AstraZeneca

Statistical Analysis Plan

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A Phase II 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 (The SAVANNAH Study)

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
1L	First-line
2L	Second-line
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BICR	Blinded independent central review
bid	Twice daily
BLQ	Below limit of quantification
BMI	Body mass index
BP	Blood pressure
C1h	Plasma concentration at 1-hour post-dose
C3h	Plasma concentration at 3-hour post-dose
C4h	Plasma concentration at 4-hour post-dose
C6h	Plasma concentration at 6-hour post-dose
Cpre-dose	Pre-dose plasma concentration
CAS	Contribution of components Analysis Set
CI	Confidence interval
CM	Concomitant medication
CRF	Case Report Form
CR	Complete response
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	Circulating tumour deoxyribonucleic acid
CV	Coefficient of Variation
DCO	Data cut-off
DoR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EGFRm+	Epidermal growth factor receptor mutation positive
EGFR-TKI	Epidermal growth factor receptor-tyrosine kinase inhibitor
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
ePRO	electronic Patient reported outcome
EQ-5D-5L	EuroQol 5 dimensions, 5 levels
ERT	E Research Technologies

FISH	Fluorescence in situ hybridisation
FUP	Follow up
GPS	Global Product Statistician
gCV	Geometric coefficient of variation
gSD	Geometric mean standard deviation
HLA	Human leukocyte antigen
HR	Hazard Ratio
HRQoL	Health-related quality of life
IA	Interim analysis
ICF	Informed consent form
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
IPD	Important protocol deviation
LDT	Laboratory Developed Tests
IUO	Investigational Use Only
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MET	Hepatocyte growth factor receptor
MRI	Magnetic resonance imaging
NA	Not applicable
NED	No evidence of disease
NCI	National Cancer Institute
NC	Not calculable
NGS	Next generation sequencing
NE	Not evaluable
NSCLC	Non-Small Cell Lung Cancer
NHP	non-compliance handling plan
NTL	Non-target lesion
OAE	Other significant adverse event
od	Once daily
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PGIS	Patient's Global Impression of Severity
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PRO	Patient reported outcome
PRO-CTCAE	Patient reported outcomes version of the Common Terminology Criteria for Adverse Events
PT	Preferred Term
QLQ-LC13	Quality of Life Questionnaire-Lung Cancer 13
QTcF	QT interval corrected for heart rate using Fridericia's formulas
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
RS	raw score

SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SI	Système International
SD	Standard deviation
SD	Stable disease
SOC	System Organ Class
SOP	Standard Operating Procedure
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TFL	Tables/Figures/Listings
TKI	Tyrosine kinase inhibitor
TL	Target lesion
TPAS	Target Population Analysis Set
Tsm	Tumour size measurement
ULN	Upper limit of normal
ULOQ	Upper limit of quantification
VAS	Visual Analogue Scale
WHO	World Health Organization
WHO-DDE + HD	World Health Organization Drug Dictionary Enhanced and Herbal Dictionary

AMENDMENT HISTORY

Date	Brief description of change
13/12/2018	Initial Approved SAP
25/03/2020	The main updates based on the amended CSP V4.0 have been the following: • The patient population for assessment of the primary objective of efficacy is broadened to include all patients treated with osimertinib (80 mg) and savolitinib (starting dose of 300 mg) and not just those patients centrally confirmed as MET+ by the FISH test (MET amplified). Correspondingly, the patient population for assessment of the secondary objective of efficacy is changed from all patients to include those patients centrally confirmed as MET+ by the FISH test as an additional population to those patients centrally confirmed as MET+ by IHC (MET overexpression) • The existing "first" interim analysis is changed to be planned after the CCI patient treated with osimertinib (80 mg) and savolitinib (starting dose of 300 mg) have had the opportunity CCI treated for 2 post-baseline RECIST scans (12 weeks) and the CCI patient treated with osimertinib (80 mg) and savolitinib (starting dose of 300 mg) has had the opportunity to be treated for 6 weeks, whichever is the later • A second interim analysis is introduced after the CCI patients treated with osimertinib (80 mg) and savolitinib (starting dose of 300 mg) in the second line setting have had the opportunity to be treated for 2 RECIST post-baseline scans (12 weeks) • Further guidance on baseline derivation for ePRO assessments • Additional safety analysis set 2 population added for interim analysis • Additional analysis for hypersensitivity/anaphylaxis adverse events has been identified. The main updates based on the amended CSP V3.0 have been the following: • All patients are assigned to 300 mg savolitinib flat dosing replacing the previous weight-based dosing regimen where patients were assigned to either 300 mg, or 600 mg savolitinib dependent upon their weight at Screening • Sample size determination is related to patients with a savolitinib starting dose of 300 mg • The proportion of patients treated in the second line setting is increased

from a third to a half

- Continuous monitoring of the discontinuation due to AE rate and the discontinuation due to a hypersensitivity/anaphylaxis AE rate as well as interim, primary, final and OS follow-up analyses are based on the number of patients treated at 300 mg savolitinib
- Clarifications on which analyses will be presented by savolitinib starting dose and/or overall
- Any reference or stratification related to the weight-based dosing regimen have been removed as no longer relevant
- Time period and frequency for collecting AE and SAE information have been updated
- Introduction of triplicated ECG on Cycle 3 Day 1
- Introduction of new sample timepoints for the PK assessments and new ratios for time dependency
- Clarification around dose reduction: Dose re-assignment to 300 mg of savolitinib is not considered as a dose reduction
- TOC have been updated considering that the mock shell TFLs is master location for output updates.

Further improvements have been implemented as follows:

- Further instructions on the definition of two missed visits for PFS as per AZ guidance
- Further clarifications on AESI definition and identification
- Concomitant medication definition has been updated
- Further instructions on identification of EGRF TKI therapies and other subgroups to be used for same efficacy and/or safety endpoints
- Primary tumour location summary has been removed as TNM classification is not collected
- The definition of the 'Expected questionnaire' has been updated as local translation of the EORTC QLQ questionnaires are available in all countries
- Further instructions on the identification of disallowed medications
- Analyses related to changes in EGFR mutation ctDNA allele frequencies have been removed as no data will be available and further instructions have been added to derive the ctDNA status at 6 weeks

- Previous platinum-based chemotherapy (Y/N), previous platinum-based chemotherapy vs. line of treatment and immediate prior platinum-based chemotherapy subgroups have been added for the investigation of some efficacy endpoints
- FISH+ allocation status (Amplified vs. Polysomy) subgroup has been added for the investigation of some efficacy endpoints.

18/11/2020 The main updates based on the IA1 and IA2 requirements have been the following:

- Response to immediately prior line of therapy, immediately prior line osimertinib, and response to immediately prior line of therapy vs. immediately prior line osimertinib subgroups have been added for the investigation of some efficacy endpoints
- Stratification by line of treatment and/or immediate prior line osimertinib have been added for some baseline information and efficacy endpoints
- Clarification around how to derive some subgroups for some efficacy endpoints has been provided
- PK analyses for the patients with a savolitinib starting dose of 600mg has been added. Box plots displaying the geometric mean +/- geometric SD of the plasma concentrations of savolitinib have been included
- Clarification around potential Hy's law derivation have been provided
- Clarification around time windows for the safety laboratory assessments and the liver function tests have been provided
- TOC have been updated to reflect the changes in IA1 and IA2 requirements considering that the mock shell TFLs is master location for output updates.

30/04/2021 The main updates based on the amended CSP V5.0 and CSP V6.0 have been the following:

- To better characterise benefit-risk at different doses of savolitinib in combination with osimertinib, 2 alternative dosing regimens have been included; savolitinib 300 mg bid plus osimertinib 80 mg od has been added, and the savolitinib 600 mg od plus osimertinib 80 mg od has been re-introduced
- The randomisation has been introduced for the new dosing regimens (2:1 to 300 mg bid:600 mg od)

- Enrolment of new patients to the 300 mg bid and 600 mg od dosing regimens has been restricted to central MET FISH+ patients and 2nd line patients only
- The primary objective and endpoint (ORR in all patients population) has been updated to clarify that this will be assessed for the savolitinib 300 mg od plus osimertinib 80 mg od dosing regimen
- A new secondary objective and endpoint has been included to assess the efficacy of savolitinib 300 mg bid and 600 mg od regimens (ORR in all patients population)
- Analysis of secondary and exploratory objectives/endpoints by centrally confirmed IHC and FISH patient populations have been removed, with the exception of the analysis of ORR in the 300 mg od dosing regimen. These analyses will be performed as sub-group analyses
- The description of interim analyses has been changed
- A third interim analysis and additional data cuts for early safety/efficacy reviews has been introduced
- Due to the introduction of the 300 mg bid regimen, the original plan for primary analysis of ORR and the final analysis could both occur before the end of the recruitment to the 300 mg bid and 600 mg od regimens. Therefore, the primary analysis and final analysis have been combined and will be performed when all patients (including 300 mg bid and 600 mg od regimens) have had the opportunity to be followed for approximately 9 months
- The timing of additional OS follow-up analysis has been amended to be until CCI of the patients treated with the 300 mg bid and 600 mg od dosing regimens have died due to any cause
- Additional PK parameters following multiple dosing for the 300 mg bid dose regimen have been included
- Language has been included relating to the COVID-19 pandemic
- TOC have been updated considering that the mock shell TFLs is master location for output updates.

21/12/2022 The main updates based on the amended CSP V7.0 have been the following:

- The study design has been updated. Approx. CCI patients with MET amplification and/or overexpression (FISH10+ and/or IHC90+) who have progressed following 1L osimertinib therapy, are expected to be

randomised in a double-blinded manner and 2:1 ratio to receive savolitinib 300 mg bid in combination with osimertinib 80 mg od CCI patients) or savolitinib 300 mg bid with placebo to osimertinib CCI patients). Patients initially randomised to the savolitinib plus placebo arm will have the opportunity to cross over to the savolitinib plus osimertinib

- New endpoints have been introduced and some other removed. Consequently, the study objective table has been updated based on the current CSP version
- IA3 has been removed and a futility analysis for the savolitinib 300 mg bid + placebo arm has been introduced
- Primary and final analyses timing have been adjusted to 6 and 15 months, respectively after the last patient under CSP version 7.0 is randomised
- The OS follow-up analysis has been removed
- New study populations for analyses have been introduced
- The diagnostic populations of interest have been changed
- Dedicated baseline rules as well as the derivation of the study days have been introduced for the efficacy variable of patients enrolled under CSP version 7.0
- A stratification factor of brain metastases (yes, no) has been introduced for patients enrolled under CSP version 7.0
- The blinded independent central review (BICR) of radiological imaging data has been introduced
- 'Analysis method' section (section 4) has been restructured to better clarify which outputs will be produced for which endpoints, study populations and subgroups
- New subgroups analyses have been introduced and some other removed
- IUO grade status analyses have been introduced
- 'Changes of analysis from protocol' section (section 6) has been updated to document the analysis not planned as per protocol but still of interest for this study.

Further improvements have been implemented as follows:

- PK parameter presentation rules have been improved.

- 'Example of patient who permanently discontinued during a dose interruption' and 'Table of contents for Tables/Figures/Listings [TFLs]' previously displayed as SAP appendices have been removed as not relevant in this context.
- Minor changes such as duplicate text removal, typographical and formatting changes have been implemented where necessary.

01/12/2023

- Unconfirmed responses clarification has been added.

03/07/2024 The main updates for the new SAP amendment for the primary analysis were:

- Total Calcium derivation formula ("Calcium corrected for Albumin") has been added
- Body Mass Index formula
- Minor changes such as typography and cosmetic checks have been implemented
- Baseline definition in section 3.2.1.1.1 has been reported as per section 3.1.1
- Added Baseline assessment definition as per section 3.1.1 and no per CSP
- PK parameter presentation rules have been improved in order to align with AstraZeneca standard rules
- Progression Free Survival has been updated to include data up to 36 months
- Treatment status at progression by 2nd and 3rd line of treatment have been removed
- TEAEs by common frequency (>5%) in descending order have been added
- TEAEs of CTCAE grade ≥3 related to osimertinib and savolitinib have been added
- SAEs and TEAEs leading to discontinuation of treatment - key patient information have been added
- AESIs by CTCAE grade have been added
- ORR subgroup analysis for IUO grade has been added

- IPD section is updated (including a new table) and global/country situation IPDs have been removed
- Gamma glutamyl transferase is added to the chemical chemistry list
- Subgroup analysis section has been aligned with Appendix “A”
- PRO CTCAE grouping has been removed from the analysis
- Wording for ‘Evaluable for Response Set’ in Table 2 has been added to specify when applicable
- DoR and PFS by >=3 line of treatment have been removed from the analysis and section 6 has been updated
- Table 3 has been updated to account for the reduction of the efficacy analyses
- Section 4 has been updated to reflect Table 3

1 STUDY OBJECTIVES

The study objectives and endpoints are shown in Table 1 below.

Table 1 Study Objectives and Endpoints

Primary Objective:	**Endpoint:**
To determine the efficacy of savolitinib (300 mg bid) in combination with osimertinib in patients with EGFRm+ and MET- amplified/overexpressed (FISH10+ and/or IHC90+)a, locally advanced or metastatic NSCLC who have progressed following treatment with 1L osimertinib. To determine the efficacy of savolitinib (300 mg od) in combination with osimertinib in patients with EGFRm+, MET-amplified/overexpressed (FISH5+ and/or IHC50+)b, locally advanced or metastatic NSCLC who have progressed following osimertinib.	• ORR by investigator assessment in accordance with RECIST 1.1.
Secondary Objectives:	**Endpoints:**
To determine the efficacy of savolitinib (300 mg bid) in combination with osimertinib in patients with EGFRm+ and MET-amplified/overexpressed (FISH10+ and/or IHC90+)[a], locally advanced or metastatic NSCLC who have progressed following treatment with 1L osimertinib.	• DoR and PFS by investigator assessment in accordance with RECIST 1.1. • OS
To describe the difference in the efficacy of savolitinib (300 mg bid) in combination with osimertinib and savolitinib (300 mg bid) in combination with placebo in patients with EGFRm+, MET-amplified/overexpressed (FISH10+ and/or IHC90+)[a], locally advanced or metastatic NSCLC who have progressed on following treatment with 1L osimertinib. therapy under CSP version 7.0.	• ORR by investigator assessment in accordance with RECIST 1.1.

To determine the efficacy of savolitinib (300 mg od and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET-amplified/overexpressed (FISH10+ and/or IHC90+)[a], locally advanced or metastatic NSCLC who have progressed following treatment with 1L osimertinib.	• ORR, DoR, and PFS, by investigator assessment in accordance with RECIST 1.1. • OS
To determine the efficacy of savolitinib (300 mg od, 300 mg bid, and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET-amplified/overexpressed (FISH10+ and/or IHC90+)[a], locally advanced or metastatic NSCLC who have progressed following treatment of ≥2L osimertinib.	• ORR by investigator assessment in accordance with RECIST 1.1. • OS
To determine the efficacy of savolitinib (300 mg od, 300 mg bid, and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET-amplified/overexpressed (FISH5+ and/or IHC50+)[b], locally advanced or metastatic NSCLC who have progressed following osimertinib.	• ORR (except 300 mg od), DoR, and PFS by investigator assessment in accordance with RECIST 1.1 • OS
To determine the efficacy of (1) 300 mg od, 300 mg bid and 600 mg od of savolitinib in combination with osimertinib in patients with EGFRm+ MET-amplified/overexpressed (FISH 10+ and/or IHC90+)[a,b]; (2) 300 mg od, 300 mg bid and 600 mg od of savolitinib in combination with osimertinib. in patients with EGFRm+ MET amplified/overexpressed (FISH5+ and/or IHC50+)[b]; (3) savolitinib 300 mg bid in combination with osimertinib and savolitinib 300 mg bid in combination with placebo, respectively, in patients with EGFRm+ MET-amplified/ overexpressed (FISH10+ and/or IHC90+)[a] following treatment with 1L osimertinib.	• ORR, DoR, and PFS assessed by BICR in accordance with RECIST 1.1.

To assess the impact of savolitinib and osimertinib on disease related symptoms and HRQoL in this patient population.	• Mean change from baseline in EORTC QLQ-C30 and QLQ-LC13.
To evaluate the pharmacokinetics of osimertinib and savolitinib in this patient population.	• Plasma concentrations of osimertinib, savolitinib and their metabolites.
To determine the prevalence of ctDNA clearance after osimertinib and savolitinib treatment in this patient population.	• Total clearance in EGFR mutations at 6-weeks after therapy initiation (percentage and absolute change from baseline in EGFR mutation allele frequencies).
Safety Objectives:	**Endpoints:**
To evaluate the safety and tolerability of savolitinib in combination with osimertinib and savolitinib in combination with placebo.	• AEs, AESI. SAEs and discontinuation rate due to AEs. • Clinical chemistry/haematology including LFTs. • ECHOs, ECGs and vital signs including blood pressure and heart rate.
Exploratory Objectives:	**Endpoints:**
To assess the efficacy of savolitinib plus osimertinib and savolitinib plus placebo, respectively, on CNS metastases in patients with CNS metastases at baseline.	• CNS PFS by BICR assessments in accordance with RECIST 1.1.
To assess the efficacy of savolitinib plus osimertinib and savolitinib plus placebo, respectively, on the prevention of CNS metastases in patients without CNS metastases at baseline.	• The presence/absence of CNS lesions at progression by BICR assessments in accordance with RECIST 1.1.

To assess the impact of savolitinib in combination with osimertinib on patient reported treatment-related symptoms.	• PRO CTCAE symptoms.
To assess patients' overall impression of severity of cancer symptoms.	• Patient's Global Impression of Severity (PGIS).
To explore the impact of treatment and disease on health state utility	• EQ-5D-5L
To explore the factors of resistance and sensitivity to treatment.	• Protein, RNA and DNA research on blood and tumour prior to treatment, during the course of treatment, at disease progression and at treatment discontinuation.
To assess the predictive value of changes in circulating biomarkers on clinical efficacy endpoints.	• Longitudinal changes in circulating DNA and/or RNA compared with PFS, OS and ORR.
To collect and store DNA (according to each country's local and ethical procedures) for future exploratory research into genes/genetic variation that may influence response (i.e., distribution, safety, tolerability and efficacy) to study treatments and or susceptibility to disease (optional).	• Pharmacogenetic analyses on blood samples.
To collect and store tissue, plasma and serum samples for diagnostic development and exploratory analyses.	• Disease-relevant or response markers in tumour tissue and circulating tumour DNA/RNA including but not limited to EGFR mutations and MET amplifications.
To collect and store germline DNA for exploration of the role of HLA alleles in developmental toxicity.	• HLA alleles associated with susceptibility to drug related AEs (such as but not limited to hypersensitivity).

[a] Patients with MET-amplified/overexpressed includes NSCLC with FISH10+ (≥10 MET gene copies according to central MET FISH test) and/or IHC90+ (≥90% of tumour cells staining at strong 3+ intensity according to central MET IHC test).

[b] Patients who are with MET-amplified/overexpressed NSCLC with FISH5+ (≥5 MET gene copies or MET:CEP7 ratio ≥2) and /or IHC50+ (≥50% of tumour cells staining at strong 3+ intensity).

