Clinical Study Protocol	
Study Intervention	Savolitinib + Osimertinib
Study Code	D5084C00009
Version	3.0
Date	09 May 2022

A Multi-centre Phase II, Double-Blind, Randomised Study of Savolitinib in Combination with Osimertinib vs Savolitinib in Combination with Placebo in Patients with EGFRm+ and MET Amplified Locally Advanced or Metastatic Non-Small Cell Lung Cancer who have Progressed Following Treatment with Osimertinib

Sponsor Name: AstraZeneca

Legal Registered Address:

AstraZeneca AB, 151 85 Södertälje, Sweden

AstraZeneca K.K., 3-1, Ofuka-cho, Kita-ku, Osaka 530-0011, Japan

Regulatory Agency Identifier Number(s)

EudraCT number: 2020-000813-33

IND: 133248

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number: D5084C00009

Amendment Number: 2

Study Intervention: Savolitinib in combination with osimertinib, and savolitinib in combination with placebo to osimertinib

Study Phase: Phase II

Short Title: Savolitinib plus osimertinib versus savolitinib plus placebo in EGFRm+/MET amplified NSCLC following prior osimertinib

Medical Monitor Name and Contact Information will be provided separately

International co-ordinating investigator: PPD , PPD , Department of Oncology, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei, Taiwan, 10002.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	09 May 2022
Amendment 1	28 May 2021
Original Protocol	9 June 2020

Amendment 2 (09 May 2022)

Overall Rationale for the Amendment:

The main reason for this global amendment is to implement early termination of study recruitment, explain the sponsor's decision to terminate recruitment early and to clarify the necessary changes to planned processes as a result of this. The design of this contribution of component study is no longer supportive of the savolitinib development programme in this study population. The contribution of component of savolitinib monotherapy (savolitinib plus placebo to osimertinib) versus savolitinib in combination with osimertinib will continue to be assessed in the ongoing SAVANNAH study. Further changes include additional instructions in relation to the management of toxicities to align with emerging safety data, the addition of an Independent Hepatic Assessment Committee upon Regulatory request, updates to text to align with the current CSP template, minor administrative changes, and the correction of minor errors. Changes in Global CSP Amendment 2 are presented in the table below.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.1 Synopsis, 4.1.1 Randomised Study Design, 9.2 Sample Size Determination	Text amended and added to explain that the planned number of randomised patients will not be met due to early termination of study recruitment.	To provide clarification following AstraZeneca's decision to terminate study recruitment.	Substantial
1.1 Synopsis, 4.1.1 Randomised Study Design, 4.1.2 Cross-over Study Design, 9.5 Interim Analyses, 9.6.1 Independent Data Monitoring Committee, Appendix A5 Committees Structure	Text amended and added to explain that the planned interim futility analysis will no longer be performed due to termination of study recruitment. Alternatively, an early review of the data will be performed following study recruitment termination.	To provide clarification following AstraZeneca's decision to terminate study recruitment.	Substantial
1.1 Synopsis, 4.1.1 Randomised Study Design, 9.4.1.2 Multiplicity Strategy for Primary and Key Secondary Endpoints, 9.4.2.2 Analysis of Secondary Efficacy Endpoints	CCI [redacted]	To provide clarification following AstraZeneca's decision to terminate study recruitment.	Substantial
1.1 Synopsis, 4.1.2 Cross-over Study Design, 9.5 Interim Analyses, 9.6.1 Independent Data Monitoring Committee, Appendix A5 Committees Structure	Text amended and added to explain that the IDMC, which was planned to monitor efficacy, is no longer required, as a result of early termination of study recruitment.	To provide clarification following AstraZeneca's decision to terminate study recruitment.	Substantial
1.3 Schedule of Activities, Table 1 and Table 2, 8.5.1 Pharmacokinetics, Table 10	Removal of the requirement for PK sample collection at Cycle 11 and Treatment Discontinuation Visit during the randomised treatment period, and for all PK sample collection during the cross-over treatment period.	No longer required following AstraZeneca's decision to terminate study recruitment.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.3 Schedule of Activities, Table 1 and Table 2	CCI [redacted]	To provide clarification.	Non-substantial
1.3 Schedule of Activities, Table 1 and Table 2	Added text pertaining to activities for those patients that continue on study after the final DCO.	To provide clarification.	Non-substantial
1.3 Schedule of Activities, Table 2, 8.1.1 CT and MRI Scans Tumour Assessments (RECIST 1.1)	Added text to clarify timings for tumour assessment schedules for patients who cross-over to savolitinib plus osimertinib.	To provide clarification.	Non-substantial
1.1 Synopsis, 4.1.1 Randomised Study Design, 4.1.2 Cross-over Study Design, 4.1.4 Early Study Recruitment Termination, 9.4.1.2 Multiplicity Strategy for Primary and Key Secondary Endpoints, 9.4.2.2 Analysis of Secondary Efficacy Endpoints	Text amended to describe the changes to the original planned timepoints for analysis, and to explain that the final analysis will occur following a final DCO, which will occur 9 months after the last patient has been randomised.	To provide clarification following AstraZeneca's decision to terminate study recruitment.	Substantial
4.1.2 Cross-over Study Design, 4.1.4 Early Study Recruitment Termination, 9.4.2.2 Analysis of Secondary Efficacy Endpoints, 9.5 Interim Analyses	Text amended to clarify that following AstraZeneca's early review of data after recruitment termination, the study will be unblinded, and patients randomised to the savolitinib plus placebo arm will be given the opportunity to cross-over to the savolitinib plus osimertinib arm.	To provide clarification following AstraZeneca's decision to terminate study recruitment.	Substantial
4.1.2 Cross-over Study Design, 4.1.4 Early Study Recruitment Termination	Text added to explain that any patients remaining on savolitinib monotherapy at the time of final database lock will be offered the switch to savolitinib plus Osimertinib.	To provide clarification following AstraZeneca's decision to terminate study recruitment.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
4.1.4 Early Study Recruitment Termination	New section added to clarify the decision by AstraZeneca to terminate study recruitment and the study activities to be performed following termination of recruitment.	To provide clarification following AstraZeneca's decision to terminate study recruitment.	Substantial
4.4 End of Study Definition	End of study definition amended from 18 months after the last patient randomised, or when 70% of patients have progressed or died, to the date of the last visit of the last patient in the study.	To provide clarification following AstraZeneca's decision to terminate study recruitment.	Substantial
6.2 Preparation/Handling/ Storage/Accountability of Interventions	Text corrected to indicate that guidance on final disposition of unused study interventions can be found in the Pharmacy Manual and not the Central Laboratory Manual.	To correct error.	Non-substantial
6.3 Measures to Minimise Bias: Randomisation and Blinding	Text amended to clarify that the study will be unblinded following completion of data cleaning activities on the initial DCO data.	To provide clarification following AstraZeneca's decision to terminate study recruitment.	Substantial
6.7 Intervention after the End of the Study	Text added to clarify the process relating to provision of study intervention by AstraZeneca at the end of the study.	Added in line with updated CSP template language.	Non-substantial
6.7 Intervention after the End of the Study	Text added to explain how transitioning to a roll-over study (if available) would occur.	Added in line with the possibility of joining a roll-over study.	Non-substantial
8 Study Assessments and Procedures	Deletion of the last bullet point relating to the maximum amount of blood collected from each patient during the study.	To align with the current CSP template.	Non-substantial
8.2.5 Clinical Safety Laboratory Assessments	Text corrected to indicate that clinical safety laboratory assessments will be performed in a licensed local clinical laboratory according to local standard procedures and not in accordance with the Central Laboratory Manual.	To correct error.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
9.4 Statistical Analyses	Text amended to clarify that the SAP will no longer be finalised prior to the futility analysis DCO but prior to the unblinding of the study that will occur following recruitment termination.	To provide clarification following AstraZeneca's decision to terminate study recruitment.	Substantial
9.4.4 Pharmacokinetic Analyses	Removed the calculation of the ratio of $C_{pre\text{-}dose}$ Cycle 11 Day 1/$C_{pre\text{-}dose}$ Cycle 2 Day 1	No longer applicable since the requirement for PK sample collection at Cycle 11 has been removed.	Non-substantial
9.6 Data Monitoring Committee, Appendix A5 Committees Structure	Section 9.6 now split into 2 sub-sections (9.6.1 Independent Data Monitoring Committee) and 9.6.2 Independent Hepatic Assessment Committee) to incorporate the addition of the Independent Hepatic Assessment Committee, which will review safety data related to hepatic events as per case definition of drug-induced liver injury.	Program-wide introduction based on Regulatory request.	Substantial
Appendix I 1 Management of Study Treatment-related Toxicities, Table I2	Additional instruction for osimertinib discontinuation for symptomatic congestive heart failure.	To align with emerging safety data.	Substantial
Appendix I 1.1 Guidelines for the Management of Overlapping Toxicities between Osimertinib and Savolitinib, Table I3	Additional instruction for QTc prolongation included in relation to recommencement of osimertinib dosing where causality may be difficult to determine.	To align with emerging safety data.	Substantial
Appendix I 2 Osimertinib Dose Modification and Guidance	Text added to clarify that withdrawal from the study should occur 3 weeks from the time osimertinib was withheld/interrupted, rather than 3 weeks from onset of toxicity.	To provide clarification.	Non-substantial
Appendix I 3.2.1 Dose Modification Due to Drug-related Hepatotoxicity	Additional instruction included in relation to discontinuing drug when drug is already being withheld.	To align with emerging safety data.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Appendix J 1 Drugs Inducing CYP3A4 Metabolism that AstraZeneca Strongly Recommend are not Combined with Osimertinib or Savolitinib, Table J1	Clarification to highlight that phenobarbital is also known as phenobarbitone and change in required withdrawal period for phenobarbitone prior to osimertinib or savolitinib start from 5 weeks to 3 weeks.	To provide clarification.	Non-substantial
Appendix J 5.1 Drugs with a Known Risk of TdP, Table J4	Footnote "b" added to clarify that the values for each drug are determined from internal review of PK half-life of each compound.	To provide clarification.	Non-substantial
Appendix K Abbreviations	New abbreviations added	Administrative change.	Non-substantial
Appendix L Summary of Changes	Created to cover summary of changes to Amendment 1 (28 May 2021)	Administrative change.	Non-substantial
11 References	Addition of one new reference (Aithal et al 2011)	In line with updated text in Section 9.6.2.	Non-substantial

