481 msec or recovery to baseline if baseline QTcF is >481 msec and then restarted at a reduced dose of 80mg. If the toxicity does not resolve to ≤ grade 1 within 21 days the patient will be permanently withdrawn from study treatment.

6.7.3 Keratitis

Keratitis was reported in 0.7% (n=8) of the 1142 patients treated with osimertinib in the AURA and FLAURA studies. Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.

6.7.4 Haematological events

Early reductions in the median laboratory counts of leukocytes, lymphocytes, neutrophils and platelets have been observed in patients treated with osimertinib, which stabilised over time and then remained above the lower limit of normal. AEs of leukopenia, lymphopenia, neutropenia and thrombocytopenia have been reported, most of which were mild or moderate in severity and did not lead to dose interruptions.

6.7.5 Erythema multiforme and Stevens-Johnson syndrome

Case reports of erythema multiforme (EM) and Stevens-Johnson syndrome (SJS) have been uncommonly and rarely reported, respectively, in association with osimertinib treatment. Before initiating treatment, patients should be advised of signs and symptoms of EM and SJS. If signs and symptoms suggestive of EM develop, close patient monitoring and drug interruption or discontinuation of osimertinib should be considered. If signs and symptoms suggestive of SJS appear, osimertinib should be interrupted or discontinued immediately.

6.7.6 Changes in cardiac contractility

Across clinical trials, Left Ventricular Ejection Fraction (LVEF) decreases greater than or equal to 10% and a drop to less than 50% occurred in 4.0% (26/655) of patients treated with osimertinib who had baseline and at least one follow-up LVEF assessment. Based on the available clinical trial data, a causal relationship between effects on changes in cardiac contractility and osimertinib has not been established. In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including an assessment of LVEF at baseline and during treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.

6.7.7 Permanent discontinuation due to toxicity

Patients experiencing Interstitial Lung Disease (ILD) or QTc prolongation with signs/symptoms of serious arrhythmia will not be permitted to restart study treatment.

Patients experiencing Grade 3 or higher adverse reaction that does not improve to Grade 0-2 after withholding osimertinib for up to 3 weeks will not be permitted to restart study treatment.

6.7.8 Toxicity management for the initial 3- day high dose (240 mg) period

During the Initial 3-day high dose (240 mg) treatment period, toxicities will be monitored closely by daily communication between subject(s) and investigator(s).

If a subject experiences a CTCAE grade 3 or higher (other than lymphopenia) and/or unacceptable toxicity (any grade) during the 3-day high dose treatment period, the patient will be permanently withdrawn from study treatment and observed until resolution of the toxicity. Post-high dose osimertinib 18-FDG-PET scan will not be performed on this subject if it hasn't been done. The subject will then be replaced by investigator(s).

If a subject experiences a CTCAE grade 3 or higher (other than lymphopenia) and/or unacceptable toxicity (any grade) after the 3-day high dose treatment period but before the initiation of the 160 mg treatment cycle, the initiation of 160 mg dosing cycle will be withheld until the toxicity resolve to $\leq$ CTCAE grade 1. After the initiation of 160 mg dosing cycle, the toxicity management will follow the rules listed on table 5 and Table 6.

6.8 Study governance and oversight

6.8.1 Data Monitoring Committee

This is an investigator sponsored clinical trial and is oversight by UCLA Jonsson Comprehensive Cancer Center Internal Quality Assurance program. The JCCC Data and Safety Monitoring Board (DSMB) serves as the primary data safety-monitoring agency. JCCC DSMB provides “real time” adverse event review and actively monitors the trial for adverse event reporting, regulatory and protocol compliance, and data accuracy. The JCCC DSMB also monitors the protocol's regulatory requirements, accrual goals and study objectives to ensure the study is completed in a timely manner within all required regulatory mandates.

Monitoring and Auditing Activities

The compliance officer of the JCCC Office of Regulatory Compliance (ORC) will monitor the clinical records for all enrolled subjects. The JCCC compliance officer will perform real time review of informed consent processes and the meeting of all inclusion and exclusion criteria and screening results at study entry. Active monitoring will offer the JCCC study team prospective information that can be used to enhance the quality of research being performed contemporaneously. Auditing is a review of historic performance of the research effort and is performed on case report forms, regulatory files and source documents to measure the quality of the research effort in a retrospective manner. The Sponsor-Investigator will be responsible for ensuring that study monitoring requirements are met.

Summary reports

The summary reports of data and safety reports should be submitted to the JCCC DSMB at predetermined intervals (annually, biannually, quarterly etc.).

SAE reporting

SAEs occurring within this study shall be reported to the JCCC DSMB in a timely manner consistent with the UCLA IRB time requirements [ten days, two days for a death] regardless of relationship, expectedness or severity. The JCCC Office of Regulatory Compliance (ORC) will review all submissions and the ORC staff will enter the information into the JCCC Clinical Trials database. Reports are generated for full JCCC DSMB review of those SAEs that have some component of relatedness to the study drug and may, at the discretion of the JCCC compliance officers, include SAE reports that may require DSMB review. The DSMB will request that the PI generate cumulative adverse event reports for quarterly, biannual or annual review.

The JCCC DSMB meets monthly to review all serious adverse event reports for this study. The DSMB reviews each SAE report and determines whether or not protocol modifications are warranted to ensure subject safety. In this review, prior occurrences of similar toxicity with the therapy under study are taken into consideration, as well as the severity of the event and the likelihood that it was related to a study drug. The DSMB may recommend no changes to the study if the event is expected or related to other causes such as the subject's underlying condition. The DSMB may request an expert's advice of another non-Principal Investigator with national experience to support their deliberations and decisions. The JCCC DSMB has the authority to recommend to the UCLA IRB the immediate halt to the study (i.e., discontinuation of any further treatment of enrolled subjects and discontinuation of enrollment of new subjects) should there be any serious unexpected toxicity that warrants further investigation.

Single subject exception/waiver

Requests for single subject exceptions/waivers from the approved study protocol, including out of window procedures and eligibility deviations, must be reviewed and approved by a member of the DSMB. Each trial is assigned a primary and secondary reviewer who is responsible for reviewing each exception/waiver request for that trial. Approvals and disapprovals of the request are sent to the Principal Investigator via email and copied to the UCLA IRB. Requests for single subject exceptions/waivers are made by the Principal Investigator via email utilizing the "Single Subject Exception Request Form." JCCC DSMB correspondences are addressed to the Principal Investigator and copied to the UCLA IRB. Minutes of the DSMB meetings are recorded and processed into the computer file.

JCCC Data safety monitoring Plan (**Appendix G**) will be adhered throughout the conducting of this trial.