2 DEFINITION OF ANALYSIS SETS

2.1 Study Design and Number of Patients

The study has a total of 4 dosing combinations:

- Osimertinib (80 mg od + savolitinib (300 mg od) (explored under Clinical Study Protocol [CSP] versions 1.0 to 4.0)
- Osimertinib (80 mg od) + savolitinib (300 mg bid) (explored under CSP versions 5.0 to 7.0)
- Osimertinib (80 mg od) + savolitinib (600 mg od) (explored under CSP versions 1.0 to 2.0 and reintroduced under CSP versions 5.0 to 6.0)
- Placebo to osimertinib + savolitinib (300 mg bid) (explored under CSP version 7.0)

The savolitinib 300 mg od [Once daily] regimen was originally sized to ensure there were sufficient patients in each of the diagnostic populations. Approximately CCI centrally confirmed Hepatocyte growth factor receptor [MET] Fluorescence in situ hybridisation+ [FISH+] patients were planned to be treated with osimertinib 80 mg od plus savolitinib 300 mg od. To achieve CCI centrally confirmed MET FISH+ patients at this dose, it was anticipated that CCI patients at this dose would be treated in this study, assuming CCI of these would be centrally confirmed FISH+ patients and CCI (CCI patients) would be centrally confirmed MET Immunohistochemistry+ [IHC+] patients. As the overall prevalence rates and the level of concordance between FISH and IHC methods may vary and a small number of patients recruited by pre-existing Next generation sequencing [NGS] may not have a central confirmation, it was anticipated that greater or less than CCI patients would be required to achieve CCI centrally confirmed MET FISH+ patients, however this was not expected to exceed CCI treated patients at this dose. If the proportion of patients who had central confirmation by IHC was lower than expected, additional patients were to be recruited to ensure there were at least CCI centrally confirmed MET IHC+ patients.

Under CSP version 5.0. approximately CCI patients (post First-line [1L] or Second-line [2L] osimertinib) were planned to be randomised in a 2:1 ratio to receive osimertinib 80 mg od in combination with either savolitinib 300 mg bid (approximately CCI patients) or savolitinib 600 mg od (approximately CCI patients). Since CCI patients had already received the 600 mg od dose (enrolled prior to CSP version 5.0,

under the previous weight- based dosing schedule), approximately CCI patients in total were planned to receive osimertinib in combination with savolitinib 600 mg od.

Under CSP version 6.0, the enrolment was further restricted to post 1L osimertinib and central MET FISH+ only, therefore approximately CCI patients that were planned to be randomised in a 2:1 ratio to osimertinib 80mg od in combination with either savolitinib 300 mg bid or savolitinib 600 mg od applied to the new population (ie, post 1L osimertinib and central MET FISH+).

Under CSP version 7.0, approximately CCI patients (post 1L osimertinib with MET amplification/overexpression [FISH10+ and/or IHC90+] will be randomised in a 2:1 ratio to receive savolitinib 300 mg bid + osimertinib 80 mg (approximately CCI patients) or savolitinib 300 mg bid + placebo to osimertinib (approximately CCI patients). With assumed objective response rates [ORRs] of

CCI and CCI, for the savolitinib 300 mg bid + osimertinib 80 mg and the savolitinib 300 mg bid + placebo arms respectively, there will be at least CCI power at a 2-sided 0.05 significance level to detect a difference in ORRs of the 2 arms.

Overall, approximately CCI to CCI patients are anticipated to be pre-screened for MET-amplified/overexpressed status in this study.

All patients confirmed as eligible will begin treatment on Day 1 with osimertinib + savolitinib combination therapy or placebo to osimertinib + savolitinib. Treatment will continue in 28-day cycles until objective disease progression by investigator per Response Evaluation Criteria in Solid Tumours [RECIST] 1.1 is assessed, unacceptable toxicity, withdrawal of consent or another discontinuation criterion is met.

Under CSP version 7.0 only, at investigator-assessed progressive disease [PD] per RECIST 1.1, treatment allocation will be unblinded and those patients randomised to the savolitinib plus placebo arm will have the opportunity to cross over to the savolitinib plus osimertinib regimen.

To be noted, all patients treated with savolitinib 300 mg od or 600 mg od indiscriminately of CSP versions will be analysed all together (e.g. all 300 mg od or all 600 mg od, respectively).

Primary and final analyses:

For the savolitinib 300 mg bid dosing regimen, with approximately CCI patients (approximately CCI patients under CSP version 7.0 and approximately CCI patients under CSP version 5.0 and version 6.0) with FISH10+ and/or IHC90+ status who have progressed following 1L osimertinib treatment, Confidence intervals [CIs] will be provided and be compared with the historical reference platinum-pemetrexed chemotherapy ORR of approximately CCI.

For the savolitinib 300 mg od dosing regimen, with approximately CCI patients with FISH5+ and/or IHC50+ status who have progressed following osimertinib treatment, there will be at least CCI power for an exact binomial test with a two-sided significance level of 0.05 to detect a difference between the null hypothesis proportion of CCI and the alternative hypothesis proportion of CCI.

For the centrally confirmed IHC+ and all patient populations at the savolitinib 300 mg od dosing regimen, with CCI and CCI patients there would be CCI and CCI power, respectively, to detect a difference.

For interim analyses:

Please refer to Section 5.

2.2 Analysis Sets

The analysis sets are presented in Table 2.

Patients will be assigned to each of the populations in Table 2 and to the diagnostic populations (centrally confirmed by FISH [FISH5+, FISH10+] and centrally confirmed by IHC [IHC50+, IHC90+]), prior to any analyses being performed. Additional details on diagnostic populations can be found in section 4.1.

Table 2 Analysis Sets

Analysis Set	Definition
Target Population Analysis Set (TPAS)	All patients assigned to savolitinib 300 mg bid + osimertinib who have FISH10+ and/or IHC90+ status, have progressed following 1L osimertinib, and have taken ≥1 dose of either study drug.
Contribution of Components Analysis Set (CAS)	All patients randomised under CSP version 7.0 with treatment groups assigned in accordance with the randomisation, regardless of the treatment actually received.
Safety Analysis Set (SAF)	All enrolled patients who take ≥1 dose of either study drug.
PK Analysis Set	All patients who receive at least 1 dose of savolitinib or osimertinib as per the protocol for whom any post-dose PK data are available and do not violate or deviate from the protocol in ways that would significantly affect the PK analyses will be included in the PK analysis set.
Evaluable for Response	Dosed patients who have measurable disease at baseline. This population will only be used for interim analyses.
Evaluable for Response 2	Dosed patients with measurable disease at baseline who have had the opportunity for 2 on-treatment RECIST scans. This population will only be used for interim analyses.
Safety Analysis Set 2 (SAF2)	All enrolled patients who take ≥1 dose of either study drug who have had the opportunity to be treated for 6 weeks. This population will only be used for interim analyses.

CSP Clinical study protocol; FISH Fluorescence in situ hybridisation; IHC immunohistochemistry; PK Pharmacokinetic(s); RECIST Response Evaluation Criteria in Solid Tumor.

If during the study a patient stops one of the two study treatments and continues on monotherapy or a patient crossover to the combo treatment, the data for the patient will continue to be treated as per the initial treatment allocation.

For the Pharmacokinetic [PK] analysis set, where a protocol deviation impacts only part of a patient's data, the affected portion of the patient's PK data will be excluded from PK analysis and summary statistics, and the remaining valid data will be utilised.

The Target Population Analysis Set (TPAS) will be used as the population for reporting efficacy and to summarise baseline characteristics for patients dosed with savolitinib 300 mg bid + osimertinib who are FISH10+ and/or IHC90+ and have progressed following treatment with 1L osimertinib (primary endpoint population).

The Contribution of Components Analysis Set (CAS) will be used as the population for reporting efficacy and to summarise baseline characteristics for patients randomised under CSP version 7.0.

The Safety Analysis Set (SAF) will be used for reporting efficacy of savolitinib 300 mg od + osimertinib in FISH5+ and/or IHC50+ patients (primary endpoint population). The SAF will also be used as the population for reporting efficacy and to summarise baseline characteristics for patients dosedunder all CSP versions. The SAF will be used as the population for reporting safety for patients dosed under all CSP versions.

The PK analysis set will be used for reporting PK for patients dosed under all CSP versions. For the PK analysis set, where a protocol deviation impacts only part of a patient's data, the affected portion of the patient's PK data will be excluded from PK analysis and summary statistics, and the remaining valid data will be utilised.

Table 3 Summary of outcome variables, analysis sets and MET Status.

Outcome Variable	*Analysis set and Doses*	*MET status*
Demography and baseline characteristics	TPAS Savolitinib 300 mg bid + osimertinib	FISH10+ and/or IHC90+
	SAF Savolitinib (300 mg od, 300 mg bid, 600 mg od) + osimertinib Savolitinib (300 mg od, 300 mg bid, 600 mg od) + osimertinib Savolitinib 300 mg bid + placebo	FISH5+ and/or IHC50+ FISH10+ and/or IHC90+
	CAS Savolitinib 300 mg bid + osimertinib Savolitinib 300 mg bid + placebo	FISH10+ and/or IHC90+
Exposure	TPAS Savolitinib 300 mg bid + osimertinib	FISH10+ and/or IHC90+
	SAF Savolitinib (300 mg od, 300 mg bid, 600 mg od) + osimertinib Savolitinib (300 mg od, 300 mg bid, 600 mg od) + osimertinib Savolitinib 300 mg bid + placebo	FISH5+ and/or IHC50+ FISH10+ and/or IHC90+

Primary Objective	***Endpoint***	***Analysis set and Doses***	***MET status***
Primary endpoint			
Efficacy Data			
To determine the efficacy of savolitinib (300 mg bid) in combination with osimertinib in patients with EGFRm+ and MET amplified/overexpressed (FISH10+ and/or IHC90+)[a], locally advanced or metastatic NSCLC who have progressed following treatment with 1L osimertinib	ORR by investigator assessment in accordance with RECIST 1.1.	TPAS Savolitinib 300 mg bid + osimertinib	FISH10+ and/or IHC90+
To determine the efficacy of savolitinib (300 mg od) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH5+ and/or IHC50+)[b], locally advanced or metastatic NSCLC who have progressed following osimertinib.	ORR by investigator assessment in accordance with RECIST 1.1.	SAF Savolitinib 300 mg od + osimertinib	FISH5+ and/or IHC50+
Secondary Objective	***Endpoint***	***Analysis set and Doses***	***MET status***
Secondary endpoints			
Efficacy Data			
To determine the efficacy of savolitinib (300 mg bid) in combination with osimertinib in patients with EGFRm+ and MET amplified/overexpressed (FISH10+ and/or IHC90+)[a], locally advanced or metastatic NSCLC who have progressed following treatment with 1L osimertinib.	DoR and PFS by investigator assessment in accordance with RECIST 1.1 OS	TPAS Savolitinib 300 mg bid + osimertinib	FISH10+ and/or IHC90+

To describe the difference in the efficacy of savolitinib (300 mg bid) in combination with osimertinib and savolitinib (300 mg bid) in combination with placebo in patients with EGFRm+, MET amplified/ overexpressed (FISH10+ and/or IHC90+)[a], locally advanced or metastatic NSCLC who have progressed following treatment with 1L osimertinib therapy under CSP version 7.0.	ORR by investigator assessment in accordance with RECIST 1.1	CAS Savolitinib 300 mg bid + osimertinib Savolitinib 300 mg bid + placebo	FISH10+ and/or IHC90+
To determine the efficacy of savolitinib (300 mg od and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET- amplified/overexpressed (FISH10+ and/or IHC90+)[a], locally advanced or metastatic NSCLC who have progressed following treatment with 1L osimertinib.	ORR, DoR, and PFS, by investigator assessment in accordance with RECIST 1.1. OS	SAF Savolitinib (300 mg od, 600 mg od) + osimertinib	FISH10+ and/or IHC90+
To determine the efficacy of savolitinib (300 mg od, 300 mg bid, and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET-amplified/overexpressed (FISH10+ and/or IHC90+)[a], locally advanced or metastatic NSCLC who have progressed following treatment of ≥ 2L osimertinib.	ORR by investigator assessment in accordance with RECIST 1.1.	SAF Savolitinib (300 mg od, 300 mg bid, 600 mg od) + osimertinib	FISH10+ and/or IHC90+
To determine the efficacy of savolitinib (300 mg od, 300 mg bid, and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET-amplified/overexpressed (FISH5+ and/or IHC50+)[b], locally advanced or metastatic NSCLC who have progressed following osimertinib.	ORR (except 300 mg od), DoR, and PFS by investigator assessment in accordance with RECIST 1.1. OS	SAF Savolitinib (300 mg bid, 600 mg od) + osimertinib	FISH5+ and/or IHC50+

To determine the efficacy of (1) 300 mg od, 300 mg bid and 600 mg od of savolitinib in combination with osimertinib in patients with EGFRm+ MET amplified/overexpressed (FISH 10+ and/or IHC90+)[a,b]; (2) 300 mg od, 300 mg bid and 600 mg od of savolitinib in combination with osimertinib in patients with EGFRm+ MET amplified/overexpressed (FISH5+ and/or IHC50+)[b] (3) savolitinib 300 mg bid in combination with osimertinib and savolitinib 300 mg bid in combination with placebo, respectively, in patients with EGFRm+ MET amplified/ overexpressed (FISH10+ and/or IHC90+)[a] following treatment with 1L osimertinib.	ORR, DoR, and PFS assessed by BICR in accordance with RECIST 1.1	SAF Savolitinib (300 mg od, 300 mg bid, 600 mg od) + osimertinib CAS Savolitinib 300 mg bid + osimertinib Savolitinib 300 mg bid + placebo TPAS Savolitinib 300 mg bid + osimertinib	FISH5+ and/or IHC50+ FISH10+ and/or IHC90+ FISH10+ and/or IHC90+ FISH10+ and/or IHC90+
To assess the impact of savolitinib and osimertinib on disease-related symptoms and HRQoL in this patient population.	Mean change from baseline in EORTC QLQC30 and QLQ- LC13.	TPAS Savolitinib 300 mg bid + Osimertinib SAF Savolitinib (300 mg od, 300 mg bid, 600 mg od) + osimertinib	FISH10+ and/or IHC90+ FISH5+ and/or IHC50+ FISH10+ and/or IHC90+
Pharmacokinetics Data			
To evaluate the pharmacokinetics of osimertinib and savolitinib in this patient population.	Plasma concentrations of osimertinib, savolitinib and their metabolites.	PK Set Savolitinib (300 mg od, 300 mg bid, 600 mg od) + osimertinib	FISH5+ and/or IHC50+

Biomarker Data			
To determine the prevalence of ctDNA clearance after osimertinib and savolitinib treatment in this patient population.	Total clearance in EGFR mutations at 6-weeks after therapy initiation (percentage and absolute change from baseline in EGFR mutation allele frequencies).	TPAS Savolitinib 300 mg bid + osimertinib SAF Savolitinib (300 mg od, 300 mg bid, 600 mg od) + osimertinib	FISH10+ and/or IHC90+ FISH5+ and/or IHC50+ FISH10+ and/or IHC90+
Safety Objective	***Endpoint***	***Analysis set and Doses***	***MET status***
Safety Endpoint			
To evaluate the safety and tolerability of savolitinib in combination with osimertinib and savolitinib in combination with placebo.	AEs, SAEs and discontinuation rate due to AEs. Clinical chemistry/haematology including LFTs. ECHOs, ECGs and vital signs including blood pressure and heart rate.	SAF Savolitinib (300 mg od, 300 mg bid, 600 mg od) + osimertinib Savolitinib 300 mg bid + placebo	FISH5+ and/or IHC50+ FISH10+ and/or IHC90+ FISH 10+ and/or IHC90+
Exploratory Objective	***Endpoint***	***Analysis set and Doses***	***MET status***
Exploratory Endpoint			
To assess the efficacy of savolitinib plus osimertinib and savolitinib plus placebo, respectively, on CNS metastases in patients with CNS metastases at baseline	CNS PFS by BICR assessments in accordance with RECIST 1.1.	CAS Savolitinib 300 mg bid + osimertinib Savolitinib 300 mg bid + placebo	FISH10+ and/or IHC90+
To assess the efficacy of savolitinib plus osimertinib and savolitinib plus placebo, respectively, on the prevention of CNS metastases in patients without CNS metastases at baseline.	The presence/absence of CNS lesions at progression by BICR assessments in accordance with RECIST 1.1.	CAS Savolitinib 300 mg bid + osimertinib Savolitinib 300 mg bid + placebo	FISH10+ and/or IHC90+
To assess the impact of savolitinib in combination with osimertinib on patient reported treatment-related symptoms.	PRO CTCAE symptoms.	SAF Savolitinib (300 mg od, 300 mg bid, 600 mg od) +	FISH5+ and/or IHC50+ FISH10+ and/or IHC90+

		osimertinib	
To assess patients' overall impression of severity of cancer symptoms.	Patient's Global Impression of Severity (PGIS).	SAF Savolitinib (300 mg od, 300 mg bid, 600 mg od) + osimertinib	FISH5+ and/or IHC50+ FISH10+ and/or IHC90+
To explore the impact of treatment and disease on health state utility	EQ-5D-5L	SAF Savolitinib (300 mg od, 300 mg bid, 600 mg od) + osimertinib	FISH5+ and/or IHC50+ FISH10+ and/or IHC90+
Supplementary Analyses	***Endpoint***	***Analysis set and Doses***	***MET status***
Efficacy Data			
	ORR, DoR (TPAS and SAF only) by investigator assessment in accordance with RECIST 1.1 using retrospective IUO grade MET testing	TPAS Savolitinib 300 mg bid + osimertinib SAF Savolitinib (300 mg od, 300 mg bid, 600 mg od) + osimertinib	FISH10+ and/or IHC90+ FISH10+ and/or IHC90+
	PFS by investigator assessment in accordance with RECIST 1.1 using retrospective IUO grade MET testing	TPAS Savolitinib 300 mg bid + osimertinib SAF Savolitinib (300 mg od, 300 mg bid, 600 mg od) + osimertinib	FISH10+ and/or IHC90+ FISH10+ and/or IHC90+
Additional Analyses not in the CSP	***Endpoint***	***Analysis set and Doses***	***MET status***
Efficacy Data			
	DoR, PFS by investigator assessment in accordance with RECIST 1.1	CAS Savolitinib 300 mg bid + osimertinib Savolitinib	FISH10+ and/or IHC90+

		300 mg bid + placebo	
	CNS ORR and CNS DoR by BICR assessments in accordance with RECIST 1.1	CAS Savolitinib 300 mg bid + osimertinib Savolitinib 300 mg bid + placebo	FISH10+ and/or IHC90+
	Change in tumour size by investigator assessment in accordance with RECIST 1.1	TPAS Savolitinib 300 mg bid + osimertinib SAF Savolitinib (300 mg od, 300 mg bid, 600 mg od) + osimertinib	FISH10+ and/or IHC90+ FISH5+ and/or IHC50+ FISH10+ and/or IHC90+

[a] Patients with MET-amplified/overexpressed NSCLC with FISH10+ (≥10 MET gene copies according to central MET FISH test) and/or IHC90+ (≥90% of tumour cells staining at strong 3+ intensity according to central MET IHC test).