$C_{pre\text{-}dose}$ = plasma concentration pre-dose; CSP = Clinical Study Protocol; CT = computed tomography; DCO = data cut-off; IDMC = independent data monitoring committee; MRI = magnetic resonance imaging; PK = pharmacokinetics; QTc = corrected QT interval; RECIST = Response Evaluation Criteria in Solid Tumours; SAP = Statistical Analysis Plan; TdP = Torsades de Pointes.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Multi-centre Phase II, Double-Blind, Randomised Study of Savolitinib in Combination with Osimertinib vs Savolitinib in Combination With Placebo in Patients with EGFRm+ and MET Amplified Locally Advanced or Metastatic Non-Small Cell Lung Cancer who have Progressed Following Treatment with Osimertinib

Short Title: Savolitinib plus osimertinib versus savolitinib plus placebo in EGFRm+/MET amplified NSCLC following prior osimertinib

Rationale: Resistance to EGFR-TKIs is a clinical problem. One of the mechanisms for resistance to osimertinib is amplification of the MET receptor tyrosine kinase, which activates downstream intracellular signalling independent of EGFR. This study will explore the individual contribution of savolitinib to MET-mediated osimertinib resistance.

This study will assess the response to dual pathway blockade of EGFRm and MET to overcome MET-mediated resistance to osimertinib versus inhibition of the MET pathway alone by investigating the efficacy of savolitinib plus osimertinib versus savolitinib plus placebo to osimertinib (hereafter referred to as placebo) in patients with EGFRm+ and MET amplified, locally advanced or metastatic NSCLC who have progressed following treatment with osimertinib.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the ORR of savolitinib in combination with osimertinib versus savolitinib in combination with placebo in patients with EGFRm+, MET amplified locally advanced or metastatic NSCLC who have progressed on previous osimertinib therapy.	Objective response rate is defined as the proportion of patients with measurable disease who have a CR or PR as determined by the investigator at the local site per RECIST 1.1.

Objectives	Endpoints
Secondary	
To determine the efficacy of savolitinib in combination with osimertinib versus savolitinib in combination with placebo in patients with EGFRm+, MET amplified locally advanced or metastatic NSCLC who have progressed on previous osimertinib therapy.	• Progression-free survival is defined as time from randomisation until progression per RECIST 1.1 as assessed by the investigator or death due to any cause. • Duration of response is defined as the time from the date of first documented response until date of documented progression per RECIST 1.1 as assessed by the investigator or death in the absence of disease progression. • Tumour size assessment is defined as the percentage change from baseline in TLs at 12 weeks per RECIST 1.1 as assessed by the investigator. • Overall survival is defined as time from randomisation until the date of death due to any cause.
To evaluate the efficacy of savolitinib plus osimertinib in patients who cross-over after progression on savolitinib plus placebo [a]	• Objective response rate is defined as the proportion of patients with measurable disease who have a CR or PR as determined by the investigator at the local site per RECIST 1.1. • Progression-free survival is defined as time from the first dose in the cross-over period until progression per RECIST 1.1 as assessed by the investigator or death due to any cause. • Duration of response is defined as the time from the date of first documented response during the cross-over period until date of documented progression per RECIST 1.1 as assessed by the investigator or death in the absence of disease progression. • Tumour size assessment is defined as the percentage change from baseline in TLs at 12 weeks per RECIST 1.1 as assessed by the investigator.
To evaluate the PK of savolitinib and osimertinib.	Plasma concentrations of savolitinib, osimertinib, and their metabolites.
To determine the prevalence of ctDNA clearance after savolitinib plus osimertinib or savolitinib plus placebo 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).

Objectives	Endpoints
Safety	
To evaluate the safety and tolerability of savolitinib plus osimertinib or savolitinib plus placebo.	Safety and tolerability will be evaluated in terms of AEs, SAEs and discontinuation rate due to AEs. Clinical chemistry/haematology including LFTs. ECHOs, ECGs and vital signs including blood pressure and heart rate.

[a] Baseline for ORR, PFS, DoR and tumour size assessments of patients who cross-over to savolitinib plus osimertinib from savolitinib plus placebo will be the progression scan on savolitinib plus placebo acquired within 28 days of the start of treatment in the cross-over period.

AE = Adverse event; CR = Complete response; ctDNA = Circulating tumour DNA; DoR = Duration of response; ECG = Electrocardiogram; ECHO = Echocardiogram; EGFRm+ = Epidermal growth factor receptor mutation positive; LFT = Liver function test; MET = Hepatocyte growth factor receptor; NSCLC = Non-small cell lung cancer; ORR = Objective response rate; PFS = Progression-free survival; PK = Pharmacokinetics; PR = Partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SAE = Serious adverse events; TL = Target lesion.

For Exploratory objectives and the respective endpoints, see Section 3 of the CSP.

Overall Design

This is a multi-centre, Phase II, double-blind, randomised study designed to determine the efficacy of savolitinib administered orally in combination with osimertinib versus savolitinib in combination with placebo in patients with EGFRm+ and MET amplified, locally advanced or metastatic NSCLC who have progressed on previous osimertinib treatment. The evaluation of the individual contribution of savolitinib will be assessed by treating these patients with savolitinib in combination with either placebo or osimertinib.

Prior to CSP V3.0, approximately 56 patients were planned to be randomised in a ratio of 1:1 to receive treatment with CCI savolitinib CCI plus CCI osimertinib CCI or CCI savolitinib CCI plus placebo. At least half of the patients randomised into the study will be second-line patients who were treated with osimertinib as first-line therapy. Randomisation will be stratified according to the number of prior lines of therapy (ie, osimertinib monotherapy as first line or ≥ second line [which includes patients who received osimertinib monotherapy before or after chemotherapy]).

Disclosure Statement: This is a parallel treatment study with 2 arms that is patient and investigator blinded.

Number of Patients:

The study planned to randomise 56 patients, with at least half of the patients in the study (28 patients) being second-line patients who were treated with osimertinib in the first-line setting.

Under CSP V3.0, the planned number of randomised patients will not be met. This is a result of the decision by AstraZeneca to terminate study recruitment early.

Intervention Groups and Duration:

All patients confirmed as eligible will begin treatment on Day 1 with savolitinib plus osimertinib or savolitinib plus placebo. Treatment will continue [redacted] in 28-day cycles until either objective PD by RECIST 1.1 is assessed, unacceptable toxicity occurs, consent is withdrawn, or another discontinuation criterion is met.

Patients randomised to the savolitinib plus placebo arm may cross-over to open-label savolitinib plus osimertinib following investigator-assessed objective PD to ensure that all patients enrolled may have the opportunity to receive the combination of savolitinib plus osimertinib.

Data Monitoring Committee:

An IDMC was to meet for the planned interim futility analysis to provide a recommendation for the continuation of this study based on efficacy observed.

Under CSP V3.0, as a result of AstraZeneca's decision to terminate study recruitment early, the planned interim futility analysis will not be performed and there will be no requirement for data review by the IDMC. Alternatively, an early review of the data will occur following the early termination of study recruitment.

Statistical methods:

The primary objective of this study is to assess the ORR of savolitinib in combination with osimertinib versus savolitinib in combination with placebo in patients with EGFRm+, MET amplified locally advanced or metastatic NSCLC who have progressed on previous osimertinib therapy. The ORR is defined as the proportion of patients with measurable disease who have a CR or PR as determined by the investigator at the local site per RECIST 1.1.

Secondary efficacy variables include PFS, DoR, percentage change in tumour size by investigator assessment and OS during randomised treatment and ORR, PFS, DoR and percentage change in tumour size by investigator assessment during the cross-over period.