6.8.2 Scientific Advisory Committee

This is an investigator sponsored clinical trial and is oversight by UCLA Jonsson Comprehensive Cancer Center Internal Scientific Peer Review committee (JCCC ISPRC). Initial protocol and subsequent protocol amendments if applicable will need to be reviewed and approved by JCCC ISPRC before the implantation.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Study Drug	Dosage form and strength	Manufacturer
osimertinib	beige, film-coated tablet 80 mg	AstraZeneca

7.2 Dose and treatment regimens

Osimertinib will be administered orally. Subjects will receive 3 days of osimertinib at a daily dose of 240 mg. Following the short course initial treatment, subjects will receive 160 mg osimertinib administered orally on Days 1 to 28 of a 28-day cycle. Dosing is continuous; there are no planned rest periods.

Subjects will be dispensed the appropriate number of Sponsor-packaged, labelled bottles to allow for at least 28 days of dosing on pre-Day -3 and prior to 28 days of dosing on C1D1. Alternatively, they may be dispensed appropriate bottle(s) until the next scheduled visit.

Subjects are to return all unused tablets (or the empty bottles) at the next scheduled visit. Subjects will be given a dosing diary for each treatment cycle including the initial 3 days treatment. They should record relevant information regarding their study drug in the diary (eg, confirmation that each daily dose was taken, reasons for missed doses).

Subjects should be instructed to take their daily dose(s) at approximately the same time each day. Each dose should be taken with a glass of water and consumed over as short a time as possible. Subjects should be instructed to swallow tablets whole and to not chew the tablets. Subjects may take osimertinib tablets with or without food.

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

The label will include the following information:

- Name of Sponsor: UCLA Neuro-Oncology
- Investigational product/study drug dosage form, route of administration, and quantity of dosage units
- Storage conditions
- Protocol #
- Subject ID
- Directions for use

- The name of the Principal Investigator, where applicable (this may be pre-printed or to be added on the label when the investigational product / study drug is dispensed)
- The period of use e.g., expiry date.

The label will include the following statements:

- ‘for clinical study use only’
- ‘keep out of reach of children’.

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The osimertinib label on the bottle specifies the appropriate storage.

7.5 Compliance

The administration of study drug osimertinib should be recorded in the appropriate sections of the Case Report Form.

Subjects will be dispensed the appropriate number of study drug bottles to allow dosing for a full cycle or until the next scheduled visit. Subjects are to return all unused tablets (or the empty bottles) on Day 1 of each treatment cycle or at the next scheduled visit. Subjects will also be given a dosing diary for each treatment cycle in which to record relevant information regarding their study drug. Compliance with the dosing regimen will be assessed based on return of unused drug (or empty bottles) and the dosing diary.

7.6 Accountability

Accountability for the study drug at the study site is the responsibility of the Investigator. The Investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the Investigator may choose to assign drug accountability responsibilities to a pharmacist or other qualified individual. The study personnel will account for all study drugs dispensed to and returned from the subject.

The Investigator or delegate will maintain accurate drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each subject, and return to AstraZeneca or its designee (or disposal of the drug, if approved by AstraZeneca). These records will adequately document that the subjects were provided the doses as specified in the protocol and should reconcile all study drug received from AstraZeneca. Accountability records will include dates received/dispensed, quantities, strength, batch/serial numbers, expiration dates (if applicable), and subject ID numbers. The Sponsor-investigator or its designee (JCCC DSMB) will review drug accountability at the site on an ongoing basis during monitoring visits.

Study drug must not be used for any purpose other than the present study. Study drug which has been dispensed to a subject and returned unused must not be re-dispensed to a different subject.

Subjects will receive instructions for home administration along with a diary to record the date and time of each dose as well as the number and strength (mg) of tablets taken.

All unused and used study drug should be retained at the site until they are inventoried by the JCCC DSMB monitor. All used, unused, or expired study drug will be returned to AstraZeneca

or its designee, or if authorized, disposed of at the study site per the site's Standard Operating Procedures and documented. All material containing osimertinib will be treated and disposed of as hazardous waste in accordance with governing regulations.

7.7 Concomitant and other treatments

All enrolled subjects must try to avoid concomitant use of medications, herbal supplements and/or ingestion of foods that are known to be strong inducers of CYP3A4 whenever feasible, but patients may receive any medication that is clinically indicated for treatment of adverse events. Such drugs must have been discontinued for an appropriate period before they enter screening and for a period of 3 months after the last dose of osimertinib. All concomitant medications should be captured on the CRF. Guidance on medicines to avoid, medications that require close monitoring and on washout periods is provided (see Appendix A).

It is recommended that concomitant use of strong CYP3A inducers (eg, Phenytoin, rifampicin, carbamazepine and St. John's Wort) with osimertinib should be avoided. Based on physiologically-based pharmacokinetic (PBPK) model simulations, no dose adjustments are required when osimertinib is used with moderate and/or weak CYP3A inducers.

Rescue/Supportive Medication/Class of drug:	Usage:
medication for rash (topical medication, corticosteroid) , antibiotics	To be administered as directed by the investigator
diarrhea (loperimide or other over the counter medication)	To be administered as directed by the investigator
anti-nausea meds	To be administered as directed by the investigator

Other medication other than that described above, which is considered necessary for the subject's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form.

8. STATISTICAL ANALYSES

8.1 Statistical considerations

This phase II study was designed to validate 18F-FDG PET imaging as a non-invasive, repeatable early response biomarker to measure a change in glucose utilization in glioblastoma as a way to provide a proof of concept evaluation of osimertinib. A total of 12 Glioblastoma (GBM) patients with EGFR activation and/or mutation and p53 wild type will have double baseline 18F-FDG PET scans (18 to 54 hours apart) prior to osimertinib dosing and one 18F-FDG PET scan early, post dosing (24-72 hour) to retest variance of tumor FDG uptake and

evaluate the osimertinib-induced attenuation in tumor glucose uptake. All subjects will continue with the osimertinib treatment until disease progression, intolerable toxicity or consent withdrawal.

8.2 Sample size estimate

Overall a total of 12 subjects will be enrolled in the study.

Our first primary objective is to estimate intra-subject variability between the first and second baseline F-DG PET scans. Using a sample of 12 measurements, targeting a Bayesian average coverage of 80%, we expect High Posterior Density HPD intervals of length equal to 0.7 or less for the standard deviation, with probability 95%. Our calculations were based on Monte Carlo simulations, using informative conjugate Inverse Gamma priors for variance components of Gaussian quantities.

Our second primary objective is to estimate the change in FDG uptake in tumor after a short course of exposure to osimertinib. Considering a conservative analysis based on paired sample T-test for differences in mean uptake, we are able to identify a standard effect size of 1.8 or larger with 80% power (type I error controlled at 10%). This analysis is merely indicative of post-hoc expected sensitivity, as the main goal of our investigation is that of estimation rather than formal testing of hypotheses.