[b] Patients with MET-amplified/overexpressed NSCLC with FISH5+ (≥5 MET gene copies or MET:CEP7 ratio ≥2) and/or IHC50+ (≥50% of tumour cells staining at strong 3+ intensity)

2.3 Protocol Deviations

Important protocol deviations [IPDs] related to, but not limited to, study inclusion or exclusion criteria, conduct of the study, patient management or patient assessment will be described in the Clinical Study Report [CSR]. The following general categories will be considered important protocol deviations that may significantly impact the overall interpretation of the primary and/r secondary study results, some of which will be programmatically derived from the eCRF data, and all will be listed in the CSR. A full list of IPDs and descriptions can be found in the study non-compliance handling plan [NHP].

Table 4 IPDs and descriptions

Criteria	IPD Description
1. Inclusion criteria deviations	1.03: Histologically or cytologically confirmed locally advanced or metastatic EGFRm+ NSCLC harbouring an EGFR mutation known to be associated with EGFR TKI sensitivity (including either exon 19 deletion and/or L858R) which is not amenable to curative therapy. 1.04: Documented radiologic disease progression on 1L osimertinib. 1.05: MET amplification/ and/or overexpression (FISH10+ and/or IHC90+) as determined by FISH (central) and IHC (central) testing on tumour sample collected following progression on 1L osimertinib treatment. 1.06: At least 1 lesion, not previously irradiated, not biopsied during the screening period, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) which is suitable for accurate repeated measurements. If only 1 measurable lesion exists, it is acceptable to be used as long as baseline tumour assessment scans are done at least 14 days after the screening tumour sample collection is performed. 1.07: Prior lines of therapy in locally advanced /metastatic setting: Only prior 1L osimertinib treatment in metastatic setting is permitted. – applicable for patients enrolled in CSP v7.0. Patients must have received at least one but no more than 3 prior lines of therapy (including

	investigational therapy) in the locally advanced/metastatic setting - applicable for patients enrolled before CSP v.7.0. 1.09: Adequate liver function defined as: • Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x the upper limit of normal (ULN) with total bilirubin (TBL) ≤ ULN OR • TBL >ULN to ≤1.5x ULN with ALT and AST ≤ ULN
2. Exclusion criteria deviations	2.03: Any of the following cardiac diseases currently or within the last 6 months: • Unstable angina pectoris • Congestive heart failure (New York Heart Association [NYHA] ≥Grade 2) • Acute myocardial infarction • Stroke or transient ischemic attack • Uncontrolled hypertension (blood pressure [BP] ≥150/95 mmHg despite medical therapy). • Mean resting correct QT interval (QTcF) >470 msec for women and >450 msec for men at Screening, obtained from 3 ECGs using the screening clinic ECG machine derived QTcF value. • Any factors that may increase the risk of QTcF prolongation or risk of arrhythmic events such as heart failure, chronic hypokalaemia not correctable with supplements, congenital or familial long QT syndrome, family history of unexplained sudden death under 40 years of age in first-degree relatives or any concomitant medication known to prolong the QT interval and cause Torsade de Pointes. Any clinically important abnormalities in rhythm, conduction or morphology of resting ECGs, eg, complete left bundle branch block, third degree heart block, second degree heart block, P-R interval >250 msec. Acute coronary syndrome. 2.07: Active hepatitis B (HBV) (positive HBV surface antigen [HBsAg] result) or hepatitis C (HCV). Viral testing is not required for assessment of eligibility for the study. Patients

	with a past or resolved HBV infection are eligible if: - Negative for HBsAg and positive for hepatitis B core antibody [anti-HBc-IgG]. In addition, patients must be receiving anti-viral prophylaxis for 2 to 4 weeks prior to study treatment and 6 to 12 months (to be determined by hepatologist) post treatment] or - Positive for HBsAg, but for >6 months have had normal transaminases and HBV DNA levels < 100 IU/mL (i.e., are in an inactive carrier state). In addition, patients must be receiving anti-viral prophylaxis for 2 to 4 weeks prior to study treatment and 6 to 12 months (to be determined by hepatologist) post treatment. Patients with a past or resolved HBV infection must have monthly monitoring of ALT and HBV DNA (see Appendix I 2). HBV DNA levels >2000 IU/mL but on prophylactic antiviral treatment for the past 3 months and will maintain the antiviral treatment during the study. Patients with positive HCV antibody are eligible only if the polymerase chain reaction is negative for HCV ribonucleic acid. 2.10: Spinal cord compression or brain metastases unless asymptomatic, stable and not requiring steroids for at least 2 weeks prior to start of study treatment 2.11: Past medical history of ILD, drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD. 2.29: History of liver cirrhosis of any origin and clinical stage; or history of other serious liver disease or chronic disease with relevant liver involvement, with or without normal LFTs, such as: • Haemochromatosis • Alpha 1 antitrypsin deficiency • Autoimmune hepatitis • Primary sclerosing cholangitis • Primary biliary cirrhosis

	• Biopsy confirmed non alcoholic steatohepatitis with advanced fibrosis • Biopsy confirmed alcoholic steatohepatitis with advanced fibrosis • Wilson's disease • Hepatocellular carcinoma.
3. Discontinuation criteria for study product met but patient not withdrawn from study treatment	3.01: An adverse event that, in the opinion of the investigator or AstraZeneca, warrants discontinuation from further dosing. 3.02: Patient noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal (e.g., refusal to adhere to scheduled visits).
4. Discontinuation criteria for overall study withdrawal met but participant not withdrawn from study	4.02: Where a patient does not meet all the key eligibility criteria but is enrolled in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately.
5. IP deviation	5.04: Participant received incorrect treatment. 5.07: Patient assigned to treatment but who did not receive study treatment.
6. Excluded medication taken	6.01: Participant received medication prohibited by the CSP at any time or failed to comply with specified washout periods, see Prohibited Meds section in CSP. 6.02: Participant received other cancer therapies, prohibited whilst on study drug. 6.03: Participant received prohibited procedures, see exclusion criteria.
7. Deviations to study procedure	7.04: Critical efficacy data not collected or not compliant with CSP assessment schedule for study: baseline RECIST >42 days before date of randomisation, and no baseline RECIST on or before the date of first dose. Include patients with no post-baseline RECIST assessments (at least one post-dose, non target lesions and target lesions assessment is required for efficacy study endpoints) unless prematurely patient withdrawal or death. Missed scan for confirmation of CR or PR. 7.05: Critical data missing/not evaluable from other data sources.

	- ctDNA: total clearance in EGFR mutations at baseline and 6-weeks after therapy initiation - PK: baseline plasma concentrations of osimertinib, savolitinib and their metabolites. 7.07: Patient was not given fully informed consent, but study related procedures were performed. 7.10: Misstratification of baseline brain metastases.

The number and percentage of patients meeting each IPD criterion will be summarised for the safety analysis set. Patients deviating from a criterion more than once will be counted once for that criterion. Any patients who have more than one protocol deviation will be counted once in the overall summary. A data listing of patients who meet at least one IPD criterion will be provided for the safety analysis set.

3 DESCRIPTION OF VARIABLES

3.1 General principles

3.1.1 Baseline measurements and change from baseline variables

Baseline for patients allocated/randomised to treatment will be the last assessment of the variable under consideration prior to the intake of the first dose, except for efficacy variables. For efficacy variables, baseline is defined as the last non-missing assessment prior to randomisation (patients enrolled under CSP version 7.0) or last non-missing assessment prior to first dose (patients enrolled prior to CSP version 7.0). For patients who cross over from savolitinib plus placebo to savolitinib plus osimertinib, their data will be cut off for the purposes of any savolitinib plus placebo assessment at the last assessment of the variable under consideration prior to the intake of the first dose of the combination therapy.

If two assessments are equally eligible to assess patient status at baseline (e.g. on the same date prior to first dose with no time recorded to distinguish the assessments), the average should be taken as the baseline value. For non-numeric laboratory tests (i.e. some of the urinalysis parameters) where taking an average is not possible then the best value would be taken as baseline as this is the most conservative. In the scenario where there are two assessments on Day 1, one with time recorded and the other without time recorded, the one with time recorded would be selected as baseline, assuming it could be determined that it occurred prior to first dose. Where safety data are summarised over time, study day will be calculated in relation to date of first treatment. If no value exists before the first dose/administration, then the baseline value will be treated as missing.

Regarding electronic Patient reported outcome [ePRO] questionnaires, the baseline is defined as the non-missing assessment collected at Day 1, as it is assumed it is taken prior to start of the study treatment. If an assessment is missing at Day 1, the prior non-missing assessment will be used as baseline.

In all summaries change from baseline variables will be calculated as the post treatment value minus the

value at baseline. For % change from baseline, calculate:

$$\%\ change\ from\ baseline = \frac{(Post\ baseline\ value - Baseline\ Value)}{Baseline\ value}\ x\ 100$$

3.1.2 Stratification factor(s)

There is one stratification factor of baseline brain metastases (Yes/No) introduced for patients randomised under CSP version 7.0. When necessary, and only for patients belonging to CAS, the stratification in the statistical analyses will be based on the baseline brain scan assessed by the investigator using the values entered in the IWRS at randomisation, even if it is subsequently discovered that these values were incorrect.

3.1.3 Time Windows

The date of first dose of study treatment will be considered Day 1, and the day before the first dose of study treatment will be Day -1. Relative days will be calculated as follows:

For days on or after the first dose of study treatment:

Date of assessment – Date of first dose of study treatment +1.

For days before the first dose of study treatment:

Date of assessment – Date of first dose of study treatment.

For analyses of efficacy variables for patients enrolled under CSP version 7.0, the date of randomisation will be considered Day 1, and the day before date of randomisation will be Day -1. Relative days will be calculated as follows:

For days on or after the randomisation date:

Date of assessment – Date of randomisation +1.

For days before the randomisation date:

Date of assessment – Date of randomisation.

For non-efficacy analysis, the study day is still relative to first dosing date of study treatment.

Study days will only be calculated for complete assessment dates (i.e. partial dates will have missing study day).

The time from last dose of treatment to death will be derived for complete dates as follows:

Date of death – Date of last dose of treatment

For the purpose of the statistical analysis and if not otherwise specified, all the variables (primary, secondary and exploratory variables) will be assigned to the visit/assessment timepoint in which they were collected depending on the following analysis time windows in Table 5. Where appropriate, the window for assessment days following baseline will be constructed in such a way that the upper limit of the interval falls halfway between the two timepoints.

Table 5 Time Windows

Cycle	Week	Study Day	Cycle Day	Study Day window for weekly assessments	Cycle Day window for weekly assessments	Cycle Day window for Cycle Day 1 assessments (from Cycle 2 and onwards)	Study Day window for assessments scheduled every 4 weeks [b]	Study Day window for assessments scheduled every 6 weeks	Cycle Day window for liver function tests (ALT, AST, ALP and total bilirubin)	Cycle Day window for safety laboratory assessments (other than liver function tests)
		-1	-1	-28 to -1	-1	-1	-1	-1	-1	-1
1	1	1 [a]	C1D1	1	C1D1	C1D1	1	1	C1D1	C1D1
1	2	8	C1D8	2-11	C1D2-C1D11	C1D2-C1D11	2-42	2-63	C1D8	C1D8
1	3	15	C1D15	12-18	C1D12-C1D18	C1D12-C1D18			C1D15	C1D15
1	4	22	C1D22	19-25	C1D19-C1D25	C1D19-C1D25			C1D22	C1D22
2	5	29	C2D1	26-32	C1D26-C2D4	C1D26-			C2D1	C2D1 [d]

2	6	36	C2D8	33-39	C2D5-C2D11	C2D25			C2D8	
2	7	43	C2D15	40-46	C2D12-C2D18				C2D15	
2	8	50	C2D22	47-53	C2D19-C2D25				C2D22	
3	9	57	C3D1	54-60	C2D26-C3D4		43-70		C3D1	C3D1 [d]
3	10	64	C3D8	61-67	C3D5-C3D11	C2D26-C3D25			C3D8 [e]	
3	11	71	C3D15	68-74	C3D12-C3D18					
3	12	78	C3D22	75-81	C3D19-C3D25				C4D1 [d]	
4	13	85	C4D1	82-88	C3D26-C4D4		71-98	64-105		C4D1 [d]
4	14	92	C4D8	89-95	C4D5-C4D11	C3D26-C4D25				
4	15	99	C4D15	96-102	C4D12-C4D18		99-126			

4	16	106	C4D22	103-109	C4D19-C4D25			106-147		
5	17	113	C5D1	110-116	C4D26-C5D4	C4D26-C5D25			C5D1 [d]	C5D1 [d]
5	18	120	C5D8	117-123	C5D5-C5D11					
5	19	127	C5D15	124-130	C5D12-C5D18					
5	20	134	C5D22	131-137	C5D19-C5D25					
				Etc. for Cycles 6 and above						After Week 24, tumour assessments will be every 8 weeks [c]

[a] Measurements collected before the first dose of study treatment/randomisation on Day 1 are pre-dose values and measurements collected after first dose of study treatment/randomisation on Day 1 are post-baseline values. For ePRO questionnaires, the baseline is defined as the non-missing assessment collected at Day 1, as it is assumed it is taken prior to start of the study treatment. If an assessment is missing at Day 1, the prior non- missing assessment will be used as baseline.

[b] The Week 24 window would start approximately halfway through a 6-week period and end halfway into an 8-week period, i.e. Day 196. Week 32 window will be Day 197-252, etc.

[c] For assessments occurring every 12 weeks, the same schedule should be used, i.e. for the first assessment on Day 84 the window will be Day 1-126, for the second assessment on Day 168 the window will be Day 127-210, etc.

[d] The target day will be the study day at CXD1

[e] The target day will be the study day at C3D8

The treatment discontinuation visit should occur within 7 days of the final dose of the last study treatment. For the 28-day follow-up visit a 7-day window is allowed, i.e., it should occur 21-35 days following discontinuation of both study treatments.

On treatment period includes a safety follow-up period following discontinuation of both study treatments of 28+7 days. Therefore, discontinuation visit and follow up [FUP] visit will be slotted into the appropriate analysis visit using the time windowing described in Table 5. Assessments performed after 28+7 days from final dose (i.e., outside the on-treatment period) will be labelled as 'Post follow-up' and they will be only listed.

Unscheduled visit data will be considered when assigning assessments to the analysis visit. If more than one assessment of the variable (scheduled or unscheduled) falls in the same time window but on different days, the closest to the scheduled visit day will be taken, or the earlier, in the event the values are equidistant from the nominal visit date. If several measurements are collected during the selected day, the average (for numeric values)/worst (for categorical values) of the measurements will be taken.

In summaries of extreme values as opposed to visit-based summaries, all post baseline values collected are used including those collected at unscheduled visits regardless of the value being closest to the scheduled visit date or not. For summaries at a patient level, all values should be included, regardless of whether they appear in a corresponding visit-based summary, when deriving a patient level statistic such as a maximum.

Listings will display all values contributing to a time point for a patient.

3.1.4 Handling of missing data

In general, there is no imputation of missing data for efficacy analyses.

For RECIST, in case of partially missing Target lesion [TL] measurements the results will be scaled up as detailed in section 3.2.1.1.1.

3.1.4.1 Imputation of Adverse Event Onset Date

Missing onset dates (where in electronic Case Report Form [eCRF] UN, UNK and 0000 indicate unknown or missing Day, Month and Year respectively for partial missing dates; while completely missing dates would be left empty) will imputed according to the following rules:

- Completely missing dates will be not imputed.
- If the day is missing and the month and year are different from the month and year of the first dose of study treatment, assume 01-MMM-YYYY. If the month and year are the same as the first dose of study treatment month and year and the end date (after any imputation) is on or after (including still on-going at the end of the study) the first dose of study treatment, then assume the date of the first dose of study treatment. If the month and year are the same as the first dose of study treatment month and year and the end date (after any imputation) is prior to the first dose of study treatment, then assume the end date for the onset date.

- If the month is missing and the year is different from the year of first dose of study treatment, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of study treatment year and the end date (after any imputation) is on or after (including still on-going at the end of the study) the first dose of study treatment, then assume the date of the first dose of study treatment. If the year is the same as the first dose of study treatment and the end date (after any imputation) is prior to the first dose of study treatment, then assume the end date for the onset date.
- After applying these rules, if the imputed AE onset date is after a complete adverse event[AE] end date (or date of death), the imputed onset date will be the same as the complete AE end date (or date of death).
- Missing start dates for concomitant medications will not be imputed. Missing dates for medical history will not be imputed.

3.1.4.2 Imputation of Adverse Event / Concomitant Medication Stop Date:

Missing stop dates will be imputed according to the following rules:

- Completely missing dates will be not imputed.
- If the day is missing: Assume the last day of the month.
- If the month is missing: Assume 31-DEC-YYYY.

After applying these rules, if the imputed AE or concomitant medication [CM[stop date is after the date of death, the imputed stop date will be the same as the date of death.

If the AE/CM is ongoing, the stop date will remain missing.

The imputed onset and/or stop AE dates will not be used to calculate durations.

3.1.4.3 Imputation rules for lab values outside of quantification range

Lab values below the lower limit of quantification [LLOQ] that are reported as "<LLOQ" or "≤LLOQ" in the database will be imputed by LLOQ x 0.99 for analysis purposes. The original value will be listed.

Lab values above the upper level of quantification [ULOQ] that are reported as ">ULOQ" or "≥ULOQ" in the database will be imputed by ULOQ x 1.01 for analysis purposes. The original value will be listed.

3.2 Outcome variables

3.2.1 Efficacy Outcome Variables

3.2.1.1 Calculation or derivation of tumour response variables

3.2.1.1.1 RECIST visit responses

For all patients, the RECIST tumour response data will be used to determine each patient's visit response according to RECIST version 1.1. It will also be used to determine if and when a patient has progressed in accordance with RECIST and also their best objective response to study treatment.

Baseline radiological tumour assessments are performed as defined in Section 3.1.1. Follow-up assessments should be performed every 6 weeks (±7 days) until Cycle 7 (i.e., 24 weeks) and then every 8 weeks (±7 days) (relative to randomisation [patients recruited under CSP v7.0] or the first dose of treatment)[patients recruited prior to CSP v7.0] until objective disease progression as defined by RECIST 1.1 even if a patient discontinues treatment prior to progression (unless they withdraw consent). Any other regions suspected, or with known metastasis at baseline, will be assessed by imaging and recorded at baseline. The same imaging modality and the same assessment should be performed at baseline and at all subsequent assessments. If scans are performed outside of the scheduled visit ±1 week window interval and the patient has not progressed, every attempt should be made to perform the subsequent scans at their scheduled time points.

From the investigator's review of the imaging scans, the RECIST tumour response data will be used to determine each patient's visit response according to RECIST version 1.1. At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD or PD, using the information from TLs, NTLs and new lesions and depending on the status of their disease compared with baseline and previous assessments. If a patient has had a tumour assessment which cannot be evaluated, then the patient 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).