Efficacy data will be summarised and analysed using the FAS. The FAS will include all randomised patients with treatment groups assigned in accordance with the randomisation, regardless of the treatment actually received. Patients who were randomised but did not subsequently receive treatment will be included in the FAS. The analysis of data using the FAS therefore follows the principles of intention-to-treat. Safety data will be summarised using the SAS, and PK data will be summarised using the PK Analysis Set.

Prior to CSP V3.0, a primary analysis was planned to occur 6 months after the last patient was

randomised. With 56 patients (28 per arm)[redacted].

A non-comparative interim futility analysis for the savolitinib plus placebo arm was planned after 20 patients overall (10 per arm) had the opportunity to be treated for 2 RECIST post-baseline scans (12 weeks). The outcome of the interim futility analysis was to be as follows:

- Stop further enrolment into the study if no responses are observed.
- If true rate = 5%, there is a 59.9% probability of observing no responses.
- If true rate = 10%, there is a 34.9% probability of observing no responses.
- If true rate = 43%, there is a 0.4% probability of observing no responses.

Recruitment was to continue during the interim futility analysis.

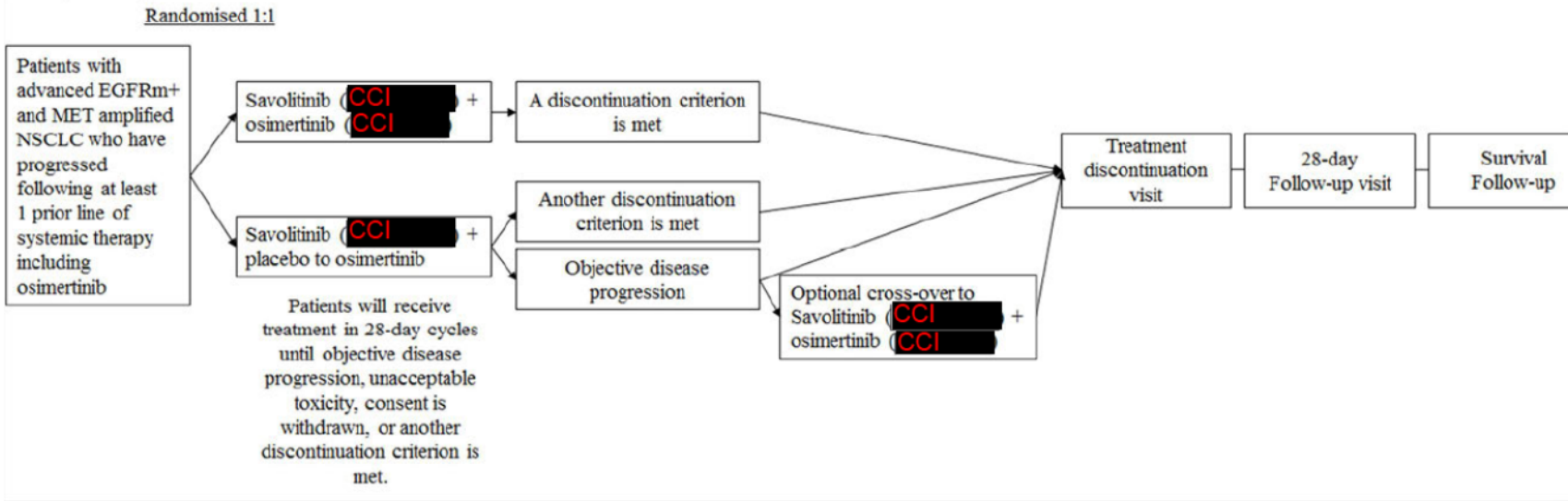
Under CSP V3.0, as a result of the decision by AstraZeneca to terminate study recruitment early, the planned interim futility analysis and primary analysis will not be performed. Alternatively, an early review of the data by AstraZeneca will occur following the early termination of study recruitment. The final DCO will occur 9 months after the last patient has been randomised, after which the final analysis will be performed. [redacted]

The ORR will be analysed using a logistic regression model adjusting for the stratification used in the randomisation. The results of the analysis will be presented in terms of an odds ratio (an odds ratio greater than 1 will favour savolitinib in combination with osimertinib versus savolitinib plus placebo) together with its associated profile likelihood 95% CI and p-value (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model). If there are not enough responses for a meaningful analysis using logistic regression then a CMH test will be presented. Summaries will be produced that present the number and percentage of patients in each treatment group with a tumour response (CR/PR).

Safety data will be summarised descriptively and will not be formally analysed.

1.2 Schema

Figure 1 Study Design



The definition of MET amplified is as an increased gene copy number.
EGFRm+ = Epidermal growth factor receptor mutation positive; MET = Hepatocyte growth factor receptor; NSCLC = Non-small cell lung cancer.

1.3 Schedule of Activities

Table 1 Schedule of Activities for Randomised Treatment

Visit	Pre-screening	Screening	Intervention Period						Follow-up [a]			Details in CSP Section or Appendix
			Cycle 1 (28-day cycle)				Cycles 2 to 6 (28-day cycle)	Cycle 7 onwards (28-day cycle)	Treatment discontinuation visit	28-Day follow-up visit [b]	Survival follow-up visit	
Week (Day 1 of)		-4 to 0	1 to 4				5 to 24	25 onwards				
Study day		-28 to -1	1 to 28				29 to 168	169 onwards				
Day of cycle	NA		1	8	15	22	1	1				
Visit window			± 1 day				± 3 days	± 3 days	Within 7 days of the final dose of study intervention	± 7 days		
Informed consent for MET status testing	X											5.1
Retrieve or collect tumour specimen for MET status testing	X [c]											5.1 and 8.6
Confirm tumour harbours EGFRm	X [d]											5.1
Cancer therapy record	X	X								X	X	4.1.1 and 5.2
Informed consent for main study		X										5.1
Inclusion and exclusion criteria		X										5.1 and 5.2
Randomisation		X										6.3

Table 1 Schedule of Activities for Randomised Treatment

Visit	Pre-screening	Screening	Intervention Period						Follow-up [a]			
			Cycle 1 (28-day cycle)				Cycles 2 to 6 (28-day cycle)	Cycle 7 onwards (28-day cycle)	Treatment discontinuation visit	28-Day follow-up visit [b]	Survival follow-up visit	Details in CSP Section or Appendix
Week (Day 1 of)		-4 to 0	1 to 4				5 to 24	25 onwards				
Study day		-28 to -1	1 to 28				29 to 168	169 onwards				
Day of cycle	NA		1	8	15	22	1	1				
Visit window			± 1 day				± 3 days	± 3 days	Within 7 days of the final dose of study intervention	± 7 days		
Routine clinical procedures												
Demography	X											5.1
Physical examination		X	X	X	X	X	Every visit		X			8.2.1
Height		X										8.2.2
Weight [e]		X	X				Day 1 of every cycle	Q8W	X			8.2.2
Medical/surgical history	X	X										5.1
ECOG/WHO performance score		X	X	X	X	X	Day 1 of every cycle		X	X		5.1
Vital signs		X	X	X	X	X	Day 1 of every cycle		X	X		8.2.2
Triplicate ECG		X	X	X	X	X	Day 1 of every cycle [f]		X	X [g]		8.2.3
MUGA/ECHO		X	Q12W (± 2 weeks) relative to randomisation						X	X [g]		8.2.4
Concomitant medication and procedures		X	At every visit and may be conducted by phone if not tied to a clinical visit						X	X		6.5

Table 1 Schedule of Activities for Randomised Treatment

Visit	Pre-screening	Screening	Intervention Period						Follow-up [a]			
			Cycle 1 (28-day cycle)				Cycles 2 to 6 (28-day cycle)	Cycle 7 onwards (28-day cycle)	Treatment discontinuation visit	28-Day follow-up visit [b]	Survival follow-up visit	Details in CSP Section or Appendix
Week (Day 1 of)		-4 to 0	1 to 4				5 to 24	25 onwards				
Study day		-28 to -1	1 to 28				29 to 168	169 onwards				
Day of cycle	NA		1	8	15	22	1	1				
Visit window			± 1 day				± 3 days	± 3 days	Within 7 days of the final dose of study intervention	± 7 days		
Routine safety measurements												
Adverse events		X	At every visit and may be conducted by phone if not tied to a clinical visit						X	X		8.3
Pregnancy test (serum or urine, WOCBP only)		X	Day 1 of every cycle						X			8.3.11
Safety laboratory assessments (clinical chemistry, haematology and urinalysis)		X	X	X	X	X	Every visit		X			8.2.5
Coagulation		X										5.1
Liver function tests [h]		X	Weekly for the first 10 weeks relative to randomisation, then Day 1 of every subsequent cycle and at the time of disease progression						X			8.2.5

Table 1 Schedule of Activities for Randomised Treatment

Visit	Pre-screening	Screening	Intervention Period						Follow-up [a]			Details in CSP Section or Appendix
			Cycle 1 (28-day cycle)				Cycles 2 to 6 (28-day cycle)	Cycle 7 onwards (28-day cycle)	Treatment discontinuation visit	28-Day follow-up visit [b]	Survival follow-up visit	
Week (Day 1 of)	NA	-4 to 0	1 to 4				5 to 24	25 onwards				
Study day		-28 to -1	1 to 28				29 to 168	169 onwards				
Day of cycle			1	8	15	22	1	1				
Visit window			± 1 day				± 3 days	± 3 days	Within 7 days of the final dose of study intervention	± 7 days		
Biomarker analyses												
CCI												