Secondary endpoints for this analysis include: 6 months PFS, changes in the odds of PFS as they relate to changes in glucose utilization after treatment, safety intended as NCI CTCAE, and PK of osimertinib, and metabolites AZ51104, AZ7550. Due to the small sample size, all analyses involving time to event quantities will be inherently descriptive.

In designing the study, all sample size calculations are conducted to insure estimability of primary objective quantities.

8.3 Definitions of analysis sets

8.3.1 Efficacy analyses set

The efficacy evaluable population will be used for the analysis of both primary endpoints.

8.3.2 Safety analysis set

The safety analysis includes all the enrolled patients who have received at least one dose of the study drug and for whom data are available after the administration of the drug.

8.3.3 Efficacy analysis set

The Efficacy analysis set includes all enrolled patients who received at least one post-treatment disease evaluation.

8.3.4 PK analysis set

The PK analysis set includes all enrolled patients who have at least one measurable PK concentration, supported by the relevant date and time of this sample are included. For each time a PK sample was taken the dosing data for that day and—for samples taken after multiple dosing—the dosing data for the 2 days prior to the sample day as well as the sample day are needed. For any individual sample to be included in the PK analysis set the full sample data and dosing data needs to be present for that sample.

Population	Definition	Use
Efficacy evaluable	All enrolled patients who completed two baseline 18F-FDG-PET scans and one post-high dose treatment period scan.	Will be used for primary variable analysis
Safety evaluable	All enrolled patients who received at least one dose of treatment and for whom post dose data are available	Will be used for all safety analyses
PK	All enrolled patients who have at least one measurable PK concentration, supported by the relevant date and time of this sample. For each multiple dosing PK sample, dosing data are needed for the 2 days prior to the sample day as well as the sample day. For any individual sample to be included in the PK analysis set, the full sample data and dosing data needs to be present for that sample.	Will be used for all PK calculations

8.4 Outcome measures for analyses

8.4.1 Calculation or derivation of efficacy variables

Investigator RANO based assessments

From the investigators review of the imaging scans, the RANO tumour response data will be used to determine each subject's visit response according to RANO. It will also be used to determine the endpoints ORR, DoR, DCR and PFS from the overall visit response and scan dates.

At each visit, subjects will be programmatically assigned a RANO visit response of CR, PR, SD or PD depending on the status of their disease compared with baseline and previous assessments. If a subject has had a tumour assessment, which cannot be evaluated, then the

subject will be assigned a visit response of not evaluable (NE) (unless there is evidence of progression in which case the response will be assigned as PD).

Progression Free Survival (PFS)

PFS is defined as the time from enrollment until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the subject withdraws from study therapy or receives another anti-cancer therapy prior to progression. Subjects who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RANO assessment. However, if the subject progresses or dies after two or more missed visits, the subject will be censored at the time of the latest evaluable RANO assessment. If the subject has no evaluable visits or does not have baseline data they will be censored at 0 days unless they die within two visits of baseline, in which case PFS will be defined as the time from enrollment to death.

The PFS time will always be derived based on scan/assessment dates not visit dates.

Objective Response Rate (ORR)

ORR rate is defined as the number (%) of subjects with measurable disease with at least one visit response of CR or PR that is confirmed at least 4 weeks later. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. However, any complete response or partial response, which occurred after a further anticancer therapy was received, will not be included in the numerator for the ORR calculation.

In the case where a subject has two non-consecutive visit responses of PR, then, as long as the time between the 2 visits of PR is greater than 4 weeks and there is no PD between the PR visits, the subject will be defined as a responder. Similarly, if a subject has visit responses of CR, NE, CR, then, as long as the time between the 2 visits of CR is greater than 4 weeks, then a best response of CR will be assigned.

Duration of Response (DoR)

Duration of response will be defined as the time from the date of first documented response, (that is subsequently confirmed) until date of documented progression or death in the absence of disease progression, the end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR. If the response is not confirmed, it will not be included. If a subject does not progress following a response, then their duration of response will use the PFS censoring time.

Disease control rate (DCR)

Disease control rate is defined as the percentage of subjects who have a best overall response of CR or PR or SD.

Overall Survival (OS)

Overall survival is defined as the time from the date of initiation of study drug until death due to any cause. Any subject not known to have died at the time of analysis will be censored based on the last recorded date on which the subject was known to be alive.

Note: Survival calls will be made in the 2 weeks following the date of the data cut-off for each OS analysis, and if subjects are confirmed to be alive, or if the death date is post the final data cut-off date, these subjects will be censored at the date of the final data cut off. Death dates may be found by checking publicly available death registries.

Health Resource Utilisation

Health resource utilisation will be assessed in terms of hospitalization, outpatient visits and emergency department visits

8.4.2 Calculation or derivation of safety variable(s)

Safety and tolerability will be assessed in terms of AEs, deaths, laboratory data, vital signs (pulse and BP). These will be collected for all subjects.

Adverse events

AEs (both in terms of MedDRA preferred terms and CTCAE grade) will be listed individually by subject.

Any AE occurring before treatment with osimertinib will be included in the data listings but will not be included in the summary tables of AEs.

Any AE occurring within 28 days of discontinuation of investigational product (ie, the last dose of osimertinib/chemotherapy) will be included in the AE summaries. Any events in this period that occur after a subject has received further therapy for cancer (following discontinuation of osimertinib) will be flagged in the data listings. Please refer to Section 6.3.1

Other significant adverse events (OAEs)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the CSR. A similar review of laboratory/vital signs (pulse and BP)/ECG data will be performed for identification of OAEs.

Examples of these could be marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

8.4.3 Calculation or derivation of pharmacokinetic variables

Pharmacokinetic analysis of the plasma concentration data for osimertinib and AZ5104 and AZ7550 will be performed by Nathanson Lab at UCLA or delegate on behalf of Sponsor-investigator. Plasma concentration will be summarized by normal time window. The ratio of metabolite to osimertinib will be calculated.

The plasma concentration data for osimertinib and metabolites will also be analysed using a population pharmacokinetic approach, which may include exploring the influence of covariates on PK, if the data allows. A pharmacokinetic-pharmacodynamic approach will be used to investigate the relationship between PK and selected primary, secondary and/or exploratory endpoints, where deemed appropriate. Results may be reported separately from the Clinical Study Report for the main study.

The data collected in this study may also be combined with similar data from other studies and explored using population pharmacokinetic and/or pharmacokinetic-pharmacodynamic method. The results of any such analyses will be reported separately from the Clinical Study Report.

8.5 Methods for statistical analyses

All efficacy analyses will be performed on the intent to treat analysis set (population described in 8.3.1). All safety analyses will be performed on the population described in 8.3.2. Results of all statistical analyses will be presented using a 95% confidence interval and 2-sided *p*-value, combined with Bayesian posterior means and High Posterior Density intervals. Descriptive summaries and data visualization will be used for all analyses.