Unless futility is declared, investigator assessment of PD per RECIST 1.1 of patients receiving savolitinib + placebo is required prior to cross over to savolitinib plus osimertinib. In addition, if at the futility analysis the decision is made that treatment with savolitinib plus placebo arm is futile all patients will be unblinded and those randomised to savolitinib plus placebo will be given the opportunity to cross-over to savolitinib plus osimertinib. For patients who cross over based on confirmed objective disease progression during the initial randomised treatment period, scheduled RECIST 1.1 tumour assessments are not required, and the subsequent assessment of disease progression will be based on standard-of-care scan or investigator determined clinical progression. Scheduled RECIST 1.1 tumour assessments are required (the scan frequency is against initial randomisation) for patients who cross over based on a declaration of futility of the savolitinib monotherapy arm and who have not objectively progressed during the initial randomised treatment period. Patients who cross over based on a declaration of futility, who have no objective progression during initial randomisation period, and who discontinue study drug after cross-over for reasons other than investigator-confirmed disease progression will continue scheduled RECIST 1.1 tumour assessments until objective disease progression per RECIST 1.1 as assessed by investigator, unless they withdraw consent to the entire study.

RECIST outcomes (i.e. Progression-free survival [PFS], ORR etc.) will be calculated programmatically for

the site investigator data (see Sections 3.2.1.1.5 and 3.2.1.1.6 for PFS and Overall survival [OS] respectively) from the overall visit responses.

All computed tomography [CT]/ magnetic resonance imaging [MRI] scans and all imaging assessments performed for RECIST 1.1 tumour assessment will be reviewed at site. Duplicates must be available at the site in readiness to be sent for retrospective independent central RECIST 1.1 review, if deemed appropriate. If an independent central review is conducted the SAP will be amended accordingly.

Target lesions [TLs]
Measurable disease is defined as having at least one measurable lesion, not previously irradiated, which is ≥10 mm in the longest diameter [LD] (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography [CT] or magnetic resonance imaging [MRI] (clinical examination will not be used as a method of assessment of TL) and which is suitable for accurate repeated measurements.
A patient can have a maximum of 5 measurable lesions recorded at baseline with a maximum of 2 lesions per organ (including lymph nodes and representative of all lesions involved and suitable for accurate repeated measurement) and these are referred to as target lesions [TLs]. If more than one baseline scan is recorded, then measurements from the one that is closest and prior to first dose/administration of study medication (patients recruited prior to CSP v7.0) or to randomisation (patients recruited under CSP v7.0) will be used to define the baseline sum of TLs. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

All other lesions (or sites of disease) not recorded as TL should be identified as NTLs at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits.

Note: Only patients with measurable disease at baseline should be enrolled in this study. However, in case a patient is enrolled and does not have measurable disease at entry (i.e. no TLs) but have non-measurable disease, evaluation of overall visit responses will be based on the overall NTL assessment and the absence/presence of new lesions. If a patient does not have measurable disease at baseline, then the TL visit response will be not applicable [NA].

Table 6 TL Visit Responses

Visit Reponses	Description
Complete Response [CR]	Disappearance of all TLs. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10mm.
Partial response [PR]	At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters, as long as criteria for PD are not met.
Progressive disease [PD]	A ≥20% increase in the sum of diameters of TLs and an absolute increase of ≥ 5mm, taking as reference the

	smallest sum of diameters since treatment started including the baseline sum of diameters.
Stable disease [SD]	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Not Evaluable [NE]	Only relevant in certain situations (i.e. if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit; and scaling up could not be performed for lesions with interventions). Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response
Not applicable [NA]	No TLs are recorded at baseline

Rounding of TL data

For calculation of PD and PR for TLs percentage changes from baseline and previous minimum should be rounded to 1 decimal point before assigning a TL response. For example, 19.95% should be rounded to 20.0% but 19.94% should be rounded to 19.9%.

Missing TL data

If all TL measurements are missing, then the TL visit response is not evaluable [NE]. Overall visit response will also be NE, unless there is a progression of non-TLs or new lesions, in which case the response will be PD.

Lymph nodes

For lymph nodes, if the size reduces to <10mm then these are considered non-pathological. However, a size will still be given, and this size should still be used to determine the TL visit response as normal. In the special case where all lymph nodes are <10mm and all other TLs are 0mm then although the sum may be >0mm the calculation of TL response should be over-written as a CR.

TL visit responses subsequent to CR

A CR can only be followed by CR, PD or NE. If a CR has occurred, then the following rules at the subsequent visits must be applied:

- Step 1: If all lesions meet the CR criteria (i.e. 0mm or < 10mm for lymph nodes) then response will be set to CR irrespective of whether the criteria for PD of TL is also met i.e. if the sum of diameters for lymph node short axis increases by 20% but all lymph node TL remain < 10mm.
- Step 2: If some lesion measurements are missing but all other lesions meet the CR criteria (i.e.

0mm or < 10mm for lymph nodes) then response will be set to NE irrespective of whether, when referencing the sum of TL diameters, the criteria for PD are also met.

- Step 3: If not all lesions meet the CR criteria and the sum of lesions meets the criteria for PD then response will be set to PD.
- Step 4: If after steps 1 – 3 a response can still not be determined the response will be set to remain as CR.

TL too big to measure

If a TL becomes too big to measure this should be indicated in the database and a size ('x') above which it cannot be accurately measured should be recorded. If using a value of x in the calculation of TL response would not give an overall visit response of PD, then this will be flagged and reviewed by the study team. It is expected that a visit response of PD will remain in the vast majority of cases.

TL too small to measure

If a TL becomes too small to measure, then this will be indicated as such on the case report form and a value of 5mm will be entered into the database and used in TL calculations. However, a smaller value may be used if the radiologist has not indicated 'too small to measure' on the case report form and has entered a smaller value that can be reliably measured. If a TL response of PD results, then this will be reviewed by the study team.

Irradiated lesions/lesion intervention

Previously irradiated lesions (i.e. lesion irradiated prior to entry into the study) should be recorded as NTLs and should not form part of the TL assessment.

Any TL (including lymph nodes), which has had intervention during the study (for example, irradiation / palliative surgery / embolisation), should be handled in the following way and once a lesion has had intervention then it should be treated as having intervention for the remainder of the study noting that an intervention will most likely shrink the size of tumours:

- Step 1: the diameters of the TLs (including the lesions that have had intervention) will be summed and the calculation will be performed in the usual manner. If the visit response is PD this will remain as a valid response category.
- Step 2: If there was no evidence of progression after step 1, treat the lesion diameter (for those lesions with intervention) as missing and if ≤1/3 of the TLs have missing measurements then scale up as described in the 'Scaling' section below. If the scaling results in a visit response of PD then the patient would be assigned a TL response of PD.
- Step 3: If, after both steps, PD has not been assigned, then, if appropriate (i.e. if ≤1/3 of the TLs have missing measurements), the scaled sum of diameters calculated in step 2 should be used, and PR or SD then assigned as the visit response. Patients with intervention are evaluable for CR as long as all non-intervened lesions are 0 (or <10mm for lymph nodes) and the lesions that have been subject to intervention have a value of 0 (or <10mm for lymph nodes) recorded.

If scaling up is not appropriate due to too few non-missing measurements, then the visit response will be set as NE.

At subsequent visits the above steps will be repeated to determine the TL and overall visit response. When calculating the previous minimum, lesions with intervention should be treated as missing and scaled up (as per step 2 above).

Scaling

If >1/3 of TL measurements are missing then TL response will be NE, unless the sum of diameters of non-missing TL would result in PD (i.e. if using a value of 0 for missing lesions, the sum of diameters has still increased by 20% or more compared to nadir and the sum of TLs has increased by ≥5mm from nadir).

If ≤1/3 of the TL measurements are missing, then the results will be scaled up (based on the sizes at the nadir visit) to give an estimated sum of diameters and this will be used in calculations; this is equivalent to comparing the visit sum of diameters of the non-missing lesions to the nadir sum of diameters excluding the lesions with missing measurements.

Example of scaling

Lesion 5 is missing at the follow-up visit; it had a BL measure of 29.3cm. The sum of lesions 1-4 at the follow-up is 26 cm. The sum of the corresponding lesions at nadir visit is 26.8 cm.

Scale up as follows to give an estimated TL sum of 28.4cm:

$$\frac{26}{26.8} \times 29.3 = 28.4cm$$

CR will not be allowed as a TL response for visits where there is missing data. Only PR, SD, or PD (or NE) could be assigned as the TL visit response in these cases. However, for visits with ≤1/3 lesion assessments not recorded, the scaled-up sum of TLs diameters will be included when defining the nadir value for the assessment of progression.

Lesions that split in two

If a TL splits in two, then the LDs of the split lesions should be summed and reported as the LD for the lesion that split.

Lesions that merge

If two TLs merge, then the LD of the merged lesion should be recorded for one of the TL sizes and the other TL size should be recorded as 0cm.

Change in method of assessment of TLs

CT and MRI are the only methods of assessment of TLs that can be used in this trial. If a change in method of assessment occurs between CT and MRI this will be considered acceptable and no adjustment within the programming is needed.

If a change in method involves clinical examination (e.g. CT changes to clinical examination or vice versa), any affected lesions should be treated as missing. The TL visit response may still be evaluable if the number of missing TL measurements at a visit is ≤1/3 of the total number of TLs.

Non-Target Lesions [NTLs] and new lesions – site investigator data

At each visit, the investigator should record an overall assessment of the NTL response. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.
NTL response will be derived based on the Investigator's overall assessment of NTLs as follows:

Table 7 NTL Visit Responses

Visit Responses	Description
Complete Response [CR]	Disappearance of all NTLs present at baseline with all lymph nodes non-pathological in size (<10 mm short axis).
Progressive Disease [PD]	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Non-CR/Non-PD	Persistence of one or more NTLs with no evidence of progression.
Not Evaluable [NE]	Only relevant when one or some of the NTLs were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
Not Applicable [NA]	Only relevant if there are no NTLs at baseline

To achieve ‘unequivocal progression’ on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in TLs, the overall tumour burden has increased sufficiently to merit a determination of disease progression. A modest ‘increase’ in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

New lesions will be identified via a Yes/No tick box. The absence and presence of new lesions at each visit should be listed alongside the TL and NTL visit responses.

A new lesion indicates progression so the overall visit response will be PD irrespective of the TL and NTL response.

If the question ‘Any new lesions since baseline’ has not been answered with Yes or No and the new lesion details are blank this is not evidence that no new lesions are present but should not overtly affect the derivation.

Symptomatic progression is not a descriptor for progression of NTLs: it is a reason for stopping study therapy and will not be included in any assessment of NTLs.

Patients with ‘symptomatic progression’ requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

Overall visit response

Table 8 defines how the previously defined TL and NTL visit responses will be combined with new lesion information to give an overall visit response.

Table 8 Overall Visit Responses

TARGET	NON-TARGET	NEW LESIONS	OVERALL VISIT RESPONSE
CR	CR or NA	No (or NE)	**CR**
CR	Non-CR/Non-PD or NE	No (or NE)	**PR**
PR	Non-PD or NE or NA	No (or NE)	**PR**
SD	Non-PD or NE or NA	No (or NE)	**SD**
PD	Any	Any	**PD**
Any	PD	Any	**PD**
Any	Any	Yes	**PD**
NE	Non-PD or NE or NA	No (or NE)	**NE**
NA	CR	No (or NE)	**CR**
NA	Non-CR/Non-PD	No (or NE)	**SD**
NA	NE	No (or NE)	**NE**

Central review of RECIST 1.1 based assessments

The blinded independent central review [BICR] of radiological imaging data will be carried out using RECIST 1.1. All radiological scans for all patients (including those unscheduled visits, or outside visit windows) will be provided to the BICR. The imaging scans will be reviewed by 2 independent radiologists using RECIST 1.1 criteria and will be adjudicated if required. The independent reviewers will be blinded to study intervention. Further details of the BICR will be documented in the independent review charter.

For each patient, the BICR defines the overall visit response (i.e. the response obtained overall at each visit by assessing TLs, NTLs and new lesions) data and no programmatic derivation of visit response will be necessary. (For patients with TLs at baseline: CR, PR, SD, PD, NE; for patients with NTLs only: CR, SD, PD, NE; for patients with no disease identified at baseline: PD, no evidence of disease [NED], NE). If a patient has had a tumour assessment that cannot be evaluated, then the patient will be assigned a visit response of NE (unless there is evidence of progression in which case the response will be assigned as PD). RECIST assessments/scans contributing towards a particular visit may be performed on different dates and for the central review the date of progression for each reviewer will be provided based on the

earliest of the scan dates of the component that triggered the progression.

If adjudication is performed, the reviewer that the adjudicator agreed with will be selected as a single reviewer (note in the case of more than one review period, the latest adjudicator decision is used). In the absence of adjudication, the records for all visits for a single reviewer will be used. The reviewer selected in the absence of adjudication will be the reviewer who read the baseline scan first. The records from the single selected reviewer will be used to report all BICR RECIST information including dates of progression, visit response, censoring and changes in TL dimensions. Endpoints of ORR, PFS and duration of response [DoR] will be derived programmatically from this information.

3.2.1.1.2 Best Objective Response [BoR] and Objective response rate [ORR]

BoR is calculated based on the overall visit responses from each RECIST assessment, described in Section 3.2.1.1.1. It is the best response a patient has had following first dose but prior to starting any subsequent cancer therapy and up to and including RECIST progression or the last evaluable assessment in the absence of RECIST progression. Categorisation of BoR will be based on RECIST using the following response categories: CR, PR, SD, PD and NE.

For the primary analysis of the primary endpoint CR or PR must be confirmed. Additional secondary analysis is planned to include assessment of unconfirmed responses for the primary endpoint (ORR by investigator assessment in accordance with RECIST 1.1) and secondary endpoint (ORR by BICR assessment in accordance with RECIST 1.1). A confirmed response of CR/PR means that a response is recorded at 1 visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit. For determination of a best response of SD, the earliest of the dates contributing towards a particular overall visit assessment will be used. SD should be recorded at least 6 weeks minus 1 week (to allow for an early assessment within the assessment window), after first dose of study treatment. For CR/PR, the initial overall visit assessment which showed a response will use the latest of the dates contributing towards a particular overall visit assessment.

ORR is defined as the percentage of patients with a confirmed (or unconfirmed - depending on the analysis) investigator-assessed response of CR or PR and will be based on all treated patients (or a subset of all treated centrally confirmed FISH+, or all treated centrally confirmed by IHC).

Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who discontinue study treatment without progression, receive a subsequent anti-cancer therapy (note that for this analysis radiotherapy is not considered a subsequent anti-cancer therapy) and then respond will not be included as responders in the ORR (i.e. the initial and confirmatory scan for a response must be prior to subsequent therapy for the patient to be considered as a responder).

In the case where a patient 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 patient will be defined as a responder. Similarly, if a patient has visit responses of CR, NE, CR, then, as long as the time between the 2 visits of CR is greater than 4 weeks, a best response of CR will be assigned.

3.2.1.1.3 Duration of response [DoR]

Duration of response will be defined as the time from the date of first documented response (which is subsequently confirmed) until date of documented progression or death in the absence of disease progression (i.e., date of PFS event or censoring – date of first response + 1). 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 that was PR or CR that was subsequently confirmed.

If a patient does not progress following a response, then their DoR will use the PFS censoring time.

3.2.1.1.4 Change in tumour size

Change in tumour size at Week 12

Change from baseline in TL's tumour size at 12 weeks and over time will be based on RECIST TLs measurements taken at baseline and at post-baseline assessments. Tumour size is the sum of the longest diameters (or short axis measurements for lymph nodes) of the target lesions. Target lesions are measurable tumour lesions. Baseline for RECIST is defined to be the last evaluable assessment prior to starting treatment.

The percentage change in TL tumour size at post-baseline assessments will be obtained for each patient taking the difference between the sum of the TLs at timepoint and the sum of the TLs at baseline divided by the sum of the TLs at baseline times 100 (ie, [timepoint- baseline]/baseline×100). Only patients with measurable disease at baseline should be included in summaries of best percentage change in tumour size (measurable disease is as denoted on the CRF by the investigator).

No imputation will be used for summaries of the percentage change in tumour size from baseline by visit, but for summaries of the percentage change at Week 12, imputation will be used.

For patients who have less than or equal to one-third of TLs missing at week 12, assessment data from missing lesions may be scaled up proportionally to the sum of the corresponding lesions at baseline to give an estimated sum of diameters as described in the RECIST section of the protocol and Section 3.2.1.1.1 of this SAP. Whenever TL tumour size data for the visit is available then this should be used in the summary tables and figures.

If after applying these considerations there is still missing TL tumour size measurement data [tsm data] at week 12, the following imputation process for each individual patient where data is missing should be applied:

a) If there is no observed TLtsm data at week 12, but there is TL tsm data collected at a visit prior to week 12 or the first visit after week 12, use all of the available data up to and including the first visit after week 12 (i.e. baseline and all visits up to and including the first visit after week 12) to fit a linear regression to the individual patient's baseline and follow-up assessment(s). Note that actual day of the measurement rather than planned day should be used in the fitting of this model. This model can then be used to generate an estimated value for TL tsm at week 12

and hence impute a change from baseline at week 12.

b) If there is no observed TL tsm data at week 12 but there is evidence of progression for the individual prior to the end of the time window used to select week 12 data, where evidence of progression is defined as progression of NTLs, the appearance of new lesions or as determined by an investigator (i.e. investigator's opinion of response recorded on the RECIST CRF is PD at that assessment or study treatment was discontinued for progression in the assessment time window), and there are at least 5 patients with non-missing TL tumour size who have also progressed then impute a change from baseline at week 12 as the median percentage change from patients with non-missing TL tumour size who also have progressed. If the patient has an imputed value from a), use the maximum of this median value or the imputed value in the tumour size analysis. However, if there are less than 5 patients with non-missing tumour size who have also progressed then impute a change from baseline at week 12 as 20%. If the patient has an imputed value from a), use the maximum of 20% or the imputed value in the tumour size analysis.

c) If there is no evidence of progression for the individual, use the imputed value calculated in a) if data available. If there is no evidence of progression for the individual and no observed TL tsm data is collected at a visit prior to week 12 or the first visit after week 12, assume that the data is missing completely at random. The patient will be excluded from the analysis.

d) If it is known that the patient has died prior to the end of the time window used to select week 12 data, impute a change from baseline at week 12 as the maximum of the observed or imputed (from step b) percentage change reported in the study for week 12.

Best percentage change in tumour size

The best percentage change in tumour size for each patient is the biggest decrease or the smallest increase in TL tumour size from baseline in the absence of a decrease.

If, a patient has no post baseline assessments, then the following imputation rules should be applied:

a) If there is no observed TL tsm data post progression but there is evidence of progression for the individual during their time on study, where evidence of progression is defined as progression of NTLs, the appearance of new lesions or as determined by an investigator (i.e. investigator's opinion of response recorded on the RECIST CRF is PD at that assessment or study treatment was discontinued for progression in the assessment time window), and there are at least 5 patients with non-missing TL tumour size who have also progressed then impute a best percentage change from baseline as the median best percentage change from patients with non-missing TL tumour size who also have progressed. However, if there are less than 5 patients with non-missing TL tumour size who have also progressed then impute a best percentage change from baseline as 20%.

b) If there is no evidence of progression, assume that the data is missing completely at random; the patient will be excluded from the analysis.

c) If it is known that the patient has died, impute a best percentage change from baseline as the minimum (i.e. corresponding to the biggest increase in TL tumour size) best percentage change reported on the study.