Table 1 Schedule of Activities for Randomised Treatment

Visit	Pre-screening	Screening	Intervention Period						Follow-up [a]			
			Cycle 1 (28-day cycle)				Cycles 2 to 6 (28-day cycle)	Cycle 7 onwards (28-day cycle)	Treatment discontinuation visit	28-Day follow-up visit [b]	Survival follow-up visit	Details in CSP Section or Appendix
Week (Day 1 of)		-4 to 0	1 to 4				5 to 24	25 onwards				
Study day		-28 to -1	1 to 28				29 to 168	169 onwards				
Day of cycle	NA		1	8	15	22	1	1				
Visit window			± 1 day				± 3 days	± 3 days	Within 7 days of the final dose of study intervention	± 7 days		
PK measurements												
Blood sample for PK analysis of savolitinib [m, n]			X [n]				Day 1 of Cycles 2, 3, and 6 [n]					8.5.1
Blood sample for PK analysis of osimertinib [m, n]			X [n]				Day 1 of Cycles 2, 3, and 6 [n]					8.5.1
Efficacy measurements												
Tumour imaging [o] (RECIST 1.1)		X [p]	Q6W (± 7 days) up to 24 weeks relative to randomisation, then Q8W (± 7 days) until objective disease progression									8.1
Study intervention administration												
Dose with osimertinib or placebo			X (daily dosing)									6.1
Dose with savolitinib			X (daily dosing)									6.1

Table 1 Schedule of Activities for Randomised Treatment

Visit	Pre-screening	Screening	Intervention Period						Follow-up [a]			
			Cycle 1 (28-day cycle)				Cycles 2 to 6 (28-day cycle)	Cycle 7 onwards (28-day cycle)	Treatment discontinuation visit	28-Day follow-up visit [b]	Survival follow-up visit	Details in CSP Section or Appendix
Week (Day 1 of)		-4 to 0	1 to 4				5 to 24	25 onwards				
Study day		-28 to -1	1 to 28				29 to 168	169 onwards				
Day of cycle	NA		1	8	15	22	1	1				
Visit window			± 1 day				± 3 days	± 3 days	Within 7 days of the final dose of study intervention	± 7 days		
Survival follow-up												
Survival status											Q12W [q]	8.1.2

[a] The follow-up period is only applicable for those who discontinue randomised treatment and do not cross-over to treatment with savolitinib plus osimertinib. Patients who cross-over are to carry on assessments as per the SoA in Table 2.

[b] As a minimum, telephone contact should be made with the patient 28 days following the discontinuation of study intervention to collect new AEs and follow up on any ongoing AEs and concomitant medications (including any subsequent cancer therapy, if appropriate).

[c] At pre-screening, testing for MET amplified tumour by central FISH testing must be performed on an FFPE tumour specimen collected after progression of previous osimertinib treatment, which may or may not have been the most recent treatment. Testing may be performed as initial pre-screening with consent obtained using the Pre-screening ICF in advance of obtaining consent for the main study. Detailed sample requirements will be defined in study Laboratory Manual. MET amplified is defined as increased gene copy number. Samples > 2 years old will not be accepted. New tumour specimens should only be collected specifically for pre-screening for this study where the expected risk of an AE related to the procedure is < 2%.

[d] EGFRm status is an inclusion criterion and part of disease diagnosis and a criterion to receive osimertinib; prospective central testing is not required.

[e] Weight will be assessed as shown above and more frequently if clinically indicated.

[f] Triplicate ECGs will be required on Cycle 3 Day 1 collected pre-dose and at 1, 3, 4 and 6 hours post-dose to coincide with collection of blood samples for assessment of PK of osimertinib and savolitinib at this visit.

[g] A 28-day follow-up assessment will be required if an on-treatment assessment was abnormal at the time of discontinuation of study therapy to confirm reversibility of the abnormality.

[h] Liver function tests will be performed weekly for the first 10 weeks, then Day 1 of every subsequent cycle and at progression. Where a liver function test is the only assessment, a clinic visit is not required as the test may be performed offsite. In the case of elevated liver function tests, please refer to Appendix I 3.2 for enhanced monitoring and management procedures.

CCI [redacted]

CCI [redacted]

[m] Date and time of last osimertinib dose prior to Cycle 1 Day 1 (prior to PK sample) will be collected. In addition, date and time of last osimertinib/placebo dose and last savolitinib dose prior to each PK sample will be collected.

[n] Plasma concentrations of osimertinib, savolitinib and their metabolites. Collected on: Cycle 1, Day 1: Pre-dose and 1 and 3 hours post-dose; Cycle 2, Day 1: Pre-dose and 1 and 3 hours post-dose; Cycle 3, Day 1: Pre-dose and 1, 3, 4, and 6 hours post-dose; Cycles 6, Day 1: Pre-dose only. PK sample collection windows are: Pre-dose, up to 2 hours Pre-dose; 1 hour post-dose, ± 5 minutes; 3 hours post-dose, ± 10 minutes; 4 hours and 6 hours post-dose, ± 30 minutes.

[o] Patients who discontinue study intervention for reasons other than investigator-assessed disease progression will continue RECIST 1.1 tumour assessments Q6W (± 7 days) relative to randomisation up to 24 weeks, then Q8W (± 7 days) relative to randomisation until objective disease progression. At the same time points, ECOG/WHO performance status, vital signs, ECGs, and plasma samples for ctDNA will be collected. Serious adverse events considered related to study intervention and/or study procedures will be collected throughout progression follow-up.

[p] At screening the MRI/CT scans will include brain imaging for all patients. Those determined to have brain metastases will have their brain rescanned at all subsequent tumour assessments.

[q] Patients will be contacted for survival follow-up Q12W. Patients should be contacted in the week after data cut-off for each study analysis to establish survival status. Serious adverse events considered related to study intervention will be collected throughout survival follow-up.

Note: For patients continuing in the study after final DCO, refer to Section 6.7 for required activities.

AE = Adverse event; CSP = Clinical Study Protocol; CT = Computed tomography; ctDNA = Circulating tumour DNA; DCO = data cut-off; ECG = Electrocardiogram; ECHO = Echocardiogram; ECOG = Eastern Cooperative Oncology Group; EGFR = Epidermal growth factor receptor; EGFRm = Epidermal growth factor receptor mutated; FFPE = Formalin fixed, paraffin embedded; FISH = Fluorescence in situ hybridisation; CCI [redacted] ICF = Informed Consent Form; MET = Hepatocyte growth factor receptor; MRI = Magnetic resonance imaging; MUGA = Multi-gated acquisition; NA = Not applicable; PK = Pharmacokinetics; Q6/8/12W = Every 6/8/12 weeks; RECIST = Response Evaluation Criteria in Solid Tumours; SoAs = Schedule of activities; CCI [redacted] WHO = World Health Organization; WOCBP = Women of childbearing potential.

Table 2 Schedule of Activities for Patients who Cross-over to Savolitinib plus Osimertinib from Savolitinib Plus Placebo

Cross-over Visit	**Prior to cross-over**	**Cross-over Period**						**Follow-up**			**Details in CSP Section or Appendix**
		Cycle 1 (28-day cycle)				**Cycles 2 to 6 (28-day cycle)**	**Cycle 7 onwards (28-day cycle)**	**Treatment discontinuation visit**	**28-Day follow-up visit [a]**	**Survival follow-up visit**	
Week (Day 1 of)		**1 to 4**				**5 to 24**	**25 onwards**				
Study day of cross-over		**1 to 28**				**29 to 168**	**169 onwards**				
Day of cycle		**1**	**8**	**15**	**22**	**1**	**1**				
Visit window	**NA**	**± 1 day**				**± 3 days**	**± 3 days**	**Within 7 days of the final dose of study intervention**	**± 7 days**		
Informed consent for cross-over	X										5.1
Cancer therapy record	X								X	X	4.1.1 and 5.2
Routine clinical procedures											
Physical examination		X				Every visit		X			8.2.1
Weight [b]		X				Day 1 of every cycle	Q8W	X			8.2.2
ECOG/WHO performance score		X				Day 1 of every cycle		X	X		5.1
Vital signs		X				Day 1 of every cycle		X	X		8.2.2
Triplicate ECG		X				Day 1 of every cycle [c]		X	X [d]		8.2.3
MUGA/ECHO		Q12W (± 2 weeks) relative to randomisation						X	X [d]		8.2.4
Concomitant medication and procedures		At every visit, may be conducted by phone if not tied to a clinical visit						X	X		6.5

Table 2 Schedule of Activities for Patients who Cross-over to Savolitinib plus Osimertinib from Savolitinib Plus Placebo