8.5.1 Analysis of the primary variable (s)

8.5.1.1 Estimation of retest variance of tumor FDG uptake

Test-retest variances in FDG uptake will be estimated considering the variance of sample-specific differences between first and second PET scans. This variance component will be estimated using a Bayesian conjugate analysis of Gaussian variates. In our analysis we consider both uninformative and calibrated Inverse Gamma priors, to assess sensitivity of our estimates to prior choices. Model adequacy diagnostics will compare predictive distributions to the observed data via posterior predictive assessment. Bayesian (95%) high posterior density intervals, and Bayesian posterior means will be used as the basis for statistical inference.

8.5.1.1 Estimation of changes in FDG tumor uptake after treatment with osimertinib

In order to estimate the difference in FDG tumor uptake between pre and post exposure to osimertinib, we consider a simple change model, comparing the mean baseline uptake with the mean uptake, after treatment. A formal test for difference in mean will be based on a paired T statistic for difference in mean. 95% confidence intervals will be used to quantify uncertainty in estimation.

8.5.2 Analysis of the secondary variable(s)

8.5.2.1 Safety Analysis

Adverse events, as described by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03. All events will be recorded from the time a subject has signed the Informed Consent Form. AE analyses will include only Treatment Emergent Adverse Events. Specifically, we plan to estimate the following quantities:

- 1) The incidence (no. of patients) and frequency (no. of events) overall and broken down by System Organ Class.
- 2) The incidence (no. of patients) and frequency (no. of events) broken down by severity.

8.5.2.2 Analysis of PFS

Progression-free survival at six months, is defined as the proportion of subjects surviving six months or longer from the start of the study treatment without progression of disease. Our estimate and characterization of statistical uncertainty will be based on the sampling distribution of a simple binomial proportion. Additionally, descriptive data will be provided for the duration of PFS as a Kaplan-Meier curve.

8.5.2.3 Analysis of PFS and Glucose Uptake

Correlations between 6 months PFS and changes in glucose uptake after treatment will be analyzed using a logistic regression model, with a change in glucose uptake used as a predictor. The results of the analysis will be presented in terms of an odds ratio together with its associated 95% profile likelihood confidence interval and 2-sided p-value. Additionally, an informal predictive assessment will be conducted by calculating the ROC curve associated with differential thresholding of the effect size in glucose uptake.

8.5.2.8 Pharmacokinetics

Pharmacokinetic concentration data will be summarised using appropriate summary statistics and further details will be provided in the SAP.

9. STUDY AND DATA MANAGEMENT

9.1 Training of study site personnel

Before initiation of the study, the Sponsor-Investigator, or its designated representatives will review and discuss the following items with the Investigators and clinic staffs: the protocol, study procedures, record keeping and administrative requirements, drug accountability, AE reporting, Good Clinical Practice guidelines, CRF completion guidelines, monitoring requirements, and the ability of the site to satisfactorily complete the protocol. Additional documents with instructions for study compliance and CRF completion will be provided to the clinical site by the Sponsor-Investigator or its designated representatives.

9.2 Monitoring of the study

During the study, The Sponsor-Investigator will permit the compliance officer of the JCCC Office of Regulatory Compliance [ORC] to monitor the study as frequently as the JCCC DSMB

deems necessary to determine that protocol adherence and data recording are satisfactory. The CRF and related source documents will be reviewed in detail by the Compliance Officer of JCCC ORC at each site visit.

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (e.g., clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

9.2.1 Source data

The following documentation required by the FDA must be filed by the Sponsor-Investigator, or its designee, prior to initiation of the trial: FDA Form 1571, FDA Form 1572; curricula vitae of the Sponsor-Investigator and all Sub-Investigators; signed Protocol Agreement; copy of the correspondence from the IRB/EC indicating approval of the protocol and Informed Consent Forms, signed by the IRB/EC chairperson or designee; an IRB/EC membership list containing the names and occupations of the IRB/EC members; copy of the Informed Consent Forms that were reviewed and approved by the IRB/EC.

Case report forms must be completed and documented for each subject enrolled in the study. Any changes or corrections made to the CRF must be subsequently reviewed and signed by the PI. All data fields in the CRF must be completed to avoid queries. Paper-based CRFs will be stored within Sponsor-Investigator's Clinical Trial Office.

9.2.2 Archiving of study documents

The documentation of clinical data needs to be stored by the Sponsor-Investigator according to legal requirements. The Sponsor-Investigator, sub-investigators and study staff has responsibility for maintaining a comprehensive and centralized filing system containing all study-related documentation. These files must be suitable for inspection by the the FDA, and/or other applicable regulatory agencies/competent authorities at any time, and should consist of the following elements: subject files (complete medical records, laboratory data, supporting source documentation, and the Informed Consent forms); study files (the protocol with all amendments, copies of all pre-study documentation, and all correspondence between the Competent Authorities, IRB/EC, site, and study drug suppliers); and drug accountability files, containing a complete account of the receipt and disposition of the study drug.

9.3 Study timetable and end of study

The end of the study is defined as ‘the last visit of the last subject undergoing the study’.

The study is expected to start in June 2018 and to end by June 2020.

Sponsor-investigator may terminate the entire study prematurely if concerns for safety arise within this study or in any other study with osimertinib.

9.4 Data management

Data management will be performed by Sponsor-investigator data coordinating center according to the Data Management Plan. Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the Anatomical Therapeutic Chemical (ATC). Classification coding will be performed by Sponsor-investigator’s representative.

When the completed paper Case Report Forms have been scanned and indexed, the data are entered into the study database and proofread.

The data collected through third party sources will be obtained and reconciled against study data.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Serious Adverse Event (SAE) Reconciliation

SAE reconciliation reports are produced and reconciled with the sponsor-investigator’s database.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory (ies) internal or external to Sponsor-investigator.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the Sponsor policy on Bioethics and Human Biological Samples.

10.2 Subject data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

Sponsor-investigator will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, a Sponsor Physician or an Investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

10.3 Ethics and regulatory review

The Sponsor-Investigator will assure that an appropriately constituted IRB/EC that complies with the requirements of 21 CFR Section 56 or written assurance of compliance with ICH (E6) guidelines will be responsible for the initial and continuing review and approval of the clinical study. Before initiation of the study, the Sponsor-Investigator or designee will forward copies of the protocol and Consent Form to be used for the study to the IRB/EC for its review and approval. A photocopy of the IRB/EC notification of approval must be forwarded to the study drug supplier or its designee before any investigational supplies will be shipped to the Sponsor-Investigator.