3.2.1.1.5 Progression Free Survival [PFS]

PFS is defined as the time from first dose randomisation (patients recruited under CSP version 7.0) or start of treatment (patients recruited prior to CSP version 7.0) until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from study therapy or receives another anti-cancer therapy prior to progression (i.e. date of PFS event or censoring – date of first dose + 1). Patients 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 RECIST assessment. However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the two missed visits.

If the two missed visits are immediately after the baseline scan then the definition of two missed visits should be calculated as 2*(the protocolled time between scans) + the protocol allowed visit window (since there is no need to account for an early initial visit in this case), otherwise this should be calculated as 2*(the protocolled time between scans + the protocol allowed visit window). Given the scheduled visit assessment scheme (i.e. six-weekly for the first 24 weeks then eight-weekly thereafter) the definition of 2 missed visits will change as follows:

Last evaluable RECIST assessment before event	**Length of time of 2 missed visits**
Baseline	2 x 6 weeks + 1 week for late assessment = 13 weeks
RECIST visit 1	2 x (6 weeks + 1 week) = 14 weeks
RECIST visit 2	2 x (6 weeks + 1 week) = 14 weeks
RECIST visit 3	(6 weeks + 1 week) + (8 weeks + 1 week) = 16 weeks
RECIST visit 4	2 x (8 weeks + 1 week) = 18 weeks
RECIST visit 5 etc	2 x (8 weeks + 1 week) = 18 weeks

If the patient has no evaluable visits or does not have baseline data, they will be censored at Day 1 unless they die within 2 visits of baseline (12 weeks plus 1 week allowing for a late assessment within the visit window).

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

RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- For investigational assessments, the date of progression will be determined based on the **earliest** of the dates of the component that triggered the progression
- When censoring a patient for PFS the patient will be censored at the **latest** of the dates contributing to a particular overall visit assessment

  Note: for TLs only, the latest scan date is recorded out of all scans performed at that assessment for the TLs and similarly for NTLs only the latest scan date is recorded out of all scans performed at that assessment for the NTLs.

3.2.1.1.6 Overall survival [OS]

Overall survival is defined as the time from randomisation (patients recruited under CSP version 7.0) or the start of treatment (patients recruited prior to CSP version 7.0) until death due to any cause (i.e. date of death or censoring – date of first dose + 1). Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

Patients will be contacted for survival follow-up every 12 weeks. In addition to survival data, information regarding any subsequent anti-cancer treatment will also be collected. The impact of cross over on OS may need to be assessed.

Patients should be contacted in the week after data cut-off [DCO] for each analysis to establish survival status, and if patients are confirmed to be alive or if the death date is after the DCO date these patients will be censored at the date of DCO. The status of ongoing, withdrawn (from the study) and "lost to follow-up" at the time of the final OS analysis should be obtained by the site personnel by checking the patient's notes, hospital records, contacting the patient's general practitioner and checking publicly-available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

It may be necessary to use all relevant eCRF fields to determine the last recorded date on which the patient was known to be alive for those patients still on treatment. The last date for each individual patient is defined as the latest among the following dates recorded on the case report forms [CRFs]:

- AE start and stop dates
- Admission and discharge dates of hospitalization
- Study treatment date
- End of treatment date
- Laboratory test dates
- Date of vital signs
- Disease assessment dates on RECIST CRF
- Start and stop dates of alternative subsequent anticancer treatment (including radiotherapy)
- Date last known alive on survival status CRF
- End of study date

3.2.2 Safety Outcome Variables

The safety outcome variables which address the safety and tolerability of savolitinib in combination with

osimertinib are described in Section 8.2 of the Clinical Study Protocol.

3.2.2.1 Duration of Exposure

Duration of exposure will be summarised for savolitinib and osimertinib separately and is defined as:

1. Total treatment duration (days) = (min(last dose date where dose > 0 in Study Treatment Log, date of death, date of data cut-off) − date of first dose +1).
2. Actual treatment duration (days) = total treatment duration, excluding dose interruptions and any planned no dose periods.

Where total and actual treatment durations are presented in months, the following conversion should be made:

Treatment duration (months) = Treatment duration (days)/(365.25/12).

Exposure will also be measured by the number of cycles started. A cycle corresponds to a period of 28 days. A cycle will be counted if treatment is started even if the full dose is not delivered.

Dose modifications

Study Treatment Log records dosing details for each dosing day. Dose interruptions and reductions will be counted for savolitinib and osimertinib separately.

Dose interruption is defined as the total number of interruptions recorded in treatment logs excluding any planned interruptions in accordance with the protocol. Dose reduction is defined as the total number of reductions recorded in treatment logs. Dose modification is defined as the total number of reductions or interruptions recorded in treatment logs. Dose interruption, dose reduction and dose modification will be calculated for savolitinib and osimertinib in the first 6 weeks and for the whole treatment period.

Missed and forgotten doses should be recorded on the dose module as a dose interruption with the reason recorded as “Patient forgot to take dose”. These missed or forgotten doses will not be included as dose interruptions in the summary tables, but the information will appear in the listing for dosing. However, these missed and forgotten doses will be considered in the derivation of actual exposure.

If a patient permanently discontinues study treatment during a dose interruption, then the date of last administration of study medication will be used in the programming.

3.2.2.2 Dose Intensity

Dose intensity of savolitinib and osimertinib will be addressed by considering relative dose intensity [RDI].

RDI is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation. RDI will be defined as follows:

RDI = 100% * d/D, where d is the actual cumulative dose delivered up to the actual last day of dosing and D is the intended cumulative dose up to the actual last day of dosing. D is the total

dose that would be delivered if there were no modification to dose or schedule.

Where appropriate, the intended dose [D] will reflect the dose reassignment from 600 mg to 300 mg of savolitinib. Therefore, if a patient, who started with savolitinib 600 mg, subsequently decides to switch to savolitinib 300 mg, the switching date should be used to adjust the intended dose.

3.2.2.3 Adverse Events

An AE is defined as the development of any untoward medical occurrence in a patient or clinical study patient administered a medicinal product, and which does not necessarily have a causal relationship with this treatment. The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence.

AEs and Serious adverse events [SAEs] will be collected from the time of signing of the main study Informed consent form [ICF] throughout the treatment period and including the follow-up period. The follow-up period is defined as 28+7 days after study treatment is discontinued.

AEs will be defined as treatment emergent adverse events [TEAEs] if they have an onset or worsen (by investigator report of a change in severity) during the study treatment period (defined from date of first dose of any study treatment to date of last dose of any study treatment) or safety follow-up period (28 days [+7 days] after last dose of study treatment). Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of study treatments) will be flagged in the data listings. AEs with a missing start time which occur on the same day as first IP administration will be reported as on-treatment.

The Medical Dictionary for Regulatory Activities [MedDRA] (version 21.0 or later) will be used to code the AEs. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for AEs [CTCAE Version 5 or later].

Other significant adverse events [OAE]

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 other significant adverse events and reported as such in the clinical study report. A similar review of laboratory/vital signs/ Electrocardiogram [ECG] data and other safety assessments will be performed for identification of other significant adverse events. This review will take place at least prior to primary and final analyses and prior to database lock, and any AEs identified will be fully documented in meeting minutes.

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.

Potential Hy's Law

Potential Hy's Law is defined as aspartate aminotransferase [AST] or alanine aminotransferase [ALT] ≥3 x upper limit of normal [ULN] together with total bilirubin [TBL] ≥2 x ULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase [ALP].

The elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified time frame within which the elevations in transaminases and TBL must occur.

Adverse events of special interest [AESI]

AESIs represent pre-specified risks that are considered to be of importance to a clinical development program. Other categories may be added as necessary or existing terms may be merged. AESIs have been identified as a list of categories provided by the patient safety team. An AstraZeneca medically qualified expert after consultation with the Global Patient Safety Physician has reviewed the AEs of interest and identified which higher-level terms and which preferred terms contribute to each AESI.

AstraZeneca medically qualified expert together with the Global Patient Safety Physician may review and update the list of the identified AESI prior to database lock to ensure any further terms not already included are captured within the categories. This review may be considered prior to planned interim, primary and final analyses.

3.2.2.4 Prior/Concomitant/Post-treatment Medications

Medications will be classified as prior or concomitant (but not both) according to its start/stop date. Prior medication is defined as any medication with a stop date prior to the first dose of study treatment (exclusive). Concomitant medication is defined as any medication with a stop date on or after the first dose of study treatment. Concomitant medication will also include any medication taken prior to or during study treatment that is on-going, including any treatment with a start date within 28+7 days after stopping study treatment.

Subsequent anti-cancer treatment includes therapies with a start date after the last dose of study treatment. Hence, patients starting subsequent anti-cancer treatment will no longer be on the study treatment combination, osimertinib monotherapy, or on savolitinib monotherapy.

The imputation method described in section 3.1.4.2 will be used in case of medication stop date partially missing. Completely missing stop date will not be imputed, and medication will be classified as concomitant.

All medications will be coded according to the World Health Organization Drug Dictionary Enhanced and Herbal Dictionary [WHO-DDE + HD] 2018Mar B3 format, or later version.

3.2.2.5 Electrocardiogram Changes

Electrocardiograms [ECG] will be collected centrally. Triplicate 12-lead ECGs will be obtained at Screening, weekly in Cycle 1, Day 1 in every subsequent cycle and treatment discontinuation, using an

ECG machine that automatically calculates the heart rate and measures, PR, QRS, QT, and QTcF intervals. A 28-day follow-up assessment will only be required if an on-treatment assessment was abnormal at the time of study treatment discontinuation.

Triplicate ECGs are required to support PK sampling timepoints. As such, triplicate ECGs will be required on Cycle 3 Day 1 pre-dose, at 1 hour (h), 3 h, 4 h, and 6 h post-dose to coincide with collection of blood samples for assessment of PK of osimertinib and savolitinib at this visit.

Categorical ECG interpretation (normal, abnormal) and whether clinically significant will also be provided.

Absolute and percentage change from baseline in ECG variables will be calculated for each post-baseline visit.

3.2.2.6 Vital Signs Changes

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated at screening, weekly during Cycle 1, Day 1 in every subsequent cycle, at treatment discontinuation, and at the 28-day follow-up visit. Weight will be assessed on Day 1 of each cycle for the first 6 cycles then every 8 weeks after; height will be assessed at screening only.

Absolute and percentage change from baseline in vital signs variables will be calculated for each post-baseline visit.

3.2.2.7 Laboratory Data

The laboratory variables will be measured at screening, weekly in Cycle 1, at every visit in subsequent cycles, and at treatment discontinuation.

Table 9 Laboratory safety variables

Clinical chemistry safety	Haematology	Urinalysis (dipstick)
S/P – Albumin	B – Haemoglobin	U – Glucose
S/P – ALT	B – Leucocyte cell count	U – Protein
S/P – AST	B – Haematocrit	U – Blood
S/P – ALP	B – Red blood cell count	U – Ketones
S/P – Bilirubin, total	B – Reticulocytes	U – Leukocyte esterase
S/P – Calcium, total	B – Absolute leucocyte differential count	
S/P – Creatinine	B – Neutrophil count	
S/P- Glucose	B – Lymphocyte count	
S/P – Magnesium	B – Eosinophil count	
S/P – Sodium	B – Platelet count	

S/P – Potassium		
S/P – Total protein		
S/P – Blood urea nitrogen (BUN) or Urea		
S/P – Lactate dehydrogenase		
S/P – Amylase		
S/P - Gamma glutamyl transferase		

ALP Alkaline phosphatase; ALT Alanine aminotransferase; AST Aspartate aminotransferase; B Blood; BUN Blood urea nitrogen; P Plasma; S Serum; U Urine.

The clinical chemistry, haematology, coagulation, and urinalysis will be performed by the local laboratory. All parameters of above will be converted to standard unit (the Système International [SI] units) when presented in summary tables and listings.

Pregnancy tests will be performed for pre-menopausal women of childbearing potential.

Corrected calcium product will be derived during creation of the reporting database using the following formula:

Corrected calcium (mmol/L) = Total calcium(mmol/L) + ([40 - albumin(G/L)] x 0.02)

Laboratory values will be classified as low (L), normal, and high (H) according to the normal ranges. The assessment of haematology, clinical chemistry, and coagulation that deviate above or below the normal range will be classified by Common Terminology Criteria [CTC] grade (NCI CTCAE v5) taking values: Grade 0, 1, 2, 3, or 4.

Absolute and percentage change in laboratory parameters will be calculated from baseline to each post-baseline visit.

3.2.3 Patient Reported Outcome Variables

3.2.3.1 Calculation or derivation of patient reported outcome variables

3.2.3.1.1 EORTC QLQ-C30 & QLQ-LC13

Symptoms and overall quality of life will be assessed using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30] and Quality of Life Questionnaire-Lung Cancer 13 [QLQ-LC13].

The QLQ-C30 consists of 30 questions, which can be combined to produce 5 functional scales (Physical, Role, Cognitive, Emotional, Social), 3 symptom scales (Fatigue, Pain, Nausea/vomiting), 6 individual items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties) and a global measure of health status.

The QLQ-LC13 is a lung cancer specific module comprising 13 questions to assess lung cancer

symptoms (cough, haemoptysis, dyspnoea, and site-specific pain), treatment related side-effects (sore mouth, dysphagia, peripheral neuropathy, and alopecia), and pain medication; with the exception of a multi-item scale for dyspnoea, all are single items. The dyspnoea scale will only be used if all 3 items have been scored, otherwise the items are treated as single-item measures.

An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales/symptom items, the functional scales and the global health status/QoL scale in the QLQ-C30 and for each of the symptom scales/items in the QLQ-LC13 according to the EORTC QLQ-C30 Scoring Manual and EORTC QLQ-LC13 instructions. The scoring is done in two steps:

1) Calculate the raw score [RS] by taking the average of the scores for the items that contribute to the scale. The range of raw scores (RS_{range}) is the difference between the maximum and the minimum possible score (e.g. if the item score range is between 1 and 4, RS_{range} is 3).
2) Use a linear transformation to standardise RS to take values from 0 to 100 as follows:

   Functional scales: $(1 - \frac{(RS-1)}{RS_{range}}) \; x \; 100$

   Symptom scales / items / global measure of health status: $(\frac{(RS-1)}{RS_{range}}) \; x \; 100$

Higher scores on the global health status and functioning scales indicate better health status/function. Higher scores on the symptom scales indicate greater symptom burden. For each subscale, if less than 50% of the subscale items are missing, then the subscale will be divided by the number of non-missing items and multiplied by the total number of items on that subscale. If at least 50% of the items are missing, then that subscale will be treated as missing. Missing single items are treated as missing. The reason for missing questionnaires will be identified and recorded. If there is evidence that the missing data are systematic, missing values will be handled to ensure that any possible bias is minimised.

The primary PRO outcome measures will be 5 patient-reported lung cancer symptoms, namely:

- Dyspnoea (multi-item scale based on three questions: “Were you short of breath when you rested; walked; climbed stairs”) (LC13),
- Cough: one item (“How much did you cough?”) (LC13),
- Pain: one item (“Have you had pain in your chest”) (LC13).
- Fatigue (a composite score of three items: “Did you need rest; Have you felt weak; Were you tired”) (C30)
- Appetite loss: one individual item (“Have you lacked appetite”) (C30)

Changes in score compared to baseline will be evaluated. A minimum clinically meaningful change is defined as a change in the score from baseline of ≥10 for scales/items from the QLQ-LC13 and the QLQ-C30.

At each post-baseline assessment, change in symptoms/functioning/items from baseline will be categorised as improved, stable, or worsening as shown in Table 10.

Table 10 Visit response for QLQ-C30/QLQ-LC13 subscales

Score	Change from baseline	Visit Response
QLQ-LC13/QLQ-C30 symptom scales/items	≥+10	Worsened
	≤-10	Improved
	Otherwise	Stable
QLQ-C30 functional scales and Global health status/QoL	≥+10	Improved
	≤-10	Worsened
	Otherwise	Stable

Time to symptom deterioration

For each of the symptoms scales/items in EORTC QLQ-C30 and QLQ-LC13, time to symptom deterioration will be defined as the time from first dose of study treatment until the date of first clinically meaningful symptom deterioration (an increase in the score from baseline of ≥10) or death (by any cause) in the absence of a clinically meaningful symptom deterioration, regardless of whether the patient withdraws from study treatment or receives another anti-cancer therapy prior to symptom deterioration.

Death will be included as an event only if the death occurs within two visits of the last PRO assessment where the symptom change could be evaluated. Patients whose symptoms (as measured by EORTC QLQ-C30 and QLQ-LC13) have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the symptom could be evaluated. Also, if symptoms progress after two or more missed PRO assessment visits or the patient dies after two or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment where the symptom could be evaluated. If a patient has no evaluable visits or does not have baseline data, they will be censored at Day 1. The population for analysis of time to symptom deterioration will include a subset of the Safety analysis set who have EORTC QLQ-LC13 or EORTC QLQ-C30 baseline scores ≤90.

Symptom improvement rate

The symptom improvement rate will be defined as the number (%) of patients with two consecutive assessments which showed a clinically meaningful improvement (a decrease from baseline score ≥10 for EORTC QLQ-LC13 scales/items and EORTC QLQ-C30 scales/items) in that symptom from baseline. The denominator will consist of a subset of the Safety analysis set who have a baseline symptom score ≥10.

Compliance rate

The compliance rate (%) and the evaluability rate (%) for EORTC QLQ-C30 and QLQ-LC13 will be calculated. This is based on:

- Received questionnaire = a questionnaire that has been received and has a completion date and at least one individual item completed.
- Expected questionnaire = a questionnaire that is expected to be completed at a scheduled assessment time, i.e. a questionnaire from a patient who has not withdrawn from the study at the scheduled assessment time.
- Evaluable questionnaire = a questionnaire with a completion date and at least one subscale that is non-missing.

The compliance rate is the number of evaluable questionnaires divided by the number of expected questionnaires, multiplied by 100. The evaluability rate is the number of evaluable questionnaires divided by the number of received questionnaires, multiplied by 100.

3.2.3.1.1 PRO-CTCAE

The PRO-CTCAE questionnaire will be used to derive patient reporting of CTCAE symptoms. The PRO-CTCAE will only be administered in those countries where a linguistically validated version exists. PRO-CTCAE is an item-bank of symptoms of the CTCAE experienced by patients while undergoing treatment of their cancer that has been converted to subject terms (i.e., CTCAE term "myalgia" converted to "aching muscles"). Six individual items from the PRO-CTCAE item-bank have been selected as being relevant for this study. These include wheezing, palpitations, rash, itchy skin, hives, aching muscles. Furthermore, items grouped based on their associated body system as assigned by the National Cancer Institute [NCI] will be presented.

3.2.3.1.2 PGIS

The Patient's Global Impression of Severity [PGIS] item is included to assess how a patient perceives his/her overall current severity of cancer symptoms. Patients will choose between 6 response options from "No symptoms" to "Very severe."