Cross-over Visit	Prior to cross-over	Cross-over Period						Follow-up			Details in CSP Section or Appendix
		Cycle 1 (28-day cycle)				Cycles 2 to 6 (28-day cycle)	Cycle 7 onwards (28-day cycle)	Treatment discontinuation visit	28-Day follow-up visit [a]	Survival follow-up visit	
Week (Day 1 of)		1 to 4				5 to 24	25 onwards				
Study day of cross-over		1 to 28				29 to 168	169 onwards				
Day of cycle		1	8	15	22	1	1				
Visit window	NA	± 1 day				± 3 days	± 3 days	Within 7 days of the final dose of study intervention	± 7 days		
Routine safety measurements											
Adverse events		At every visit, may be conducted by phone if not tied to a clinical visit						X	X		8.3
Pregnancy test (serum or urine, WOCBP only)		Day 1 of every cycle						X			8.3.11
Safety laboratory assessments (clinical chemistry, haematology and urinalysis)		X				Every visit		X			8.2.5
Liver function tests [e]		Weekly for the first 10 weeks relative to randomisation, then Day 1 of every subsequent cycle and at the time of disease progression						X			8.2.5
Biomarker analyses											
CCI											
Efficacy measurements											

Table 2 Schedule of Activities for Patients who Cross-over to Savolitinib plus Osimertinib from Savolitinib Plus Placebo

Cross-over Visit	Prior to cross-over	Cross-over Period						Follow-up			Details in CSP Section or Appendix
		Cycle 1 (28-day cycle)				Cycles 2 to 6 (28-day cycle)	Cycle 7 onwards (28-day cycle)	Treatment discontinuation visit	28-Day follow-up visit [a]	Survival follow-up visit	
Week (Day 1 of)		1 to 4				5 to 24	25 onwards				
Study day of cross-over		1 to 28				29 to 168	169 onwards				
Day of cycle		1	8	15	22	1	1				
Visit window	NA	± 1 day				± 3 days	± 3 days	Within 7 days of the final dose of study intervention	± 7 days		
Tumour imaging [h] (RECIST 1.1)		Scheduled imaging is required for patients who cross-over after study unblinding and who have not progressed during the initial randomised treatment period: Q6W (± 7 days) up to 24 weeks relative to initial randomisation, then Q8W (± 7 days) until objective disease progression									8.1
Study intervention administration											
Dose with osimertinib		X (daily dosing)									6.1
Dose with savolitinib [i]		X (daily dosing)									6.1
Survival follow-up											
Survival status										Q12W [j]	8.1.2
Subsequent anti-cancer treatment										Q12W [j]	8.1.2

[a] As a minimum, telephone contact should be made with the patient 28 days following the discontinuation of study intervention to collect new AEs and follow up on any ongoing AEs and concomitant medications (including any subsequent cancer therapy, if appropriate).

[b] Weight will be assessed as shown above and more frequently if clinically indicated.

[c] Triplicate ECGs will be required on Cycle 3 Day 1 collected pre-dose and at 1, 3, 4 and 6 hours post-dose to coincide with collection of blood samples for assessment of PK of osimertinib and savolitinib at this visit.

[d] A 28-day follow-up assessment will be required if an on-treatment assessment was abnormal at the time of discontinuation of study therapy to confirm reversibility of the abnormality.

[e] Liver function tests will be performed weekly for the first 10 weeks from randomisation, then Day 1 of every subsequent cycle and at progression. Where a liver function test is the only assessment, a clinic visit is not required as the test may be performed offsite. In the case of elevated liver function tests, please refer to Appendix I 3.2 for enhanced monitoring and management procedures.

CCI

[h] For patients who cross-over based on confirmed objective disease progression during the initial randomised treatment period (including patients who have already crossed over based on confirmed PD prior to CSP Version 3.0), 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 after study unblinding and who have not objectively progressed during the initial randomised treatment period. Patients who cross-over after study unblinding, who have no objective progression during initial randomisation period, and who discontinue study intervention 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. At the same time points, vital signs, ECGs and plasma samples for ctDNA will be collected. Serious adverse events considered related to study intervention and/or study procedures will be collected throughout progression follow-up.

[i] Patients who cross-over must not receive any other anti-cancer therapies between the assessment of PD and the addition of osimertinib. Savolitinib treatment should continue uninterrupted during this period.

[j] Patients will be contacted for survival follow-up Q12W. Patients should be contacted in the week after data cut-off for each study analysis to establish survival status. Serious adverse events considered related to study intervention will be collected throughout survival follow-up.

Note: For patients continuing in the study after final DCO, refer to Section 6.7 for required activities.

AE = Adverse event; CSP = Clinical Study Protocol; ctDNA = Circulating tumour DNA; ECG = Electrocardiogram; ECHO = Echocardiogram; ECOG = Eastern Cooperative Oncology Group; EGFR = Epidermal growth factor receptor; MUGA = Multi-gated acquisition; NA = Not applicable; PD = Progressive disease; PK = Pharmacokinetics; Q6/8/12W = Every 6/8/12 weeks; RECIST = Response Evaluation Criteria in Solid Tumours; WHO = World Health Organization; WOCBP = Women of childbearing potential.

2 INTRODUCTION

Lung cancer has been the most common cancer in the world for several decades, and by 2018, there were an estimated 2.1 million new cases, representing 11.6% of all new cancers. It was also the most common cause of death from cancer, with 1.76 million deaths (18.4% of the total; GLOBOCAN 2018). Non-small cell lung cancer represents approximately 80% to 85% of all lung cancers. Unfortunately, at the time of diagnosis approximately 70% of patients with NSCLC already have advanced or metastatic disease not amenable to surgical resection. Furthermore, a significant percentage of patients with early stage NSCLC who have undergone surgery subsequently develop distant recurrence and die as a result of their lung cancer (Pisters and Le Chevalier 2005).

In current clinical practice, therapeutic decisions for patients with advanced NSCLC are informed by the molecular subtypes of the tumour (Keedy et al 2011; Travis et al 2011; Leighl and Curigliano 2014; Reck et al 2014; Soria et al 2015; National Comprehensive Cancer Network [NCCN 2020]). Epidermal growth factor receptor mutation and anaplastic lymphoma kinase rearrangement are the most well-known genetic alterations in NSCLC. Epidermal growth factor receptor-TKIs are the established first-line therapy in patients with NSCLC possessing EGFRm+ (Reck et al 2014; Masters et al 2015; NCCN 2020). The presence of EGFRm in patients with NSCLC tumours confers sensitivity to the EGFR-TKI class of drugs in a high percentage of patients, however, the response to this class of agents is eventually lost due to development of a variety of resistance mechanisms, with the EGFR T790M mutation being a major route of development of resistance to this class of therapy. In addition to the development of T790M mutations, other routes of acquired resistance to EGFR-TKI therapy include activation of a bypass signalling pathway (such as MET amplification, human epidermal growth factor receptor 2 upregulation or reticular activating system mutations), histological transformation to small cell lung cancer and epithelial mesenchymal transition (Ohashi et al 2012; Chong and Jänne 2013; Camidge et al 2014).

Treatment following progression on EGFR-TKI therapy will be guided by patient performance status, symptoms, molecular aberration and extent of disease. In patients able to tolerate doublet chemotherapy and who are T790M-negative, or if osimertinib is unavailable, platinum-based chemotherapy would most often be the preferred second-line treatment (NCCN 2020). There is no global standard of care for later lines of therapy; following progression on an EGFR-TKI or doublet chemotherapy, the only remaining options are rechallenge with EGFR-TKI or salvage single-agent chemotherapy or clinical studies (Langer et al 2013). Platinum-based chemotherapy post EGFR-TKI for EGFRm+ NSCLC generally provides response rates in the range of 20% to 30% (Gridelli et al 2012; Soria et al 2015), and the PFS is relatively short (median PFS approximately 3 to 6 months). These data together with the toxicity burden associated with doublet chemotherapy (including nausea, vomiting, bone marrow suppression resulting in risk of infection and bleeding,

alopecia, fatigue and peripheral neuropathy) supports an unmet medical need in this patient population.

Osimertinib (TAGRISSO™, AZD9291) is a potent and specific irreversible dual inhibitor of both the sensitising EGFR mutations and the T790M resistance mutation with margin against EGFR wild type (Cross et al 2014; Ballard et al 2016). Based on recent data (Becker et al 2011; Langer et al 2013; Mok et al 2016) and FDA approval, the NCCN recommends osimertinib as a first-line treatment in patients with metastatic EGFR positive NSCLC with EGFR exon 19 deletions or exon 21 L858R mutations in tumour specimens and as subsequent therapy for patients with metastatic EGFR T790M mutation positive NSCLC who have progressed on EGFR-TKI therapy (NCCN 2020). Evidence from the AURA Phase I/II study (NCT01802632) of osimertinib in advanced NSCLC patients with PD following prior EGFR-TKI therapy, suggests that patients with T790M negative tumour status may also derive benefit from osimertinib (Jänne et al 2015). In this study, 69 pre-treated patients with T790M-negative status by central testing, received osimertinib with an ORR of 25% (95% CI: 15, 37) and disease control rate of 64% (95% CI: 51, 75). Subsequently, the Phase III study, FLAURA (NCT02296125), conducted in untreated EGFRm+ advanced NSCLC patients, has demonstrated a significantly longer PFS with osimertinib versus standard EGFR-TKIs (gefitinib or erlotinib; 18.9 months vs 10.2 months; HR 0.46; 95% CI 0.37 to 0.57; $p < 0.001$; Soria et al 2018).