The Sponsor-Investigator or designee will also assure that all changes in the research activity and all unanticipated problems involving risks to human subjects or others will be reported promptly to the IRB/EC, and that no changes will be made to the protocol without prior IRB/EC approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Copies of all study-related correspondence between the Sponsor-Investigator and the IRB/EC must be documented. The Sponsor-Investigator or designee must promptly notify the IRB/EC of any SAE occurring at the site and of any safety reports (e.g., IND Safety Reports) received from the study drug supplier, or its designee, according to the institutional policy.

The Sponsor-Investigator or designee will be responsible for submitting periodic progress reports to the IRB/EC at intervals appropriate to the degree of subject risk involved in the study, but not less than once per year and at the completion or termination of the study.

10.4 Informed consent

The Principal Investigator(s) will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by IRB.

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and Sponsor-investigator.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

Sponsor-investigator will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 10.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, Sponsor-investigator and the centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

10.6 Audits and inspections

Authorised representatives of Sponsor-investigator, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-

related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator will contact Sponsor immediately if contacted by a regulatory agency about an inspection at the centre.

11. LIST OF REFERENCES

1. Babic, I., et al., *EGFR mutation-induced alternative splicing of Max contributes to growth of glycolytic tumors in brain cancer*. Cell Metab, 2013. **17**(6): p. 1000-8.
2. Mai, W.X., et al., *Cytoplasmic p53 couples oncogene-driven glucose metabolism to apoptosis and is a therapeutic target in glioblastoma*. Nat Med, 2017. **23**(11): p. 1342-1351.
3. *AZD9291, TAGRISSO™ Osimertinib* 9ed. Investigator's Brochure. 2018: AstraZeneca.
4. Vander Heiden, M.G., *Targeting cancer metabolism: a therapeutic window opens*. Nat Rev Drug Discov, 2011. **10**(9): p. 671-84.
5. Arteaga, C.L., *The epidermal growth factor receptor: from mutant oncogene in nonhuman cancers to therapeutic target in human neoplasia*. J Clin Oncol, 2001. **19**(18 Suppl): p. 32S-40S.
6. Maity, A., et al., *Epidermal growth factor receptor transcriptionally up-regulates vascular endothelial growth factor expression in human glioblastoma cells via a pathway involving phosphatidylinositol 3'-kinase and distinct from that induced by hypoxia*. Cancer Res, 2000. **60**(20): p. 5879-86.
7. Humphrey, P.A., et al., *Amplification and expression of the epidermal growth factor receptor gene in human glioma xenografts*. Cancer Res, 1988. **48**(8): p. 2231-8.
8. Libermann, T.A., et al., *Amplification, enhanced expression and possible rearrangement of EGF receptor gene in primary human brain tumours of glial origin*. Nature, 1985. **313**(5998): p. 144-7.
9. Steck, P.A., et al., *Expression of epidermal growth factor receptor and associated glycoprotein on cultured human brain tumor cells*. J Cell Biochem, 1986. **32**(1): p. 1-10.
10. Vivanco, I. and I.K. Mellinghoff, *Epidermal growth factor receptor inhibitors in oncology*. Curr Opin Oncol, 2010. **22**(6): p. 573-8.
11. Lee, J.C., et al., *Epidermal Growth Factor Receptor Activation in Glioblastoma through Novel Missense Mutations in the Extracellular Domain*. PLoS Med, 2006. **3**(12): p. e485.
12. The Cancer Genome Atlas, *Comprehensive genomic characterization defines human glioblastoma genes and core pathways*. Nature, 2008. **455**(7216): p. 1061-8.
13. Omuro, A.M., et al., *High incidence of disease recurrence in the brain and leptomeninges in patients with nonsmall cell lung carcinoma after response to gefitinib*. Cancer, 2005. **103**(11): p. 2344-8.
14. Jamal-Hanjani, M. and J. Spicer, *Epidermal growth factor receptor tyrosine kinase inhibitors in the treatment of epidermal growth factor receptor-mutant non-small cell lung cancer metastatic to the brain*. Clin Cancer Res, 2012. **18**(4): p. 938-44.
15. Lee, Y.J., et al., *Frequent central nervous system failure after clinical benefit with epidermal growth factor receptor tyrosine kinase inhibitors in Korean patients with nonsmall-cell lung cancer*. Cancer, 2010. **116**(5): p. 1336-43.
16. Hoffknecht, P., et al., *Efficacy of the irreversible ErbB family blocker afatinib in epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)-pretreated non-small-cell lung cancer patients with brain metastases or leptomeningeal disease*. J Thorac Oncol, 2015. **10**(1): p. 156-63.

17. Ahn, M., Tsai, C., Yang, J., Shepherd, F., Satouchi, M., Kim, D. et al., *AZD9291 activity in patients with EGFR-mutant advanced non-small cell lung cancer (NSCLC) and brain metastases: data from phase II studies*. Eur J Cancer, 2015. **51**: p. 2.
18. Vansteenkiste J, R.T., Nakagawa K, Cho BC, Dols MAC, Cho EK, et al. , *LBA5: CNS response to osimertinib vs standard of care (SoC) EGFR-TKI as first-line therapy in patients (pts) with EGFR-TKI sensitising mutation (EGFRm)-positive advanced non-small cell lung cancer (NSCLC): data from the FLAURA study*. Annals of Oncology, 2017. **28(suppl_10)**: p. x186-x195.
19. Yang JC-H, K.D.-W., Kim S-W, et al., *Osimertinib activity in patients (pts) with leptomeningeal (LM) disease from non-small cell lung cancer (NSCLC): updated results from BLOOM, a phase I study*. . J Clin Oncol 2016. **34**(Suppl:9002).
20. Phelps, M.E., *Positron emission tomography provides molecular imaging of biological processes*. Proc Natl Acad Sci U S A, 2000. **97**(16): p. 9226-33.
21. Chen, W., et al., *Predicting treatment response of malignant gliomas to bevacizumab and irinotecan by imaging proliferation with [18F] fluorothymidine positron emission tomography: a pilot study*. J Clin Oncol, 2007. **25**(30): p. 4714-21.
22. Chen, W., et al., *18F-FDOPA PET imaging of brain tumors: comparison study with 18F-FDG PET and evaluation of diagnostic accuracy*. J Nucl Med, 2006. **47**(6): p. 904-11.
23. Spence, A.M., et al., *18F-FDG PET of gliomas at delayed intervals: improved distinction between tumor and normal gray matter*. J Nucl Med, 2004. **45**(10): p. 1653-9.
24. DeBerardinis, R.J., et al., *The biology of cancer: metabolic reprogramming fuels cell growth and proliferation*. Cell Metab, 2008. **7**(1): p. 11-20.

Appendix A Guidance Regarding Potential Interactions with Concomitant Medications

The use of any natural/herbal products or other “folk remedies” should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the electronic case report form (eCRF).