3.2.3.1.3 EQ-5D-5L

The EuroQol 5 dimensions, 5 levels [EQ-5D-5L] index comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). For each dimension, respondents select which statement best describes their health on that day from a possible 5 options of increasing of severity (no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems). A unique EQ- 5D health state is referred to by a 5-digit code allowing for a total of 3125 health states. For example, state 11111 indicates no problems on any of the 5 dimensions. These data will be converted into a weighted health state index by applying scores from EQ-5D value sets elicited from general population samples (the base case will be the United Kingdom valuation set). Where values sets are not available, the EQ-5D-5L to EQ-5D-3L crosswalk will be applied.

In addition to the descriptive system, respondents also assess their health on the day of assessment on a

visual analogue scale [VAS], ranging from 0 (worst imaginable health) to 100 (best imaginable health).

3.2.4 Pharmacokinetic Outcome Variables

3.2.4.1 Calculation or derivation of pharmacokinetic variables

Pharmacokinetic analysis of the plasma concentration data for osimertinib, savolitinib and, if available, their metabolites (e.g. AZ5104 for osimertinib; M2 and M3 for savolitinib) will be performed by QCP, AstraZeneca, or a delegate on behalf of QCP for relevant individuals using standard non-compartment methods. PK analysis will be performed according to AstraZeneca standard SOP, which specifies all the diagnostic parameters to be reported. Actual sampling times will be used in parameter calculations.

Where possible, the following PK parameters will be determined for osimertinib, savolitinib and their metabolites:

- After single dosing: plasma concentration at 1 hour (C1h) and 3 hours (C3h) post-dose
- After multiple dosing at Cycle 3 Day 1: plasma concentration pre-dose (Cpre-dose), and at C1h, C3h, C4h and C6h post-dose. If applicable, AUCss, Cssmax, Cssmin, tssmax, CLss/F, Vz/F and t1/2 will be calculated for savolitinib, osimertinib and their metabolites.

If possible, the time dependency of the PK on multiple dosing will be assessed by the calculation of the ratios of:

- C_{3h} Cycle 2 Day 1/C_{3h} Cycle 1 Day 1
- $C_{pre\text{-}dose}$ Cycle 3 Day 1/$C_{pre\text{-}dose}$ Cycle 2 Day 1
- $C_{pre\text{-}dose}$ Cycle 6 Day 1/$C_{pre\text{-}dose}$ Cycle 2 Day 1
- $C_{pre\text{-}dose}$ Cycle 11 Day 1/$C_{pre\text{-}dose}$ Cycle 2 Day 1.

For patients receiving savolitinib 300 mg bid, on PK sampling days, samples will be collected following the first dose of the day.

Individual concentration data may be excluded from the analysis for legitimate scientific reasons e.g., mis-dose, vomiting after dose administration, prohibited co-medication. Where a protocol deviation impacts only part of a patient's data, the affected portion of the patient's PK data will be excluded from PK analysis and summary statistics, and the remaining valid data will be utilised. Any excluded data, together with the justification for exclusion, will be clearly documented in the CSR. The concentration and any PK parameter data from this study may be combined with data from other studies in a population PK or PK-PD analysis and, if conducted, will be reported separately from the CSR.

3.2.5 Retrospective IUO Grade MET Testing

Each patient's MET status for FISH10+ and/or IHC90+ will be re-assessed retrospectively utilising Investigational Use Only [IUO] grade testing.

For CSPv1-6, where patients were enrolled using assays validated based on a cut-off of FISH5+ and/or IHC50+, retrospective re-assessment will be done using a cut-off of FISH10+ and/or IHC90+ with the

final validated IUO grade assays. The MET testing used to enroll patients under CSPv1-6 will be used for identifying FISH5+ and/or IHC50+ patients. However, the retrospective IUO grade testing will be used exclusively when identifying FISH10+ and/or IHC90+ patients, for all summaries and analyses for CSPv1-6 patients.

For CSPv7, where Laboratory Developed Tests [LDTs] have been used for patient enrolment using a cut-off of FISH10+ and/or IHC90+, data will be re-assessed using the final IUO grade assay using the cut-off of FISH10+ and/or IHC90+. The testing used to enroll patients under CSPv7 will be used for all summaries and analyses unless otherwise stated. Supplementary analyses will be produced where CSPv7 patients will be identified for FISH10+ and/or IHC90+ MET status by utilising the retrospective IUO grade testing instead.

3.2.6 Biomarker Outcome Variables

3.2.6.1 Calculation or derivation of biomarker variables

Circulating tumour deoxyribonucleic acid [ctDNA] dynamics will be evaluated as a surrogate marker of clinical efficacy.

Patients with detectable Epidermal growth factor receptor [EGFR] mutations at baseline and available data at 6 weeks will be categorised into the following groups of ctDNA status: (1) ctDNA clearance and (2) ctDNA non-clearance. Patients with undetectable EGFR mutations at baseline will be categorised as "uninformative". Additional guidance is provided in Table 11.

Table 11 Additional guidance for ctDNA status derivation

Detectable EGFR mutation at baseline	Positive pre-dose result for L858R or exon 19 deletion
Evaluable at 6-weeks	1. Detectable EGFR mutation at baseline AND 2. Evaluable result at 6-weeks[a]
ctDNA clearance	1. Evaluable at 6-weeks AND 2. Negative result at 6-weeks
ctDNA non-clearance	1. Evaluable at 6-weeks AND 2. Positive result at 6-weeks

Not evaluable at 6-weeks	Data otherwise not considered evaluable at 6-weeks
Uninformative assessment at baseline	Negative pre-dose result for L858R or exon 19 deletion
Evaluable data at 6-weeks	1. Uninformative assessment AND 2. Positive or negative post-dose result at 6-weeks
Not evaluable data at 6-weeks	1. Uninformative assessment AND 2. Data otherwise not considered at 6-weeks
Missing baseline assessment	No pre-dose result for L858R or exon 19 deletion
Evaluable data at 6-weeks	1. Missing baseline assessment AND 2. Positive or negative result at 6-weeks
Not evaluable at 6-weeks	1. Missing baseline assessment AND 2. Data otherwise not considered evaluable at 6- weeks

a: Evaluable result at 6-weeks = baseline detectable EGFR mutation for L858R AND positive/negative L858R result at 6-weeks, OR, baseline detectable EGFR mutation for exon 19 deletion AND positive/negative exon 19 deletion result at 6-weeks.

Note: Rare cases where a patient is reported to have both L858R and exon 19 deletion mutations at baseline and/or follow-up and the rules above still applicable to declare ctDNA clearance of at least one mutation. Patients with a single mutation at baseline, but the alternative mutation is observed at 6-weeks are considered not-evaluable at 6-weeks, as described in 'a' above.

The absolute change and the percentage change in EGFR mutation ctDNA allele frequencies at Week 6 will be obtained for each patient. The percentage change is calculated as the difference between the allele frequency of EGFR sensitising mutations in ctDNA at Week 6 and the ctDNA at baseline divided by the allele frequency of EGFR sensitising mutations in ctDNA at baseline multiplied by one hundred (i.e., [Week 6 - baseline]/baseline × 100). Patients with undetectable EGFR mutations at baseline will be excluded from this analysis. Samples with undetectable EGFR mutations at Week 6 will be interpreted as 0% allele frequency so that the percentage change is 100%.

All other exploratory research variables will be reported separately from the Clinical Study Report and so will be dealt with outside of this SAP.

4 ANALYSIS METHODS

4.1 General principles

The below mentioned general analyses principles will be followed throughout the study:

- Statistical tests will be performed for two-sided hypothesis. All confidence intervals [CI] will use a 95% confidence level unless otherwise stated.
- Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarised by the number of observations, mean, standard deviation [SD], median, quartiles (Q1 and Q3), minimum, and maximum. For log transformed data geometric mean [Geomean], geometric SD [gSD], geometric coefficient of variation [gCV%], median, minimum and maximum will be presented. Categorical variables will be summarised by frequency counts and percentages for each category.
- Unless otherwise stated, percentages will be calculated out of the analysis set total.
- Unless otherwise stated, for continuous data, mean, Geomean, median, quartiles as well as LSmeans will be rounded to 1 additional decimal place compared to the original data. The SD, gSD and standard error [SE] will be rounded to 2 additional decimal places compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data.
- For categorical data, percentages will be rounded to 1 decimal place.
- Ratio and CI of the ratio will be rounded to two decimal points
- P-values will be presented to three decimal points (displayed as "<0.001" for p-values lower than 0.001).
- SAS® version 9.4 (or higher) will be used for all analyses.
- There are two diagnostic populations of analytical interest as follows:
    - All Patients (FISH5+ and/or IHC50+): This population includes patients identified by lower MET biomarker cut offs (≥5 MET gene copies or MET:CEP7 ratio ≥2 [FISH5+] and/or ≥50% of tumour cells staining at strong 3+ intensity [IHC50+])
    - FISH10+ and /or IHC90+: This population includes patients identified by higher MET biomarker cut offs (≥10 MET gene copies according to central MET FISH test [FISH10+] and/or ≥90% of tumour cells staining at strong 3+ intensity according to central MET IHC test [IHC90+])

  The populations are not mutually exclusive, i.e. a patient may be a member of both populations.
- Analyses will be presented by the assigned dosing regimen (i.e., savolitinib starting dose: 300 mg od, 300 mg bid and 600 mg od (in combination with osimertinib), or 300 mg bid + placebo.

4.2 Description of Analysis methods

4.2.1 Demographics, Baseline Characteristics and other patient-specific characteristics

Demographic and baseline characteristics, patient disposition and prior/concomitant/post-treatment medication will be based on the TPAS, SAF and CAS where applicable.

Demographic and Baseline Characteristics

Demographic, baseline characteristics including height, weight, body mass index [BMI] and medical history will be summarised.

The calculation for BMI is:

$$BMI = \frac{weight\ (kg)}{(height\ [m])^2}.$$

Descriptive statistics for age at informed consent as a continuous variable and age group (>=18 to <50, >=50 to <65, >=65 to <75, >=75 years old), sex, ethnicity and race as categorical variables will be summarised. Age in years will be calculated as the rounded down integer value of [(date of informed consent - date of birth)/365.25)].

The number and percentage of patients with a medical history, including both resolved and ongoing conditions at the time of study entry, will be summarised by the primary system organ class [SOC] and preferred term [PT] in accordance with MedDRA. Patients will only be counted once per MedDRA level and the medical history will be sorted by alphabetically by SOC and PT. Relevant surgical history will be summarised similarly.

The number and percentage of patients recruited by country will be presented. EGFRm subtype status will also be summarised and listed. Disease characteristics will also be summarised and listed.

Patient Disposition

Patient disposition will be summarised for all screened patients. The number and percentage of patients who were screened, received study treatment, had ongoing treatment at data cut-off, discontinued study treatment, and who terminated the study, will be presented.

Patients discontinuing the study and patients ongoing at data cut-off will be listed.

The number of patients included/excluded from each of the analysis sets will be provided. Patients excluded and reason for exclusion from the Target Population Analysis Set, Contribution of Components Analysis Set, Safety Analysis Set, and PK Analysis Set will be listed for all patients who signed the main study ICF.

Prior/Concomitant/Post-treatment Medication

The number and percentage of patients with any concomitant medications summarised by ATC category name (ATC level 4), and generic term (product name) will be provided for the Safety analysis set. Subsequent anti-cancer treatment (including both Post-Treatment Cancer Therapies and Post Treatment Radiotherapies) will be summarised separately in similar tables.The number of regimens of previous

anti-cancer therapies at baseline will be summarised. A table of time (number of days) from the end of previous anti-cancer therapy to the start of study treatment will also be provided.

4.2.2 Efficacy analyses

4.2.2.1 Primary Endpoint - Objective Response Rate

4.2.2.1.1 Target Population Analysis Set

The primary endpoint of ORR as assessed by the investigator per RECIST 1.1 in patients treated with savolitinib 300 mg bid + osimertinib in FISH10+ and/or IHC90+ who have progressed following treatment with 1L osimertinib will be summarised using the TPAS.

The ORR and its associated 2-sided 95% CIs (Clopper-Pearson) will be provided and compared with the historical reference platinum-pemetrexed chemotherapy ORR of approximately 30%. Summaries will be produced that present the number and percentage of patients with a tumour response (CR/PR).

BoR will also be presented and summarised by n (%) for each category (CR, PR, SD, PD and NE).

4.2.2.1.1.1 Subgroup analyses

Subgroups analyses of ORR as assessed by the investigator per RECIST 1.1 will be conducted on TPAS within the following subgroups (Appendix "A"):

- Race [Asian, Non-Asian]
- Sex [Male, Female]
- Age at baseline [<65 years, ≥65 years]
- T790M status in baseline plasma [T790M+, T790M-]
- C797S mutation in baseline plasma [C797S+, C797S-]
- FISH+ allocation status [Amplified, Polysomy]. Patients can be considered FISH+ by either amplification or polysomy, where amplification is considered a ratio of 'Mean MET/CEP7 RATIO' or 'CEP7/MET RATIO' >=2 and polysomy where ratio <2. The non-FISH+ patients will be excluded. Ratio information will be provided by external vendors
- IHC+ allocation status [IHC90+, IHC90 negative (FISH10+), IHC50+, IHC50 negative (FISH5+), IHC missing/unknown (FISH+ to enter study)]
- FISH+ allocation status [FISH10+, FISH10 negative (IHC90+), FISH5+, FISH5 negative (IHC50+), FISH missing/unknown (IHC+ to enter study)]
- Overall disease classification [Metastatic, Locally advanced, Missing]
- EGFR mutation status [Exon 19 deletion, L858R]
- Known or treated brain metastases at study entry [Yes (present at baseline or not present at

baseline but with known or treated history of brain metastases), No (not present at baseline and not known or treated history of brain metastases)]. This classification will be identified by an AstraZeneca medically qualified expert during the medical review process

- Eastern Cooperative Oncology Group [ECOG] at baseline [0, 1, …]
- Histological Type [Adenocarcinoma, Other].

Forest plots of ORR with 95% Clopper-Pearson CI for each subgroup will also be produced.

4.2.2.1.2 Safety Analysis Set

The primary endpoint of ORR as assessed by the investigator per RECIST 1.1 in patients treated with savolitinib 300 mg od + osimertinib in FISH5+ and/or IHC50+ who have progressed following treatment with osimertinib will be summarised using the SAF.

The ORR and its 2-sided 95% CI (Clopper-Pearson) will be summarised and will be analysed using an exact binomial test against the null H0: ORR=30% at the significance level of α=0.05. Summaries will be produced that present the number and percentage of patients with a tumour response (CR/PR).

BoR will also be presented and summarised by n (%) for each category (CR, PR, SD, PD and NE).

4.2.2.2 Secondary Endpoint - Objective Response Rate

4.2.2.2.1 Contribution of Components Analysis Set

To describe the difference in the efficacy of savolitinib (300 mg bid) in combination with osimertinib and savolitinib (300 mg bid) in combination with placebo in patients with EGFRm+, MET amplified/overexpressed (FISH10+ and/or IHC90+), locally advanced or metastatic Non-Small Cell Lung Cancer [NSCLC] who have progressed following treatment with 1L osimertinib therapy under CSP version 7.0, ORR (as assessed by the investigator per RECIST 1.1) with 95% confidence intervals (Clopper-Pearson) will be constructed in the CAS for:

- 300 mg bid (savolitinib) + osimertinib
- 300 mg bid (savolitinib) + placebo.

BoR will also be presented and summarised by n (%) for each category (CR, PR, SD, PD and NE).

4.2.2.2.2 Safety Analysis Set

The secondary endpoints of ORR as assessed by the investigator per RECIST 1.1 will be summarised using the SAF for:

- savolitinib (300 mg od and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH10+ and/or IHC90+), locally advanced or

metastatic NSCLC who have progressed following treatment with 1L osimertinib

- savolitinib (300 mg od, 300 mg bid and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH10+ and/or IHC90+), locally advanced or metastatic NSCLC who have progressed following treatment with >=2L osimertinib
- savolitinib (300 mg bid and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH5+ and/or IHC50+), locally advanced or metastatic NSCLC who have progressed following osimertinib.

4.2.2.2.2.1 Subgroup analyses

Subgroups analyses of ORR, as assessed by the investigator per RECIST 1.1, in SAF patients treated with savolitinib 300 mg od in combination with osimertinib with EGFRm+, MET amplified/overexpressed (FISH10+ and/or IHC90+), will be conducted within the following subgroups (Appendix "A"):

- Race [Asian, Non-Asian]
- Sex [Male, Female]
- Age at baseline [<65 years, ≥65 years]
- Line of treatment [2nd line, ≥3rd line]. Line of treatment is equal to the number of regimens of previous anti-cancer therapies in metastatic setting at baseline + 1. Therefore, line of treatment = '2nd line' directly refers to the number of regimens of previous anti-cancer therapies at baseline = 1. As such line of treatment = '≥3rd line' is a combination of patients with the number of regimens of previous anti-cancer therapies at baseline = 2 or 3 or more. The number of regimens of previous anti-cancer therapies at baseline will be identified by an AstraZeneca medically qualified expert during the medical review process
- Prior platinum-based chemotherapy [Yes, No] in metastatic setting. This classification will be identified by an AstraZeneca medically qualified expert during the medical review process
- Prior platinum-based chemotherapy and line of treatment [Yes and 2nd line, Yes and ≥3rd line, No and 2nd line, No and ≥3rd line']
- Immediately prior line of therapy [Osimertinib, Prior platinum-based chemotherapy, Other]. This classification will be identified by an AstraZeneca medically qualified expert during the medical review process
- Response to immediately prior line of therapy [Yes and osimertinib, Yes and platinum-based chemotherapy, Yes and other, No and osimertinib, No and platinum-based chemotherapy, . No and other]. Response is defined as Best Response (complete or partial), as reported by the investigator and it will be identified by an AstraZeneca medically qualified expert during

the medical review process

- Immediately prior line osimertinib [Osimertinib, Not osimertinib]. This classification will be identified by an AstraZeneca medically qualified expert during the medical review process
- Response to immediately prior line of therapy, osimertinib [Yes and osimertinib, Yes and not osimertinib, No and osimertinib, No and not osimertinib]. Response is defined as Best Response (complete or partial), as reported by the investigator and it will be identified by an AstraZeneca medically qualified expert during the medical review process
- Number of previous EGFR Tyrosine kinase inhibitor [TKI] therapies [1, 2, …]. Where possible, EGFR TKI therapies will be identified programmatically, otherwise they will be identified by an AstraZeneca medically qualified expert during the medical review process
- T790M status in baseline plasma [T790M+, T790M-]
- C797S mutation in baseline plasma (C797S+, C797S-]
- FISH+ allocation status [Amplified, Polysomy]. Patients can be considered FISH+ by either amplification or polysomy, where amplification is considered a ratio of 'Mean MET/CEP7 RATIO' or 'CEP7/MET RATIO' >=2 and polysomy where ratio <2. The non-FISH+ patients will be excluded. Ratio information will be provided by external vendors
- IHC+ allocation status [IHC90+, IHC90 negative (FISH10+), IHC50+, IHC50 negative (FISH5+), IHC missing/unknown (FISH+ to enter study)]
- FISH+ allocation status [FISH10+, FISH10 negative (IHC90+), FISH5+, FISH5 negative (IHC50+), FISH missing/unknown (IHC+ to enter study)]
- Overall disease classification [Metastatic, Locally advanced, Missing].
- EGFR mutation status [Exon 19 deletion, L858R]
- Known or treated brain metastases at study entry [Yes (present at baseline or not present at baseline but with known or treated history of brain metastases), No (not present at baseline and not known or treated history of brain metastases)]. This classification will be identified by an AstraZeneca medically qualified expert during the medical review process
- ECOG at baseline [0, 1, …]
- Histological Type [Adenocarcinoma, Other].