Up to 22% of patients with NSCLC who progress on first or second generation EGFR-TKIs have MET amplification or other MET-based mechanisms of resistance (Bean et al 2007; Engelman et al 2007; Sequist et al 2011). Using tissue biopsy, MET amplification is commonly found after acquired resistance to osimertinib (Piotrowska et al 2017). Moreover, in a subgroup of the AURA patients who were treatment naïve and provided post-progression plasma samples ($n = 38$), no evidence of acquired EGFR T790M mutation was found. Nine of 19 patients had putative resistance mechanisms, including amplification of MET in one patient (Ramalingam et al 2018).

The MET pathway is one of the most frequently dysregulated pathways in human cancer. Receptor activation leads to the recruitment and activation of specific downstream signalling partners that participate in the regulation of diverse processes such as tumour cell growth, migration, scattering and metastasis. In endothelial cells and stroma cells around tumour tissue, HGF/MET works as a proangiogenesis factor to stimulate endothelial cell proliferation, migration and survival, which can cause angiogenesis and support tumour expansion and progression. Hepatocyte growth factor and MET expression have been observed in tumour biopsies of most solid tumours, and MET signalling has been documented in a wide range of human malignancies, including bladder, breast, cervical, colorectal, gastric, head and neck, liver, lung, ovarian, pancreatic, prostrate, renal and thyroid cancers, as well as in various sarcomas, haematopoietic malignancies and melanoma. Activating mutations in the tyrosine

kinase domain of MET have been positively identified in patients with a hereditary form of papillary renal cancer, directly implicating MET in human tumourigenesis (Eder et al 2009). In several clinical studies, aberrant MET overexpression has been correlated with poor clinical outcome, with rapid PD and short survival (Park et al 2012). Overexpression of MET and HGF are also thought to result in resistance of tumour cells to chemotherapy and radiotherapy, correlating with development of distant metastases and shorter metastasis-free survival (Schmidt et al 1997).

Savolitinib (international non-proprietary name; AZD6094, HMPL-504, volitinib [Chinese accepted name]) is a potent and highly selective MET kinase inhibitor (Jia et al 2014), which has demonstrated anti-tumour activity in MET driven papillary renal cell carcinoma (Choueiri et al 2017). Savolitinib has also shown activity in non-clinical studies of MET amplified NSCLC (Henry et al 2016).

The combination of savolitinib plus osimertinib in the ongoing TATTON study (NCT02143466) is exploring how to overcome MET-amplification against tumours that have developed resistance to EGFR-TKI agents in NSCLC or delay the development of subsequent resistance via these alternative routes. In the TATTON study, savolitinib plus osimertinib had an acceptable risk-benefit profile and demonstrated evidence of anti-tumour activity in patients with EGFRm+ NSCLC (Oxnard et al 2020; Sequist et al 2020). Recruitment is ongoing in the following studies:

- The Phase II SAVANNAH study (NCT03778229), which is assessing the efficacy of osimertinib in the combination with savolitinib in patients with EGFRm+ and MET amplification/high-expression NSCLC following prior osimertinib.
- The Phase II ORCHARD study (NCT03944772), which is assessing the efficacy of multiple study interventions including the combination of savolitinib and osimertinib in patients with EGFRm+ advanced NSCLC with evidence of radiological progression following first-line osimertinib therapy.

A summary of combination data is provided in the savolitinib IB.

2.1 Study Rationale

One of the major mechanisms for resistance to EGFR-TKIs is amplification of the MET receptor tyrosine kinase, which activates downstream intracellular signalling independent of EGFR. This study will explore the individual contribution of savolitinib to MET-mediated osimertinib resistance.

This study will analyse the individual contribution of savolitinib to the combination by investigating the efficacy of the combination versus savolitinib plus placebo in patients with EGFRm+ and MET amplified, locally advanced or metastatic NSCLC who have progressed

following treatment with osimertinib.

The rationale for the design of the study is presented in Section 4.2.

2.2 Background

Refer to Section 2.

A detailed description of the chemistry, pharmacology, efficacy, and safety of savolitinib and osimertinib is provided in their respective IBs.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of savolitinib and osimertinib may be found in their respective IBs.

2.3.1 Risk Assessment

Investigators for a study using savolitinib monotherapy in patients with EGFRm+ NSCLC will be cognisant of the potential risk of rapid disease progression via EGFRm tumour driver reactivation. The NCCN Guidelines for NSCLC (NCCN 2020) include a warning about the risk of flare phenomenon occurring in patients who discontinue EGFR-TKI. Tumour flare after discontinuation of EGFR-TKI has been a recognised phenomenon for many years (Chaft et al 2011; Chen et al 2013) and indicates that the EGFRm sensitising mutation is not eliminated from the tumour following treatment with an EGFR-TKI in most patients. In some patients, this may cause a rapid clinical deterioration after discontinuing EGFR-TKI prior to entering the study (see Section 4.2.1). To minimise this risk, patients will be closely monitored over the first month of participation in the study to look for evidence of tumour flare. At investigator-assessed 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. Patients will be informed of the possibility of cross-over to savolitinib plus osimertinib during the informed consent process and at the time of progression on randomised treatment. Further risks and the respective mitigation steps are presented in Table 3.

Table 3 Risk Assessment

Potential risk of clinical significance	Summary of data/rational for risk	Mitigation strategy
Study intervention: osimertinib [a]		
Interstitial lung disease	Interstitial lung disease or ILD-like adverse reactions were reported in 3.9% of patients in the osimertinib pivotal clinical studies dataset, with 1.1% of these being severe (CTCAE Grade 3 or 4) and 0.4% resulted in a fatal outcome.	Patients with past or clinically active ILD will be excluded. Specific guidance on dose modification to manage new or worsening pulmonary symptoms is included in this CSP. See Section 5.2 and Appendix I 2.1
QTc interval prolongation	In the osimertinib clinical studies dataset 0.9% of patients were reported to have a QTc greater than 500 msec and 3.6% of patients had an increase from baseline QTc greater than 60 msec.	Patients with cardiac diseases and restriction of drugs known to prolong QT interval will be excluded. Regular cardiac monitoring through ECGs has also been included in the SoAs. Specific guidance on dose modification in the event of QTc interval prolongation has been included in this CSP. See Table 1, Table 2, Sections 5.2 and 6.5, and Appendix I 1.1
Keratitis	In the osimertinib clinical studies dataset 0.7% of patients were reported to have signs or symptoms suggestive of keratitis.	Physical examinations, which include assessments of the patient's eyes will be completed at every visit. Patients presenting with signs or symptoms suggestive of keratitis will be promptly referred to an ophthalmologist. See Section 8.2.1 and Appendix I 2.2
Erythema multiforme and Stevens-Johnson syndrome	Case reports of EM and SJS have been uncommonly and rarely reported, respectively, in association with osimertinib treatment.	Before initiating treatment, patients will be advised of the signs and symptoms of EM and SJS. Physical examinations, which include assessments of the patient's skin will be completed at every visit. Specific guidance on dose modification in the event of the EM or SJS has been included in this CSP. See Section 8.2.1 and Appendix I 1.1
Changes in cardiac contractility	Left ventricular ejection fraction decreases ≥ 10 percentage points and a drop to less than 50% occurred in 3.9% of patients who had baseline and at least 1 follow-up LVEF assessment (N = 908).	Patients with cardiac diseases will be excluded. Regular cardiac monitoring through ECHO/MUGA scans has also been included in the SoAs. Specific guidance on dose modification in the event of changes in cardiac contractility has been included in this CSP. See Table 1, Table 2, Section 5.2 and Appendix I 2.3

Table 3 Risk Assessment

Potential risk of clinical significance	Summary of data/rational for risk	Mitigation strategy
Study intervention: savolitinib [b]		
Hepatotoxicity	Hepatotoxicity (AEs within standardised MedDRA query of Drug-induced hepatic disorders): was reported in 35.0% of patients, of which 4.8% were reported as serious. In total, 11.5% of patients had an AE of hepatotoxicity CTCAE Grade ≥ 3.	Patients with increased liver enzymes will be excluded. Restrictions on the use of concomitant medications that are known to effect the liver, ie, paracetamol/acetaminophen and statins have also been included. Regular LFTs and specific guidance on dose modification in the event of hepatotoxicity have been included in this CSP. See Table 1, Table 2, Sections 5.1, 5.2, and 6.5 and Appendix I 3.2
SJS	A cumulative search in the AstraZeneca's global Patient Safety database for savolitinib using the preferred terms of SJS, toxic epidermal necrolysis and EM retrieved 1 case of SJS.	Patients who show symptoms or signs suggesting emerging SJS while on study treatment (eg, progressive skin rash often with blisters or mucosal lesions), must discontinue savolitinib immediately and receive appropriate treatment. If emerging SJS is suspected, re-challenge with savolitinib must be avoided. See Section 8.2.1 and Appendix I 3.3
Hypersensitivity	Cumulatively to date, 22 SAEs of drug hypersensitivity have been received, including anaphylaxis, of which 17 occurred in Study D5160C00006 (TATTON), which studied the combination of osimertinib and savolitinib.	Specific guidance for the management of hypersensitivity has been included in the CSP. CCI [redacted] See Appendix I 3.3
QTc prolongation	Electrocardiogram QT prolonged was reported as an AE in 1.2% of patients in the savolitinib clinical database.	See above for mitigation strategy. See Table 1, Table 2, Sections 5.2 and 6.5, and Appendix I 3.3