1. Drugs Inducing CYP3A4 Metabolism That AstraZeneca Strongly Recommend Are Not Combined With Osimertinib

Osimertinib is metabolised by CYP3A4 and CYP3A5 enzymes.

A drug-drug interaction study of osimertinib evaluated in patients showed that there is potential for osimertinib being a victim when co-administered with strong inducers of CYP3A4 (osimertinib concentrations are decreased when co-dosed with rifampicin).

The following potent inducers of CYP3A4 must not be used during this study for any patient receiving osimertinib.

D1 Drugs Inducing CYP3A4

Contraindicated drugs	Withdrawal period prior to osimertinib start
Carbamazepine, phenobarbital, phenytoin, rifampicin, rifabutin, rifapentin St John’s Wort	3 weeks
Phenobarbitone	5 weeks

This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4 activity. Appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue.

2. Medicines Whose Exposures May be Affected by Osimertinib That AstraZeneca Considers May be Allowed With Caution

Osimertinib may increase the concentration of sensitive breast cancer resistance protein (BCRP) and Pgp substrates (concentration of the sensitive BCRP substrate, rosuvastatin and sensitive Pgp substrate, fexofenadine, is increased).

D2 Exposure, Pharmacological Action and Toxicity May be Increased by Osimertinib

Warning of possible interaction	Advice
Rosuvastatin Sulfasalazine	Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to

Warning of possible interaction	Advice
Doxorubicin	full prescribing information for all drugs prior to co-administration with osimertinib.
Daunorubicin	
Dabigatran	
Aliskiren	
Topotecan	
Digoxin	

3. Drugs That May Prolong QT Interval

The drugs listed in this section are taken from information provided by The Arizona Center for Education and Research on Therapeutics website: <https://www.crediblemeds.org/>. The website categorizes drugs based on the risk of inducing Torsades de Pointes (TdP).

During screening the drugs that patients are currently prescribed should be checked opposite the website.

Drugs with a known risk of Torsades de Pointes

The following drugs prolong the QT interval and are clearly associated with a known risk of TdP, even when taken as recommended. These drugs must have been discontinued prior to the start of administration of study treatment in accordance with guidance provided in Table 3 and should not be co-administered with study treatment (osimertinib) and for a period of two weeks after discontinuing study treatment. **The list of drugs may not be exhaustive and is subject to change as new information becomes available. As such investigators are recommended to search the website to provide the most up to date information.**

D3 Drugs with a known risk of TdP

Drug Name	Withdrawal period prior to osimertinib start
Aclarubicin, anagrelide, ciprofloxacin, clarithromycin, cocaine, droperidol, erythromycin, levofloxacin, ondansetron, papaverine hydrochloride, procainamide, sulpiride, sultopride, terfenadine, terlipressin	2 days
Cilostazol, Cisapride, disopyramide, dofetilide, domperidone, flecainide, gatifloxacin, grepafloxacin, ibutilide, moxifloxacin, oxaliplatin, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sparfloxacin, thioridazine	7 days
Azithromycin, bepridil, citalopram, chlorpromazine, dronedarone, escitalopram, fluconazole, halofantrine, haloperidol, levomepromazine, levosulpiride, mesoridazine	14 days
Donepezil, terodiline	3 weeks

Drug Name	Withdrawal period prior to osimertinib start
Levomethadyl, methadone, pimozone	4 weeks
Arsenic trioxide*, Ibogaine	6 weeks
Pentamidine	8 weeks
Astemizole, Probuco, vandetanib	4 months
Amiodarone, chloroquine	1 year

* Estimated value as pharmacokinetics of arsenic trioxide has not been studied.

Other TdP risk Categories

Patients receiving drugs that prolong QT interval or may increase the risk of TdP from other TdP risk categories can be enrolled, notwithstanding other exclusions and restrictions, if these drugs are considered essential for patient management and the patient has been stable on therapy. Close monitoring with ECGs and electrolytes is recommended.

Patients with **congenital long QT syndrome (CLQTS)** are excluded from this study.

Guidance regardless of TdP risk category

Following study treatment initiation if it is considered essential for patient management to give drugs known to prolong QTc interval, **regardless of TdP risk category**, close monitoring with ECGs and electrolytes is recommended.

Appendix B Karnofsky Performance Status

Description	Score
Able to carry on normal activity and to work; no special care needed.	100 Normal no complaints; no evidence of disease.
	90 Able to carry on normal activity; minor signs or symptoms of disease.
	80 Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70 Cares for self; unable to carry on normal activity or do active work.
	60 Requires occasional assistance, but is able to care for most of his personal needs.
	50 Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40 Disabled; requires special care and assistance.
	30 Severely disabled; hospital admission is indicated although death not imminent.
	20 Very sick; hospital admission necessary; active supportive treatment necessary.
	10 Moribund: fatal processes progressing rapidly

Reference: http://www.npcrc.org/usr_doc/adhoc/functionalstatus/Karnofsky%20Performance%20Scale.pdf

Appendix C Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event

Life-threatening

‘Life-threatening’ means that the patient was at immediate risk of death from the adverse event (AE) as it occurred or it is suspected that use or continued use of the product would result in the patient’s death. ‘Life-threatening’ does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious adverse event (SAE), although the reasons for it may be (e.g., bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Intervention

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious. A diagnosis of a new malignant tumor should generally be assessed as an SAE. Malignant tumours that – as part of normal, if rare, progression – undergo transformation (e.g., Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumour.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

When making an assessment of causality, consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship
- In difficult cases, other factors could be considered such as:
 - Is this a recognised feature of overdose of the drug?
 - Is there a known mechanism?

Causality of 'related' is made if, following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related.'

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix B Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with Sponsor-investigator clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) $\geq 3x$ Upper Limit of Normal (ULN) **together with** total bilirubin (TBL) $\geq 2x$ ULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT $\geq 3x$ ULN **together with** TBL $\geq 2x$ ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- $ALT \geq 3 \times ULN$
- $AST \geq 3 \times ULN$
- $TBL \geq 2 \times ULN$

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the Sponsor-investigator representative
- Determine whether the patient meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

Follow-up

Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment)
- Notify the Sponsor-investigator

The Sponsor-investigator contacts the Investigator, to provide guidance, discuss and agree on approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Sponsor-investigator.
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Sponsor) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Company contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The Sponsor Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term ‘Hy’s Law’) according to standard processes.
 - The ‘Medically Important’ serious criterion should be used if no other serious criteria apply
 - As there is no alternative explanation for the HL case, a causality assessment of ‘related’ should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term ‘Potential Hy’s Law’) applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review, amending the reported term if an alternative explanation for the liver biochemistry elevations is determined

Actions Required for Repeat Episodes of Potential Hy’s Law

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study e.g. chronic or progressing malignant disease, severe infection or liver disease?