Forest plots of ORR with 95% Clopper-Pearson CI for each subgroup will also be produced.

4.2.2.2.3 Secondary Endpoint of ORR based on BICR

Summaries will also be produced for ORR assessed by BICR using the TPAS, SAF and CAS.

In detail, for SAF:

- savolitinib (300 mg od, 300 mg bid and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH10+ and/or IHC90+), locally advanced or metastatic NSCLC who have progressed following osimertinib
- savolitinib (300 mg od, 300 mg bid and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH5+ and/or IHC50+), locally advanced or metastatic NSCLC who have progressed following osimertinib.

Finally, summaries will be produced using the CAS for:

- 300 mg bid (savolitinib) + osimertinib
- 300 mg bid (savolitinib) + placebo.

4.2.2.3 Secondary Endpoint – Duration of Response

4.2.2.3.1 Target Population Analysis Set

Duration of response and time to onset of objective response will be summarised for patients who achieved objective response during the study using the TPAS. Median duration of response, and quartiles will be summarised, including 95% CI. The percentage of patients still in response at 3, 6, 9 and 12 months, along with the 95% CI will be presented. Onset of response relative to subsequent therapy will also be summarised.

Kaplan-Meier plots of DoR in the responding patients and Swimmer plots showing the profile of each patient who responds will also be produced based on the TPAS.

4.2.2.3.2 Safety Analysis Set

The summaries described in the above section 4.2.2.3.1 will be produced using the SAF for:

- savolitinib (300 mg od and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH10+ and/or IHC90+), locally advanced or metastatic NSCLC who have progressed following treatment with 1L osimertinib

savolitinib (300 mg od, 300 mg bid and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH5+ and/or IHC50+), locally advanced or metastatic NSCLC who have progressed following osimertinib

4.2.2.3.3 Contribution of Components Analysis Set

The analyses described in the above section 4.2.2.3.1 will be produced using the CAS for:

- 300 mg bid (savolitinib) + osimertinib

- 300 mg bid (savolitinib) + placebo.

4.2.2.3.4 Secondary endpoint of DoR based on BICR

Summaries will also be produced for DoR assessed by BICR using the TPAS, SAF and

CAS. In details for SAF:

- savolitinib (300 mg od, 300 mg bid and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH10+ and/or IHC90+), locally advanced or metastatic NSCLC who have progressed following osimertinib
- savolitinib (300 mg od, 300 mg bid and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH5+ and/or IHC50+), locally advanced or metastatic NSCLC who have progressed following osimertinib.

Finally, summaries will be produced using the CAS for:

- 300 mg bid (savolitinib) + osimertinib
- 300 mg bid (savolitinib) + placebo.

4.2.2.4 Secondary Endpoint – Progression Free Survival

4.2.2.4.1 Target Population Analysis Set

PFS will be summarised using the Kaplan-Meier methodology and will be based on TPAS. Median time to progression, and quartiles will be summarised, including 95% CI. The percentage of patients being progression-free at 3, 6, 9, 12, 18, 24, 30 and 36 months, along with the 95% CI, and the median and range of duration of follow-up in censored patients, will also be presented. Kaplan Meier curves will also be plotted.

Treatment status at time of progression will be presented, showing patients who were on savolitinib and/or osimertinib at time of progression and patients who discontinued treatment prior to progression. Treatment status after progression will also be summarised, showing the patients who continued to receive savolitinib and/or osimertinib after progression.

4.2.2.4.1.1 Subgroup analyses

Subgroups analyses of PFS will be conducted on the same subgroups as for ORR and based on TPAS. Refer to section 4.2.2.1.1.1 for details on the specific subgroups and Appendix “A”.

4.2.2.4.2 Safety Analysis Set

The summaries described in the above section 4.2.2.4.1 will be produced using the SAF for:

- savolitinib (300 mg od and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH10+ and/or IHC90+), locally advanced or

metastatic NSCLC who have progressed following treatment with 1L osimertinib

- savolitinib (300 mg od, 300 mg bid and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH5+ and/or IHC50+), locally advanced or metastatic NSCLC who have progressed following osimertinib.

4.2.2.4.2.1 Subgroup analyses

Subgroups analyses of PFS in SAF patients treated with savolitinib 300 mg od in combination with osimertinib with EGFRm+, MET amplified/overexpressed, will be conducted on the same subgroups as for ORR. Refer to section 4.2.2.2.2.1 for details on the specific subgroups and Appendix "A".

4.2.2.4.3 Contribution of Components Analysis Set

PFS will be summarised using the Kaplan-Meier methodology and will be based on CAS for:

- 300 mg bid (savolitinib) + osimertinib
- 300 mg bid (savolitinib) + placebo.

Median time to progression, and quartiles will be summarised, including 95% CI. The percentage of patients being progression-free at 3, 6, 9, 12, 18, 24, 30 and 36 months, along with the 95% CI, and the median and range of duration of follow-up in censored patients, will also be presented. Kaplan Meier curves will also be plotted.

PFS will be analysed using a stratified log-rank test adjusting for the stratification used in randomisation for the generation of the p-value. The effect of treatment will be estimated by the HR together with its corresponding 95% CI for the CAS. An HR less than 1 will favour savolitinib plus osimertinib. The HR and its CI will be estimated from a Cox Proportional Hazards model (with ties = Efron and baseline stratification) and the CI calculated using a profile likelihood approach. If there are insufficient events per strata, a log-rank test will be used to analyse PFS instead of a stratified log-rank test.

Treatment status at time of progression will be presented, showing patients who were on savolitinib and/or osimertinib at time of progression and patients who discontinued treatment prior to progression.

4.2.2.4.4 Secondary endpoint of PFS based on BICR

Summaries will also be produced for PFS assessed by BICR using the TPAS and SAF.

In details for SAF:

- savolitinib (300 mg od, 300 mg bid and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH10+ and/or IHC90+), locally advanced or metastatic NSCLC who have progressed following osimertinib
- savolitinib (300 mg od, 300 mg bid and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH5+ and/or IHC50+),

locally advanced or metastatic NSCLC who have progressed following osimertinib.

4.2.2.5 Secondary Endpoint – Overall Survival

4.2.2.5.1 Target Population Analysis Set

OS will be summarised for TPAS set using the Kaplan-Meier methodology. Median time to event, and quartiles will be summarised, including 95% CI for overall survival (months). Survival rate at 12, 15, 18, 24, 30 and 36 months with 95% CI, and the median and range of duration of follow-up in censored patients, will be included. Kaplan-Meier curves will also be plotted.

4.2.2.5.2 Safety Analysis Set

The summaries described in the above section 4.2.2.5.1 will be produced using the SAF for:

- savolitinib (300 mg od and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH10+ and/or IHC90+), locally advanced or metastatic NSCLC who have progressed following treatment with 1L osimertinib

- savolitinib (300 mg od, 300 mg bid and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH5+ and/or IHC50+), locally advanced or metastatic NSCLC who have progressed following osimertinib

4.2.2.6 Secondary Endpoint – EORTC QLQ-C30 and QLQ-LC13

4.2.2.6.1 Target Population Analysis Set

For EORTC QLC-C30 and QLQ-LC13, respectively, the observed values and change from baseline of functional/symptom scales, the individual items and the global health status scores will be summarised over time using descriptive statistics.

The improvement rate, i.e. proportion of patients with improvements, and 95% Clopper-Pearson CIs for each scale/item score will be summarised. The improvement rate is based on the number of patients who have a baseline individual score $\geq$10.

Time to deterioration for the symptom scales and the individual items will be summarised using Kaplan-Meier methodology. Median and quartile time to deterioration and the percentage of patients being free of deterioration at selected timepoints, along with the 95% CI, will be presented. The population for analysis of time to symptom deterioration will include a subset of the Safety analysis set who have EORTC QLQ-LC13 or EORTC QLQ-C30 baseline scores $\leq$90.

The compliance and evaluability rate (%) will be presented together with the number of evaluable, received and expected questionnaires at each timepoint.

4.2.2.6.2 Safety Analysis Set

The summaries described in the above section 4.2.2.6.1 will be produced using the SAF for:

- savolitinib (300 mg od, 300 mg bid and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH10+ and/or IHC90+), locally advanced or metastatic NSCLC who have progressed following osimertinib
- savolitinib (300 mg od, 300 mg bid and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH5+ and/or IHC50+), locally advanced or metastatic NSCLC who have progressed following osimertinib.

4.2.2.7 Secondary Endpoint – Pharmacokinetics

4.2.2.7.1 PK Analysis Set

PK analyses will be produced using the PK analysis set for:

- savolitinib (300 mg bid, 300 mg bid and 600 mg od, respectively) in combination with (FISH5+ and/or IHC50+), locally advanced or metastatic NSCLC who have progressed following osimertinib.

Plasma concentrations of osimertinib, savolitinib and their metabolites after single and multiple dosing will be summarised by nominal sample time and visit for All Patients in the PK analysis set and by savolitinib starting dose. Concentrations and PK parameters will be summarised using descriptive statistics (geometric mean [Geomean], geometric coefficient of variation [gCV%], geometric standard deviation [gSD], arithmetic mean, standard deviation [SD], median, minimum (min), maximum (max), and n) as applicable. For diagnostic parameters, Geomean, gCV% and gSD will not be reported.

Individual plasma concentration-time profiles may be presented. Plots will be produced by actual time, and on both linear scale and semi-logarithmic scale for the All Patients population and by savolitinib starting dose.

Plasma concentrations of savolitinib, osimertinib and their metabolites by nominal visit and timepoint may also be plotted using box plots on both linear scale and semi-logarithmic scale for the All Patients population.

Finally, geometric mean (±gSD) plasma concentrations of savolitinib, osimertinib and their metabolites by nominal timepoint may be plotted on both linear scale and semi-logarithmic scale for the All Patients population.

Concentrations below the lower limit of quantitation (BLQ) will be reported in the following way:

- Individual BLQ concentrations are reported as NQ (not quantifiable).
- For summary data:
    a. If, at a given time point, 50% or less of the concentrations are not quantifiable [NQ], the geomean, gCV%, gSD, arithmetic mean and standard deviation [SD] are calculated by

substituting the LLOQ for values which are NQ.

b. If more than 50%, but not all, of the concentrations are NQ, the geomean, gCV%, gSD, arithmetic mean and SD are reported as not calculable [NC]. The maximum value is reported from the individual data, and the minimum and median are set as NQ.

c. If all the concentrations are NQ, the geomean and arithmetic mean are reported as NQ and the gCV%, gSD and SD as NC.

d. The number of values below LLOQ are reported for each time point along with the total number of collected values.

Three values >LLOQ are required as a minimum for a concentration to be summarised. Two values are presented as a minimum and maximum with the other summary statistics as NC. The lower limit of quantitation will be reported in the CSR and in PK tables, figures and listings.

PK concentration data listings will be presented to the same number of significant figures as the data received from the bioanalytical laboratory (usually but not always to 3 significant figures) and against the same units as received.

PK concentration descriptive statistics will all be presented to 4 significant figures with the exception of the min and max which will be presented to 3 significant figures and n and n<LLOQ which will be presented as integers.

Further rules regarding PK parameters presentation can be found in Appendix “B”.

4.2.2.8 Secondary Endpoint – Biomarkers

4.2.2.8.1 Target Population Analysis Set

Biomarker endpoints will be analysed for TPAS.

ctDNA status will be presented including the number and percentage of patients with detectable EGFR mutations at baseline and available data at 6-weeks, split by ctDNA clearance and non-clearance.

The absolute change and the percentage change in EGFR mutation ctDNA allele frequencies at Week 6 will be summarised with descriptive statistics (n, mean, SD, median, min, max). Individual-level changes from baseline to all post-baseline timepoints will be summarised for all patients.

4.2.2.8.2 Safety Analysis Set

The analyses described in the above section 4.2.2.8.1 will be produced using the SAF for:

- savolitinib (300 mg od, 300 mg bid and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH10+ and/or IHC90+), locally advanced or metastatic NSCLC who have progressed following osimertinib

- savolitinib (300 mg bid, 300 mg bid and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH5+ and/or IHC50+), locally advanced or metastatic NSCLC who have progressed following osimertinib

4.2.2.9 Exploratory Endpoint – CNS Metastases

4.2.2.9.1 Contribution of Components Analysis Set

The CNS metastases analyses will be produced using the CAS for:

- 300 mg bid (savolitinib) + osimertinib
- 300 mg bid (savolitinib) + placebo

The CNS PFS, CNS ORR and CNS DoR by BICR will be explored to assess the efficacy of savolitinib plus osimertinib and savolitinib plus placebo, respectively, on CNS metastases in patients with CNS metastases at baseline.

The presence/absence of CNS lesions at progression by BICR in patients without CNS metastases at baseline will be presented using descriptive statistics.

4.2.2.10 Exploratory Endpoint – PRO- CTCAE

Individual items will be summarised with the number and proportion of patients in each response category over time.

4.2.2.10.1 Safety Analysis Set

The analyses described in the above section 4.2.2.10 will be produced using the SAF for:

- savolitinib (300 mg od, 300 mg bid and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH10+ and/or IHC90+), locally advanced or metastatic NSCLC who have progressed following osimertinib
- savolitinib (300 mg bid, 300 mg bid and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH5+ and/or IHC50+), locally advanced or metastatic NSCLC who have progressed following osimertinib.

4.2.2.11 Exploratory Endpoint – PGIS

The question will be summarised with the number and proportion of patients in each of the six response categories over time. Also, the change from baseline in the severity of cancer symptoms will be presented as the proportion of patients with no change (e.g., mild to mild), 1 category improvement (e.g., mild to none), $\geq$2 category improvement (e.g., severe to mild), 1 category deterioration (e.g., none to mild), and $\geq$2 category deterioration (e.g., mild to severe) at each visit by group. The data will be analysed based

on the following re-grouped categories at baseline: None (no symptoms), Mild (very mild and mild), Moderate, and Severe (very severe and severe).

4.2.2.11.1 Safety Analysis Set

The analyses described in the above section 4.2.2.11 will be produced using the SAF for:

- savolitinib (300 mg od, 300 mg bid and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH10+ and/or IHC90+), locally advanced or metastatic NSCLC who have progressed following osimertinib
- savolitinib (300 mg bid, 300 mg bid and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH5+ and/or IHC50+), locally advanced or metastatic NSCLC who have progressed following osimertinib

4.2.2.12 Exploratory Endpoint – EQ-5D-5L

The five dimensions will be summarised with the number and proportion of patients in each response category over time for each diagnostic population and by savolitinib starting dose. The EQ-5D-5L index score and the EQ-VAS score will be summarised by descriptive statistics over time.

4.2.2.12.1 Safety Analysis Set

The analyses described in the above section 4.2.2.12 will be produced using the SAF for:

- savolitinib (300 mg od, 300 mg bid and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH10+ and/or IHC90+), locally advanced or metastatic NSCLC who have progressed following osimertinib
- savolitinib (300 mg bid, 300 mg bid and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH5+ and/or IHC50+), locally advanced or metastatic NSCLC who have progressed following osimertinib

4.2.2.13 Exploratory Endpoint – Change in TL Tumour Size and Best Percentage Change in TL tumour size

4.2.2.13.1 Target Population Analysis Set

Percentage change from baseline in target lesion tumour size at Week 12 and over time, will be summarised.

Also, the best percentage change in tumour size from baseline over all tumour assessment time points will be summarised using descriptive statistics (n, mean, standard deviation, median, minimum, maximum).

The number and percentage of patients with new lesions by lesion site (e.g., CNS) will be tabulated. Waterfall plots showing the percentage change at Week 12 and the best percentage change from baseline in sum of the diameters of TLs will be produced.

Spider plots showing the percentage change from baseline in tumour size for each patient over time may be produced. These plots depict each patient's percentage change in TL tumour size as a line over time. Imputation will not be used for spider plots.

4.2.2.13.2 Safety Analysis Set

The analyses described in the above section 4.2.2.13.1 will be produced using the SAF for:

- savolitinib (300 mg od, 300 mg bid and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH10+ and/or IHC90+), locally advanced or metastatic NSCLC who have progressed following osimertinib
- savolitinib (300 mg od, 300 mg bid and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH5+ and/or IHC50+), locally advanced or metastatic NSCLC who have progressed following osimertinib

Details of tumour assessment and response will be listed for each patient. This listing will include information on target lesion sites, the method of assessment, diameter of target lesion, sum of diameters of target lesions, percent change from baseline, non-target lesions, new lesions, the calculated visit response and best objective response.

4.2.2.14 Supplementary Analysis based on IUO grade status

4.2.2.14.1 Supplementary Analyses of Objective Response Rate and Duration of Response

4.2.2.14.1.1 Target Population Analysis set

FISH10+ and/or IHC90+ MET status will be re-assessed retrospectively utilising IUO grade MET testing. ORR and DoR will be reproduced with CSPv7 patients identified for FISH10+ and/or IHC90+ MET status using retrospective IUO grade testing. ORR and DoR will be assessed according to primary endpoint approach (by investigator).

4.2.2.14.1.2 Subgroup Analysis

Subgroups analyses of ORR re-assessed retrospectively utilising IUO grade MET testing will be conducted on TPAS within the following subgroups (Appendix "A"):

- Race [Asian, Non-Asian]
- Sex [Male, Female]
- Age at baseline [<65 years, ≥65 years]

- T790M status in baseline plasma [T790M+, T790M-]
- C797S mutation in baseline plasma [C797S+, C797S-]
- FISH+ allocation status [Amplified, Polysomy]. Patients can be considered FISH+ by either amplification or polysomy, where amplification is considered a ratio of 'Mean MET/CEP7 RATIO' or 'CEP7/MET RATIO' >=2 and polysomy where ratio <2. The non-FISH+ patients will be excluded. Ratio information will be provided by external vendor
- IHC+ allocation status [IHC90+, IHC90 negative (FISH10+), IHC50+, IHC50 negative (FISH5+), IHC missing/unknown (FISH+ to enter study)]
- FISH+ allocation status [FISH10+, FISH10 negative (IHC90+), FISH5+, FISH5 negative (IHC50+), FISH missing/unknown (IHC+ to enter study)]
- Overall disease classification [Metastatic, Locally advanced, Missing]
- EGFR mutation status [Exon 19 deletion, L858R]
- Known or treated brain metastases at study entry [Yes (present at baseline or not present at baseline but with known or treated history of brain metastases), No (not present at baseline and not known or treated history of brain metastases)]. This classification will be identified by an AstraZeneca medically qualified expert during the medical review process
- ECOG at baseline [0, 1, …]
- Histological Type [Adenocarcinoma, Other].