Table 3 Risk Assessment

Potential risk of clinical significance	Summary of data/rational for risk	Mitigation strategy
Study procedures		
Biopsies	Risks from biopsies include pain, bleeding, infection and accidental injury to nearby tissues. There is also a risk associated when anaesthetic is required.	New biopsies should only be taken specifically for Pre-screening for this study where the expected risk of an AE related to the procedure is < 2%. High-risk sites such as the brain and pancreas should be avoided. See Table 1, and Section 8.6

[a] Incidences of AEs reported for osimertinib are from the osimertinib pivotal clinical studies dataset, which is comprised of 1142 patients who received osimertinib monotherapy for NSCLC in AURA (Study D5160C00001) and FLAURA (Study D5160C00007) and includes data up to the DCO of 12 November 2019.

[b] Incidences of AEs reported for savolitinib are from the clinical database, which includes 643 patients from Studies D5081C00001, D5081C00002, D5082C00002, D5081C00003, D5160C00006, D5081C00004, D5080C00001, D5084C00001 and D5081C00013 and includes data up to the DCO of 26 February 2019.

AE = Adverse events; CTCAE = Common Terminology Criteria for Adverse Events; CSP = Clinical study protocol; DCO = Data cut-off; ECG = Electrocardiogram; ECHO = Echocardiogram; EM = Erythema multiforme; CCI [redacted] ILD = Interstitial lung disease; LFT = Liver function test; LVEF = Left ventricular ejection fraction; MedDRA = Medical Dictionary for Regulatory Activities; MUGA = Multi-gated acquisition; NSCLC = Non-small cell lung cancer; QTc = corrected QT interval; SAE = Serious adverse events; SoAs = Schedule of activities; SJS = Stevens-Johnson syndrome.

2.3.2 Benefit Assessment

Savolitinib has the potential to be active against a wide range of tumour types and is currently being assessed in Phase I, II and III of clinical development for solid tumours (including NSCLC) as monotherapy or in combination therapy with osimertinib.

Osimertinib has an established efficacy profile with proven effectiveness in adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC whose disease has progressed on or after EGFR-TKI therapy and as a first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutation. In addition, osimertinib has a well-established safety profile that is similar in both populations.

AstraZeneca believes the investigation of savolitinib and osimertinib in patients with advanced NSCLC appears acceptable based upon: the non-clinical safety profile, the emerging clinical safety profile, the risk minimisation and AE management proposals, early evidence of activity in patients with advanced cancer, the limited life expectancy due to malignant disease, the lack of effective alternative treatments, and the strength of the scientific hypothesis under evaluation.

In addition to the potential benefits from study intervention, patients will also benefit from access to medical care with regular disease assessments.

2.3.3 Overall Benefit: Risk Conclusion

Overall the benefit/risk assessment supports the further investigation of savolitinib and osimertinib in patients with locally advanced or metastatic NSCLC based upon: the non-clinical safety profile, the emerging clinical safety profile, the risk minimisation, including close monitoring for tumour flare over the first month on study, AE management proposals, the study design, the limited life expectancy due to malignant disease, the lack of effective alternative treatments, the strength of the scientific hypothesis under evaluation, and the safety and efficacy data from TATTON.

3 OBJECTIVES AND ENDPOINTS

Table 4 Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the ORR of savolitinib in combination with osimertinib versus savolitinib in combination with placebo in patients with EGFRm+, MET amplified locally advanced or metastatic NSCLC who have progressed on previous osimertinib therapy	Objective response rate is defined as the proportion of patients with measurable disease who have a CR or PR as determined by the investigator at the local site per RECIST 1.1.
Secondary	
To determine the efficacy of savolitinib in combination with osimertinib versus savolitinib in combination with placebo in patients with EGFRm+, MET amplified locally advanced or metastatic NSCLC who have progressed on previous osimertinib therapy	• Progression-free survival is defined as time from randomisation until progression per RECIST 1.1 as assessed by the investigator or death due to any cause. • Duration of response is defined as the time from the date of first documented response until date of documented progression per RECIST 1.1 as assessed by the investigator or death in the absence of disease progression. • Tumour size assessment is defined as the percentage change from baseline in TLs at 12 weeks per RECIST 1.1 as assessed by the investigator. • Overall survival is defined as time from randomisation until the date of death due to any cause.
To evaluate the efficacy of savolitinib plus osimertinib in patients who cross-over after progression on savolitinib plus placebo [a]	• Objective response rate is defined as the proportion of patients with measurable disease who have a CR or PR as determined by the investigator at the local site per RECIST 1.1. • Progression-free survival is defined as time from the first dose in the cross-over period until progression per RECIST 1.1 as assessed by the investigator or death due to any cause. • Duration of response is defined as the time from the date of first documented response during the cross-over period until date of documented progression per RECIST 1.1 as assessed by the investigator or death in the absence of disease progression. • Tumour size assessment is defined as the percentage change from baseline in TLs at 12 weeks per RECIST 1.1 as assessed by the investigator.
To evaluate the PK of savolitinib and osimertinib.	Plasma concentrations of savolitinib, osimertinib, and their metabolites.

Table 4 Objectives and Endpoints

Objectives	Endpoints
To determine the prevalence of ctDNA clearance after savolitinib plus osimertinib or savolitinib plus placebo 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	
To evaluate the safety and tolerability of savolitinib plus osimertinib or savolitinib plus placebo.	Safety and tolerability will be evaluated in terms of AEs, SAEs and discontinuation rate due to AEs. Clinical chemistry/haematology including LFTs. ECHOs, ECGs and vital signs including blood pressure and heart rate.
Tertiary/Exploratory	
CCI	

[a] Baseline for ORR, PFS, DoR and tumour size assessments of patients who cross-over to savolitinib plus osimertinib from savolitinib plus placebo will be the progression scan on savolitinib plus placebo acquired within 28 days of the start of treatment in the cross-over period.

CCI

AE = Adverse event; CR = Complete response; CCI ctDNA = Circulating tumour DNA; DoR = Duration of response; ECG = Electrocardiogram; ECHO = Echocardiogram; EGFR = Epidermal growth factor; EGFRm+ = Epidermal growth factor receptor mutation positive; CCI LFT = Liver function test; MET = Hepatocyte growth factor receptor; NSCLC = Non-small cell lung cancer; ORR = Objective response rate; CCI PFS = Progression-free survival; PK = Pharmacokinetics; PR = Partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SAE = Serious adverse events; TL = Target lesion.

4 STUDY DESIGN

4.1 Overall Design

This is a multi-centre, Phase II, double-blind, randomised study designed to determine the efficacy of savolitinib administered orally in combination with osimertinib versus savolitinib in combination with placebo in patients with EGFRm+, MET amplified, locally advanced or metastatic NSCLC who have progressed on previous osimertinib treatment.

For an overview of the study design see Figure 1 and Section 1.3. For details on treatments given during the study, see Section 6.1.

For details on what is included in the efficacy and safety endpoints, see Section 3.

4.1.1 Randomised Study Design

Prior to CSP V3.0, approximately 56 patients were planned to be randomised in a ratio of 1:1 to receive treatment with CCI savolitinib CCI plus CCI osimertinib CCI or CCI savolitinib CCI plus placebo. At least half of the patients randomised into the study will be second-line patients who were treated with osimertinib as first-line therapy. Randomisation will be stratified according to the number of prior lines of therapy (ie, osimertinib monotherapy as first line or ≥ second line [which includes patients who received osimertinib monotherapy before or after chemotherapy]).

Prospective testing of tumour specimens to determine MET amplification by central FISH using tumour specimens collected after progression on prior treatment with osimertinib should be performed at Pre-screening in advance of Screening for the main study. Patients determined to be MET amplified in Pre-screening will undergo screening during the 28 days prior to randomisation to confirm eligibility (Sections 5.1 and 5.2).

Provision of a FFPE tumour specimen is mandatory (refer to the Laboratory Manual for detailed specimen requirements). This will be used for prospective analysis of MET amplification by FISH.