If No: follow the process described in Potential Hy's Law Criteria met of this Appendix

If Yes: Determine if there has been a significant change in the patient's condition# compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section 4.2 of this Appendix

A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Company if there is any uncertainty.

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

Appendix E Definition of Women of Childbearing Potential and Acceptable Contraceptive Methods

Definition of Women of Childbearing Potential

Women of Childbearing Potential (WoCBP):

Women between menarche and menopause who have not been permanently or surgically sterilised and are capable of procreation.

Women NOT of Childbearing Potential:

Women who are permanently or surgically sterilised or postmenopausal (definitions below):

Permanent sterilisation includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal occlusion. Tubal occlusion is considered a highly effective method of birth control but does not absolutely exclude possibility of pregnancy. (The term occlusion refers to both occluding and ligating techniques that do not physically remove the oviducts).

- Women who have undergone tubal occlusion should be managed on trials as if they are of WoCBP (e.g. undergo pregnancy testing etc., as required by the study protocol)
- Women will be considered postmenopausal if they are amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply:
 - Women under 50 years old will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with luteinizing hormone and follicle-stimulating hormone levels in the postmenopausal range
 - Women over 50 years of age will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatments

Acceptable Contraception Methods

Highly effective method of birth control is defined in Note 3 in International Conference on Harmonisation Guidance M3 (Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals) as one that results in a low failure rate (e.g., less than 1 percent per year) when used consistently and correctly.

Note that women should have been stable on their chosen method of birth control for a minimum of 2 weeks before entering the trial. Generic names and examples of trade names are given. As trade names may vary, Investigators should check the generic name of any contraception to ensure suitability.

Acceptable contraception methods are:

- Total sexual abstinence (abstinence must be for the total duration of the trial and the follow-up period)
- Vasectomised sexual partner plus male condom (with participant assurance that partner received post-vasectomy confirmation of azoospermia)
- Tubal occlusion plus male condom
- Intra-uterine device – provided coils are copper-banded, plus male condom
- Intra-uterine system (IUS) levonorgestrel IUS (e.g., Mirena), plus male condom
- Medroxyprogesterone injections (Depo-Provera) plus male condom
- Etonogestrel implants (e.g., Implanon, Norplan) plus male condom
- Normal and low dose combined oral contraceptive pills, plus male condom
- Norelgestromin / ethinylestradiol transdermal system plus male condom
- Intravaginal device (e.g., ethinylestradiol and etonogestrel) plus male condom
- Cerazette (desogestrel) plus male condom (Cerazette is currently the only highly efficacious progesterone based pill)

Unacceptable Contraception Methods

The following methods are considered not to be highly effective and are therefore not acceptable contraceptive methods in AstraZeneca clinical trials:

- Triphasic combined oral contraceptives
- All progesterone only pills except, Cerazette
- All barrier methods, if intended to be used alone
- Non-copper containing intra-uterine devices
- Fertility awareness methods
- Coitus interruptus

Appendix F RANO Criteria

RANO criteria, requires confirmation of response. A response must be sustained for more than 4 weeks to be considered confirmed, or true response.

Tumor response is based on target (measurable) disease, non-target disease, new disease, corticosteroid dosage, and clinical status.

Target Measurable Disease: Contrast enhancing lesions with two perpendicular diameters measuring at least 10 millimeters (mm), that are visible on two or more axial slices (preferably, at most, 5 mm apart with 0-mm skip) will be selected as target lesions at Baseline (pre-treatment). If there are multiple lesions that qualify as measurable, then a minimum of 2 and a maximum of 5 target lesions will be selected. Target lesions will be measured bidimensionally at Baseline and follow-up time points. Response and progression will be assessed based on the sum of the products of the perpendicular diameters (SPDs) of all target lesions (bidimensional measurements).

Non-Target Disease: Contrast enhancing measurable lesions in excess of the 5 allowable target lesions, contrast enhancing lesions not meeting the size criteria for target lesions, contrast enhancing lesions with poorly defined margins, and lesions that lack contrast enhancement (non-enhancing disease visualized on T2/FLAIR), will be selected as non-target lesions at Baseline. Non-target lesions will be assessed qualitatively at Baseline and at follow-up timepoints.

New Disease: Lesions of any size that appear after Baseline, will be selected as new lesions.

The definitions of radiographic response and progression per RANO are as follows:

Complete response requires that the subject had measurable target lesions at baseline, and that ALL the following are true for a minimum duration of four weeks:

- Disappearance of all enhancing measurable and non-measurable disease sustained for at least four weeks
- Stable or improved non-contrast enhancing lesions, if any (as assessed on T2/FLAIR MRI sequence)
- No new lesions of any size
- Subject must be off corticosteroids or on physiologic replacement doses only
- Subject must be stable or improved clinically

The first instance of CR will be designated preliminary CR, until the subsequent scan is assessed. If the subsequent scan (at least four weeks later) is also CR, the first instance of CR is considered confirmed, or durable CR, and would represent the date of CR. If the CR is not sustained until the next timepoint (next timepoint is PD with respect to the preliminary CR), the first instance of CR will be designated (SD).

Partial response requires that ALL the following are true for a minimum of four weeks:

- $\geq 50\%$ decrease compared with baseline in the sum of products of perpendicular diameters (SPD) of all measurable enhancing lesions
- No progression of non-measurable disease

- No new lesions
- Stable or improved FLAIR/T2 lesions on same or lower dose of corticosteroids compared with baseline scan
- Subject is on a corticosteroid dose not greater than the dose at time of baseline scan
- Subject is stable or improved clinically

The first instance of PR will be designated preliminary PR until the subsequent scan is assessed. If the subsequent scan (at least four weeks later) is CR or PR the first instance of PR will be designated confirmed, or durable PR, and would represent the date of PR. If the PR is not sustained until the next timepoint (next timepoint is PD with respect to the preliminary PR), the first instance of PR will be designated SD.

Progression if ANY of the following are true:

- $\geq 25\%$ increase in sum of the products of perpendicular diameters (SPD) of target lesions compared with the nadir SPD, with stable or increasing doses of corticosteroids
- Significant increase in FLAIR/T2 non-contrast enhancing lesions compared with Baseline or best response (nadir), with stable or increasing doses of corticosteroids
- Presence of new lesions (of any size)
- Clear progression of non-measurable disease
- Definite clinical deterioration related to the tumor(s)

Increase in corticosteroid dose alone, is not a determinant of progression. The date of PD is the date of the first sign of progression, including the date of increased corticosteroid dose in the context of tumor progression. Confirmation of progression is not required.

Stable Disease requires that ALL the following are true:

- Subject does not qualify for CR, PR, or PD as defined above
- Non-contrast enhancing (T2/FLAIR) lesions are stable on the same or lower dose of corticosteroids
- Subject's clinical status is stable

If corticosteroid dose was increased without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that the steroid increase was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the Baseline dose.