4.2.2.14.1.3 Safety Analysis Set

FISH10+ and/or IHC90+ MET status will be re-assessed retrospectively utilising IUO grade testing. Summaries for ORR and DoR will also be re-produced utilising the IUO grade status on SAF for:

- savolitinib (300 mg od, 300 mg bid and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH10+ and/or IHC90+), locally advanced or metastatic NSCLC who have progressed following osimertinib

4.2.2.14.1.4 Contribution of Component Analysis Set

Finally, summaries for ORR will be re-produced using the CAS using retrospective IUO grade MET status for:

- 300 mg bid (savolitinib) + osimertinib
- 300 mg bid (savolitinib) + placebo.

4.2.2.14.2 Supplementary Analyses of Progression Free Survival

4.2.2.14.2.1 Target Population Analysis Set

FISH10+ and/or IHC90+ MET status will be re-assessed retrospectively utilising IUO grade MET testing. PFS will be reproduced with CSPv7 patients identified for FISH10+ and/or IHC90+ MET status using retrospective IUO grade testing. PFS will be assessed according to primary endpoint approach (by investigator).

4.2.2.14.2.2 Safety Analysis Set

Summaries for PFS will also be re-produced utilising the IUO grade status on SAF for:

- savolitinib (300 mg od, 300 mg bid and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH10+ and/or IHC90+), locally advanced or metastatic NSCLC who have progressed following osimertinib

4.2.3 Safety and Tolerability Data

Unless otherwise stated, analysis of safety data will be based on SAF for patients dosed under all CSP versions as follows:

- savolitinib (300 mg od, 300 mg bid and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH10+ and/or IHC90+), locally advanced or metastatic NSCLC who have progressed following osimertinib
- savolitinib (300 mg od, 300 mg bid and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET amplified/overexpressed (FISH5+ and/or IHC50+), locally advanced or metastatic NSCLC who have progressed following osimertinib
- savolitinib in monotherapy (i.e., 300 mg bid + placebo)

Dedicated analysis for patients randomised under CSP version 7.0 may be performed.

4.2.3.1 Exposure

Exposure will be presented based on TPAS and SAF Analysis Sets.

Actual and total treatment duration will be summarised by the following: mean, SD, minimum, maximum, median and number of observations, for both study treatments. In addition, the number and percentage of patients with dose modifications (interruptions and/or reductions) of savolitinib and osimertinib in the first 6 weeks and for the whole treatment period, respectively, will be presented. Note that dose re-assignment to 300 mg of savolitinib flat dosing is not considered a dose reduction.

Relative dose intensity will be summarised by descriptive statistics for both study treatments separately.

Dose change plots will be included showing savolitinib and osimertinib exposure for each patient. The figures will show duration of dose with indications for dose reductions, dose interruptions, overdoses,

dose re-assignment, discontinuation, and time of start and end of confirmed response when applicable.

A table of the number of treatment cycles started for each study treatment will also be provided.

Total amount of study treatment received will be listed by study treatments.

4.2.3.2 Adverse Event

Key guidelines for counting incidence proportions of adverse events are as follows:

- When a patient has the same AE reported multiple times during an analysis period based on SOC and PT, the patient will only be counted once within a level of MedDRA in an AE incidence table.
- When assessing investigator-reported relationship to study drug of the AEs, if an AE changes in causal relationship during an analysis period for a patient, the related event will be chosen. Related AEs will include those reported as related by the investigator and those with a missing relationship. AE with a missing relationship will be presented as related in summary tables but will be presented in the data listing with a missing relationship.
- When summarising intensity of the AEs, if an AE changes in CTCAE grade during an analysis period for a patient, the AE with the maximum CTCAE grade will be chosen. In case the AE term (SOC and PT) is reported more than once, one of them with missing grade, and at least another with non-missing grade, the maximum CTCAE grade will be chosen from the non-missing grade values and the missing grade can be ignored. If all are of missing grade, then the AE severity will be summarised in an additional "Unknown" intensity category.
- When summarising intensity for drug-related AEs, only drug-related AEs will be used in the analysis. If a patient has the same AE reported multiple times during an analysis period for a drug-related AE, the AE with the maximum CTCAE grade will be chosen.

The number and percentage of patients with TEAEs, as classified by SOC and PT, will be summarised for the Safety analysis set:

- Patients with TEAEs and the number of TEAEs
- TEAEs that are causally related to Osimertinib, causally related to Savolitinib, and casually related to either Osimertinib or Savolitinib,
- TEAEs of CTCAE grade ≥3
- TEAEs of CTCAE grade ≥3 related to Osimertinib or related to Savolitinib
- TEAEs by common frequency (>5%) in descending order
- TEAEs by maximum CTCAE grade
- TEAEs with death outcome
- Non-serious TEAEs that occurred in greater than 5% of patients

- Serious TEAEs
- Serious TEAEs – key patient information
- Serious TEAEs that are assessed by investigator as causally related to Osimertinib, causally related to Savolitinib, and casually related to either Osimertinib or Savolitinib
- TEAEs leading to dose modification of each study treatment
- TEAEs leading to discontinuation of each study treatment (overall and within the first 6 weeks)
- TEAEs leading to discontinuation of each study treatment - key patient information
- Other significant TEAEs
- Other significant TEAEs leading to discontinuation of each study treatment (overall and within the first 6 weeks)
- TEAEs of special interest
- TEAEs of special interest by CTCAE grade
- TEAEs of special interest leading to discontinuation of each study treatment (overall and within the first 6 weeks)
- Hypersensitivity/anaphylaxis and hepatotoxicity TEAEs of special interest leading to discontinuation of savolitinib (overall and within the first 6, 12 and 24 weeks)

An overall summary table of the number of patients experiencing at least one adverse event will be produced. An overall summary table of the number of AEs will also be provided.

TEAEs in any category, including AESI, TEAEs of CTCAE grade ≥3, deaths, SAEs, TEAEs leading to discontinuation, and other significant TEAEs will be summarised.

AEs occurring prior to first dose of study treatments (i.e., before study Day 1) which subsequently worsen in severity following dosing will be presented in the summary tables. All other AEs occurring prior to first dose of study treatments (i.e., before study Day 1), or after the 35-day follow-up period (28 days allowing for the ±7-day window) after discontinuation of study treatments will be listed, but not included in the summaries.

Details of any deaths will be listed for all patients.

All AEs will be listed, and any AEs started on or after a patient took osimertinib after crossing over from 300 mg bid + placebo to 300 mg bid + osimertinib will be flagged.

4.2.3.3 Physical Examination

Abnormal physical examination findings before the first dose will be recorded in the medical history. 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 unless unequivocally related to the disease under study.

4.2.3.4 ECG

The observed value, the change from baseline and the percentage change from baseline will be summarised for ECG parameters by analysis visit. Box plots for the absolute and change from baseline values will be provided by analysis visit. A shift table of categorical ECG interpretation (normal, abnormal) at baseline versus end of treatment will be provided. The post-dose assessments will also be presented.

The number and percentage of patients with absolute QTcF interval prolongation (>450 ms, >480 ms, >500 ms) and QTcF increase from baseline categories (>30 ms, >60 ms, >90 ms) at any time during treatment will also be summarised.

The ECG data will be listed and any assessments performed on or after a patient took osimertinib after crossing over from 300 mg bid + placebo to 300 mg bid + osimertinib will be flagged.

4.2.3.5 Vital Signs

The observed value, the change from baseline and the percentage change from baseline will be summarised for vital signs by analysis visit. Box plots for the absolute and change from baseline values will be provided by analysis visit. Furthermore, shift plots of baseline value versus minimum/maximum observations on study treatment will be produced.

4.2.3.6 Laboratory Data

The observed value, the change from baseline and the percentage change from baseline for haematology and clinical chemistry will be summarised by analysis visit using descriptive statistics. For all laboratory variables the CTCAE grade including shift from baseline to maximum post-baseline grade on treatment will be summarised. Box plots for the absolute and change from baseline values of haematology and clinical chemistry parameters will be provided by analysis visit. Moreover, clinically important changes in haematology and clinical chemistry parameters will be presented based on CTCAE grade changes to 3 or 4.

Categorical urinalysis dipstick parameters (glucose, protein, blood and leukocyte esterase) will be summarised in shift tables comparing the maximum value during treatment with baseline value. Myoglobin will be listed only.

A listing of ALT, AST, total bilirubin and ALP laboratory results will be provided for all patients with potential Hy's law by visit. Individual data will also be plotted. Potential Hy's law will be based on the liver forms.

Summary table of transaminase elevation cases will be produced. Figure of ALT/AST versus total bilirubin, expressed as multiples of ULN will also be produced. These summaries will be based on the laboratory data.

The laboratory data will be listed and any assessments performed on or after a patient took osimertinib

after crossing over from 300 mg bid + placebo to 300 mg bid + osimertinib will be flagged.

5 INTERIM, FUTILITY, PRIMARY AND FINAL ANALYSES

Interim analysis 1 was planned to assess ORR and discontinuations due to AEs. This was to occur after approximately CCI patients treated with osimertinib (80 mg od) and savolitinib (300 mg od) had the opportunity to be treated for CCI post-baseline scans (12 weeks) or CCI patients treated with osimertinib (80 mg od) and savolitinib (300 mg od) had the opportunity to be treated for 6 weeks, whichever was later. To evaluate the safety and tolerability of savolitinib in combination with Osimertinib continuous monitoring of the discontinuation due to AE rate and the discontinuation due to a hypersensitivity/anaphylaxis AE rate was to be performed after CCI patients treated with osimertinib (80 mg od) and savolitinib (300 mg od) had the opportunity to be treated for 6 weeks up to Interim Analysis [AI]1.

Interim analysis 2 was planned to assess ORR after approximately CCI post 1L patients treated with osimertinib (80 mg od) and savolitinib (300 mg od) had the opportunity to be treated for CCI postbaseline scans (12 weeks). Recruitment was not to be paused whilst the patients required for the interims were evaluated.

A futility analysis for savolitinib + placebo arm is planned after CCI patients have been randomised under CSP version 7.0 and have had an opportunity to have CCI post-baseline scans (12 weeks). The futility rule is defined as no responses observed among the first CCI randomised savolitinib + placebo arm patients who have had the opportunity for CCI post-baseline scans, assessed by investigator.

- If true savolitinib mono response rate = CCI there is a CCI probability of observing no responses out of the first CCI savolitinib + placebo patients.
- If true savolitinib mono response rate = CCI there is a CCI probability of observing no responses out of the first CCI savolitinib + placebo patients.
- If true savolitinib mono response rate = CCI there is a CCI probability of observing no responses out of the first CCI savolitinib + placebo patients.

Recruitment will not be paused during the futility analysis. If the decision is made that treatment with savolitinib + placebo is futile, further enrolment into the savolitinib + placebo arm will be stopped, all randomised patients will be unblinded, and those randomised to savolitinib + placebo will be given the opportunity to cross over to savolitinib + osimertinib. Recruitment to the savolitinib + osimertinib arm will continue regardless of the results of futility analysis until the planned sample size for the savolitinib + osimertinib arm is reached.

The primary (ORR) analysis for the study will be performed at 6 months after the last patient under CSP version 7.0 has been randomised to treatment. The final analysis for the study will be performed at 15 months, after the last patient under CSP version 7.0 has been randomised to treatment.

Additional analysis for patients enrolled prior to CSP version 7.0 may be performed, if required.

6 CHANGES OF ANALYSIS FROM PROTOCOL

Although not specified in the current CSP version 7.0, Change in tumour size by investigator assessment in accordance with RECIST 1.1, best percentage change in TL tumour size, CNS ORR and CNS DoR by BICR assessments in accordance with RECIST 1.1 have been considered of interest for this study and will be explored.

Moreover, OS and PFS timepoints will be extended compared to CSP version7.0 requirements.

DoR, PFS by investigator assessment in accordance with RECIST 1.1 will be assessed for CAS. Although present in CSP version 7.0 endpoints, DoR and PFS by >=3 line of treatment will not be explored in this statistical analysis. Baseline assessments related to RECIST 1.1 will not follow CSP version 7.0 definition where 28 days window is required.

Finally, IUO grade status has been introduced. At this regard, ORR, DoR, PFS by investigator will be assessed in accordance with RECIST 1.1 using retrospective IUO grade MET testing on TPAS, SAF and CAS.

7 REFERENCES

Frewer P, Mitchell P, Watkins C, Matcham J. Decision-making in early clinical drug development. Pharm Stat; 2016, 15(3):255-63.

Jennison C and Turnball BW. Group Sequential Methods with Applications to Clinical Trials. Chapman and Hall/CRC; 2000

8 APPENDICES

Appendix A **Subgroup Analysis list**

	ORR and PFS	
	TPAS	**SAF***
Race Asian Non-Asian	X	X
Sex Male Female	X	X

Age group <65 years >=65 years	X	X
Line of treatment 2nd line >=3rd line Missing		X
Prior platinum-based chemotherapy Yes No Missing		X
Prior platinum-based chemotherapy and line of treatment Yes and 2nd line Yes and >=3rd line No and 2nd line No and >=3rd line Missing		X
Immediately prior line of therapy Osimertinib Platinum-based chemotherapy Other Missing		X

Response to immediately prior line of therapy Yes and osimertinib Yes and platinum-based chemotherapy Yes and other No and osimertinib No and platinum-based chemotherapy No and other Missing		X
Immediately prior line osimertinib Osimertinib Not osimertinib Missing		X
Response to immediately prior line of therapy, osimertinib Yes and osimertinib Yes and not osimertinib No and osimertinib No and not osimertinib Missing		X
Number of previous EGFR TKI therapies 1 2 ... Missing		X
T790M status in baseline plasma T790M+ T790M-	X	X

C797S mutation in baseline plasma C797S+ C797S-	X	X
FISH+ allocation status Amplified (i.e., MET/CEP7 RATIO >=2) Polysomy (i.e., MET/CEP7 RATIO <2) Missing	X	X
IHC+ allocation status IHC90+ IHC90 negative (FISH10+) IHC50+ IHC50 negative (FISH5+) IHC missing/unknown (FISH positive to enter study)	X	X
FISH+ allocation status FISH 10+ FISH 10 negative (IHC90+) FISH 5+ FISH 5 negative (IHC50+) FISH missing/unknown (IHC+ to enter study)	X	X
Overall disease classification Metastatic Locally advanced Missing	X	X
EGFR mutation status [d] Exon 19 deletion L858R	X	

Known or treated brain metastases at study entry Yes (present at baseline or not present at baseline but with known or treated history) No (not present at baseline and not known or treated history of brain metastases)	X	
ECOG at baseline 0 1 ...	X	
Histological type Adenocacinoma Other	X	

* SAF: savolitinb 300 mg od + osimertinib (FISH10+ and/or IHC90+)

	OS		
	TPAS	**SAF***	**CAS**
IHC+ allocation status IHC90+ IHC90 negative (FISH10+) IHC50+ IHC50 negative (FISH5+) IHC missing/unknown (FISH positive to enter study)	X	X	X
FISH+ allocation status FISH 10+ FISH 10 negative (IHC90+) FISH 5+ FISH5 negative (IHC50+) FISH missing/unknown (IHC+ to enter study)	X	X	X

* SAF : savolitinb 300 mg od + osimertinib (FISH10+ and/or IHC90+)

Appendix B Pharmacokinetic parameter presentation rules

Parameter Symbol	Definition	Reporting in Summary Tables	Reporting in Listings
Ae	Cumulative amount of unchanged drug excreted into urine	mean/SD/med = 4 s.f min/max = 3 s.f	3 s.f
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to time t	mean/SD/Geomean/CV/GeomeanSD/med = 4 s.f. min/max = 3 s.f	3 s.f
AUC_{τ}	Area under the plasma concentration-time in the dose interval	mean/SD/Geomean/CV/GeomeanSD/med = 4 s.f. min/max = 3 s.f	3 s.f
AUC	Area under the plasma concentration-time curve from zero to infinity	mean/SD/Geomean/CV/GeomeanSD/med = 4 s.f. min/max = 3 s.f	3 s.f
C	Drug concentration in plasma at anytime	mean/SD/Geomean/CV/GeomeanSD/med = 4 s.f min/max = 3 s.f	same s.f as supplied from bioanalysis
Clast	Drug concentration at last observed time point	mean/SD/Geomean/CV/GeomeanSD/med = 4 s.f min/max = 3 s.f	same s.f as supplied from bioanalysis
Cmax	Maximum observed plasma (peak) drug concentration	mean/SD/Geomean/CV/GeomeanSD/med = 4 s.f min/max = 3 s.f	same s.f as supplied from bioanalysis
Cmin	Minimum observed plasma drug concentration	mean/SD/Geomean/CV/GeomeanSD/med = 4 s.f min/max = 3 s.f	same s.f as supplied from bioanalysis

Ctrough	Observed trough plasma drug concentration	mean/SD/Geomean/CV/GeomeanSD/med = 4 s.f min/max = 3 s.f	same s.f as supplied from bioanalysis
CL	Total body clearance of drug from plasma after intravascular administration	mean/SD/med = 4 s.f min/max = 3 s.f	3 s.f
CL/F	Apparent total body clearance of drug from plasma after extravascular administration	mean/SD/med = 4 s.f min/max = 3 s.f	3 s.f
CL_R	Renal clearance of drug from plasma	mean/SD/med = 4 s.f min/max = 3 s.f	3 s.f
λz	Terminal elimination rate constant	mean/SD/Geomean/mean/CV/SD/med = 5 s.f min/max = 3 s.f	4 s.f
F	Fraction of administered dose systemically available	mean/SD/Geomean/CV/CI/max/min as % to 2 d.p	as % to 2 d.p
F_{rel}	Fraction of administered dose systemically available relative to standard reference such as alternative formulation (note: not IV)	mean/SD/Geomean/CV/CI/max/min as % to 2 d.p	as % to 2 d.p
Fe	Fraction excreted unchanged in urine	mean/SD/med = 4 s.f min/max = 3 s.f	3 s.f
	Metabolite: parent ratio	Geomean/mean/CV/SD/med = 4 s.f min/max = 3 s.f	3 s.f
MRT	Mean residence time of the unchanged drug in the systemic circulation	mean/SD/med = 4 s.f min/max = 3 s.f	3 s.f
Rac	Accumulation ratio	Geomean/mean/CV/SD/med = 4 s.f min/max = 3 s.f	3 s.f

tlag	Time delay between drug administration and the first observed concentration in plasma	med = as actual time min/max = as actual time	same s.f as supplied
tmax	Time to reach peak or maximum observed concentration or response following drug administration	med = as actual time min/max = as actual time	same s.f as supplied
TCP	Temporal change parameter in systemic exposure (also known as: time dependency, temporal parameter change, linearity index)	Geomean/mean/CV/SD/med = 4 s.f min/max = 3 s.f	3 s.f
t½λz	Half-life associated with terminal slope (λz) of a semi- logarithmic concentration-time curve	mean/SD/med = 4 s.f min/max = 3 s.f	3 s.f
Vss	Volume of distribution at steady state from a systemic dose	mean/SD/med = 4 s.f min/max = 3 s.f	3 s.f
Vss/F	Volume of distribution (apparent) at steady state	mean/SD/med = 4 s.f min/max = 3 s.f	3 s.f

N number included in summary table for all parameters as whole numbers

d.p = decimal places

s.f = significant figures

Note: Not all the above parameters may be applicable for this study.