Appendix G UCLA JCCC Data Safety Monitoring plan (DSMP)

The JCCC DSMB meets monthly to review all SAE reports for trials overseen by the JCCC DSMB. All SAE reports, which have been filed since the previous meeting, are presented to the committee for review.

For trials overseen by the JCCC DSMB, the DSMB reviews all dose-limiting toxicities (DLTs) for dose-escalation studies. Protocol suspensions and re-opening of accrual to the next cohort based on DLT evaluation fall under the purview of the DSMB.

For all JCCC oncology trials and TRIO-US studies where the JCCC DSMB has primary oversight, all SAEs shall be reported to the JCCC DSMB in a timely manner [ten days, two days for a death] regardless of relationship and expectedness. The JCCC ORC will review all submissions and the ORC staff will enter the information into the JCCC Clinical Trials database. Reports are generated for full JCCC DSMB review. For trials where the JCCC DSMB has primary DSMB review responsibility, the DSMB requires that the PI generate cumulative adverse event reports for quarterly, biannual or annual review.

The DSMB reviews each SAE report and determines whether or not protocol modifications are warranted to ensure subject safety. In this review, prior occurrences of similar toxicity with the therapy under study are taken into consideration, as well as the severity of the event and the likelihood that it was related to a study drug. The DSMB may recommend no changes to the study if the event is expected or related to other causes such as the subject's underlying condition. The DSMB may request an expert's advice of another non-Principal Investigator with national experience to support their deliberations and decisions.

The JCCC DSMB has the authority to recommend to the UCLA IRB the immediate halt to a study (i.e., discontinuation of any further treatment of enrolled subjects and discontinuation of enrollment of new subjects) should there be any serious unexpected toxicity that warrants further investigation.

Requests for single subject exceptions/waivers from the approved study protocol, including out of window procedures and eligibility deviations, must be reviewed and approved by a member of the DSMB. Each trial is assigned a primary and secondary reviewer who is responsible for reviewing each exception/waiver request for that trial. Approvals and disapprovals of the request are sent to the Principal Investigator via email and copied to the UCLA IRB. Requests for single subject exceptions/waivers are made by the Principal Investigator via email utilizing the "Single Subject Exception Request Form."

JCCC DSMB correspondences are addressed to the Principal Investigator and copied to the UCLA IRB. Minutes of the DSMB meetings are maintained in a computer file.

Confidentiality: Each member of the JCCC DSMB is responsible for maintaining strict confidentiality of the study data. Members will not share any study data or information about the study with any individual external to the JCCC DSMB or the statistical working group for the study. The DSMB members may contact the statistical working group directly with questions regarding the operational details associated with the data analysis and summary presentations. Communication of deliberations or recommendations of the JCCC DSMB, either written or oral, should not be made outside of the Committee or the statistical working group. Outcome results are strictly confidential and must not be divulged to any non-member of the

JCCC DSMB except in those cases where DSMB is required to inform the UCLA IRB of its determinations. Disclosure of outcome results to the IRB must only occur with written approval of the DSMB. A member who believes he or she may have a potential intellectual or financial conflict of interest during the course of review of the data must inform the chairperson of the DSMB. In such case, the meeting minutes will record the disclosure of the potential conflict of interest and that the individual recuse himself from the discussions and abstains from voting on the DSMB decision.

Level of Risk of a Study

All interventional clinical trials undergo scientific review by the Internal Scientific Peer Review Committee (ISPRC) which requires that a Data and Safety Monitoring Plan is in place before a trial can be approved to begin. For trials overseen by the JCCC DSMB, the JCCC DSMB will determine the degree of risk of the study and will ensure that there are procedures in place to ensure the safety of the subjects that are enrolled in the trial. The intensity level of study oversight is determined by the risk category. Some of the factors that are considered when assigning the Level of Risk category include:

- A biostatistical design and appropriate procedures for proper data management so that the information collected can be properly validated.
- Appropriate Serious Adverse Event reporting procedures must be in place.
- The study duration must be appropriate and must be based on a realistic rate of enrollment.
- Data collection and data management must be adequate to verify and ensure subject eligibility.

Assignment of risk

Assigning risk ensures that the data and safety monitoring is based on the level of risk (low, medium, or high) to ensure that the data and safety monitoring activities are appropriate. Below are some of the criteria used to make a decision regarding the assignment of risk:

- Expected duration of the study based upon the estimated rate of enrollment.
- Type of study population (e.g., children, geriatric)
- The procedures used in the trial are commensurate with the degree of risk.
- Adequate data management systems in place and appropriate case report forms
- Proper serious adverse event reporting procedures in place
- Proper biostatistical design and data analysis procedures in place.

Level of Risk of this study: Level 1

Example of type of trial:

Investigator held IND of high complexity or of high toxicity potential. Examples are gene medicine, dendritic cell products from GMP suite, or an experimental agent still in phase I/II development. Typically these clinical trials involve the first use of the drugs in humans, so only the investigator is knowledgeable about the test article.

- The Compliance Officer meets with PI/Staff prior to study initiation and reviews regulatory requirements and operating system. Compliance Officer provides real time monitoring to determine eligibility prior to enrollment onto the protocol.
- Real time QA monitoring of the subjects and data collection occurs for all subjects entered onto the trial.
- Frequency of DSMB Summary Report is typically on a quarterly basis.
- Comprehensive QA auditing within first year or first 10 subjects enrolled, whichever comes first. Subsequent audit frequency will be annually.

APPENDIX H. Authorship and Publication

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. Authorship should be in line with International Committee of Medical Journal Editors authorship requirements and follow Good Publication Practice (GPP3).

The results of this study should be published or presented at scientific meetings. The Sponsor agrees to submit all manuscripts or abstracts to AZ before at least xxx (in line with contract language) days prior to submission. This allows AZ to protect proprietary information and to provide comments.

- The Sponsor and the Principal Investigator shall include the following acknowledgement in all publications and presentations relating to the Study, the Study Data, or the Developed Technologies, as well as in any financial disclosure information relating to the Study: “This research was conducted with support from AstraZeneca SA.” A copy of any publications and presentations relating to the Study shall be provided to the Company on publication or presentation, and the Company will be granted such rights or licenses as may be required to enable it to make copies of and distribute the publication or presentation as it considers necessary.

At the request of the Company, the Sponsor and/or Principal Investigator:

- Shall not include in or shall remove from any proposed publication any Confidential Information; and
- Shall withhold publication, submission, for publication, or presentation for a period of ninety (90) days from the date on which the Company receives the material to allow the Company to take such measures as the Company considers necessary to preserve its proprietary rights and/or protect its Confidential Information