Patients will continue to receive study medication CCI in 28-day cycles until objective PD by RECIST 1.1 is assessed, unacceptable toxicity occurs, consent is withdrawn or another discontinuation criteria is met (Section 7). At the time of investigator assessment per RECIST 1.1 of PD, the randomisation blind can be broken and patients who were initially randomised to the savolitinib plus placebo arm will be given the opportunity to cross-over (see Sections 4.1.2 and 6.3). Patients originally randomised to savolitinib plus osimertinib may continue to receive treatment with savolitinib plus osimertinib or osimertinib monotherapy (if savolitinib was stopped earlier) beyond RECIST 1.1 defined PD as long as they continue to receive clinical benefit, in the opinion of the investigator, and do not meet any of the

discontinuation criteria. No other anti-cancer agent is permitted in combination with osimertinib within this study. Patients can continue on savolitinib monotherapy (if randomised to the savolitinib plus placebo arm or if osimertinib was stopped earlier) until objective PD by RECIST 1.1 is assessed. Savolitinib monotherapy post-progression is not permitted.

Prior to CSP V3.0, a non-comparative interim futility analysis for the savolitinib plus placebo arm was planned to occur after 20 patients overall (10 per arm) had the opportunity of being treated for 2 RECIST post-baseline scans (12 weeks; Section 9.5). Recruitment was to continue during this interim futility analysis. The primary analysis was planned to occur 6 months after the last patient had been randomised. The final analysis was planned to be performed after the earlier of 18 months after the last patient was randomised or when 70% of the patients had progressed or died due to any cause.

Under CSP V3.0, as a result of AstraZeneca's decision to terminate study recruitment early, the planned number of randomised patients will not be met, and the planned interim futility analysis and primary analysis will not be performed. Alternatively, an early review of the data by AstraZeneca will occur following the early termination of study recruitment. The final analysis will be performed following the final DCO, which will take place 9 months after the last patient has been randomised. CCI [redacted]

4.1.2 Cross-over Study Design

Patients randomised to the savolitinib plus placebo arm may cross-over to open-label savolitinib plus osimertinib following investigator-assessment of PD per RECIST 1.1 to ensure that all patients enrolled may have the opportunity to receive the combination of savolitinib plus osimertinib. Patients will be informed of the possibility of cross-over to savolitinib plus osimertinib during the informed consent process and at the time of progression on randomised treatment. A separate ICF for cross-over patients must be signed prior to starting cross-over treatment.

Patients who cross-over must not receive any other anti-cancer therapies between the assessment of PD and the addition of osimertinib. Savolitinib treatment should continue uninterrupted during this period. Patients should be crossed over as soon as possible after the assessment of PD and within 28 days of their progression scan.

Patients who cross-over will receive study medication CCI [redacted] in 28-day cycles until occurrence of investigator-assessed objective PD, unacceptable toxicity occurs, consent is withdrawn or another discontinuation criteria is met. As in the randomised part of the study, patients may continue to receive treatment with osimertinib plus savolitinib or osimertinib monotherapy (if savolitinib is stopped during cross-over because of savolitinib-related toxicity) beyond RECIST 1.1 defined PD as long as they continue to receive clinical benefit, in the opinion of the investigator, and do not meet any of the discontinuation criteria. No other

anti-cancer agent is permitted in combination with osimertinib within this study.

Prior to CSP V3.0, if after the planned interim futility analysis (see Section 9.5) the study was declared futile and a recommendation to stop the study was made by the IDMC, there was to be a database lock, followed by the usual end of study reporting activities.

Under CSP V3.0, as a result of AstraZeneca's decision to terminate study recruitment early, the planned interim futility analysis will not be performed and there will be no requirement for data review by the IDMC. Alternatively, an initial DCO will occur following the early termination of study recruitment to allow an early review of the data by AstraZeneca. The study will be unblinded after completion of data cleaning activities on the initial DCO data, and patients on savolitinib monotherapy (savolitinib plus placebo) will be given the opportunity to cross-over to the savolitinib plus osimertinib arm. If it is decided that a patient will switch to savolitinib plus osimertinib before final database lock, then they will follow the scheduled procedures described in Table 2. Patients may otherwise choose to remain on savolitinib monotherapy (as long as, in the opinion of the investigator, they are still receiving clinical benefit and have not reported PD). All patients will be followed until the final analysis. All decisions regarding the evaluability of the data from each individual patient will be made and documented, before the study is unblinded. Any patients remaining on savolitinib plus placebo arm at the time of final database lock, will be contacted and offered the switch to the savolitinib plus osimertinib arm.

4.1.3 End of Study Design

For patients who continue to receive treatment beyond the time of the DCO for the final analysis, investigators will continue to report all SAEs to AstraZeneca Patient Safety until the end of the follow-up period, post-treatment discontinuation, in accordance with Section 8.3.10 (Reporting of SAEs). If an investigator learns of any SAEs, including death, at any time after a patient has completed the study, and he/she considers there is a reasonable possibility that the event is causally related to the one or more of the products used in this study, the investigator should notify AstraZeneca, Patient Safety. Additionally as stated in Section 8.3.2 (Follow-up of AEs and SAEs), any SAE or non-serious AE that is ongoing at the time of the final DCO, must be followed up by the investigator for as long as medically indicated.

4.1.4 Early Study Recruitment Termination

On 22 February 2022, AstraZeneca made the decision to terminate study recruitment. This was based on programme development strategy considerations, because the design of the contribution of component study is no longer supportive of the savolitinib development programme in this study population. The contribution of component of savolitinib monotherapy (savolitinib plus placebo to osimertinib) versus savolitinib in combination with osimertinib will continue to be assessed in the ongoing SAVANNAH study. Following early termination of study recruitment, an initial DCO will occur to allow an early review of the

data by AstraZeneca. The study will be unblinded after completion of data cleaning activities on the initial DCO data, and patients on savolitinib monotherapy (savolitinib plus placebo) will be given the opportunity to cross-over to the savolitinib plus osimertinib arm. Patients may otherwise choose to remain on savolitinib monotherapy (as long as, in the opinion of the investigator, they are still receiving clinical benefit and have not reported PD). All patients will be followed until the final analysis. Patients already in pre-screening/screening (who have signed the pre-screening/main ICF) at the time of study recruitment termination will have the option to be randomised if eligible. The final DCO will occur 9 months after the last patient has been randomised. Following the final database lock, any patients who are still on the savolitinib plus placebo arm will be given the opportunity to cross-over to the savolitinib plus osimertinib arm. Randomised patients may continue to receive their assigned treatment for as long as they are deriving clinical benefit, or until they meet any discontinuation criteria, and will be monitored according to routine clinical practice as defined by the investigator. For the definition of the end of the study please see Section 4.4. For access to study intervention after the end of the study please see Section 6.7.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Study Design

The expansion cohort Part B of the TATTON study demonstrated anti-tumour activity of osimertinib in combination with savolitinib (ORR 30%, 95% CI: 20, 43) in MET amplified NSCLC patients (confirmed centrally by FISH; MET gene copy ≥ 5 or MET/CEP7 ratio ≥ 2) who were treated with prior 3rd generation T790M-directed EGFR-TKI (Sequist et al 2020).

This Phase II study has been designed to analyse the individual contribution of savolitinib to the efficacy seen with the combination by assessment of ORR in patients with EGFRm+ and MET amplified, locally advanced or metastatic NSCLC who have progressed following treatment with osimertinib. This study will enrol patients who have received up to 3 lines of prior therapy, which must include osimertinib but could also include other EGFR-TKIs, chemotherapy or chemotherapy in combination with an immuno-oncologic agent.

Around 5% to 22% of patients who receive a 3rd generation EGFR-TKI develop MET amplification (Bean et al 2007; Engelman et al 2007; Sequist et al 2011; Ramalingam et al 2018). Hepatocyte growth factor receptor amplification provides a by-pass mechanism of resistance to EGFR-TKIs activating the phosphoinositide 3-kinase pathway. However, simply targeting the emergent MET amplification without maintaining control of the EGFR sensitising mutation has been demonstrated to be inadequate to suppress tumour growth inhibition in non-clinical models (Engelman et al 2007). In order to overcome resistance to EGFR-TKI, the EGFR must still be inhibited, and EGFR inhibition is required to maintain remission. Furthermore, literature data demonstrate that for cancers that start to progress on EGFR-TKIs, discontinuation of the EGFR-TKI can lead to an acceleration of PD

(Chaft et al 2011; Chen et al 2013). This further supports evidence that the EGFR mutation is not eliminated from the tumour following treatment with an EGFR-TKI and is capable in some patients to cause a rapid clinical deterioration once the EGFR blockade is removed. The NCCN Guidelines for NSCLC, V3.2020 include a warning about the risk of flare phenomenon occurring in patients who discontinue EGFR-TKI (NCCN 2020). Thus, continuing EGFR-TKI is beneficial in many patients even after cancer regrowth on EGFR-TKI. However, the IMPRESS study demonstrated there was no clinical benefit in continuation of first generation EGFR tyrosine kinases beyond radiologic PD when chemotherapy is initiated (Mok et al 2017). A similar study has not been performed in the post-3rd generation EGFR TKI patient population.

In order to demonstrate the individual contribution of savolitinib in the treatment of patients with MET-driven resistance to osimertinib, a savolitinib plus placebo arm has been included in the study design. Patients will be randomised on a 1:1 basis to receive either savolitinib plus osimertinib or savolitinib plus placebo. To address clinical concern about the potential for tumour flare with the withdrawal of EGFR-TKI cover in an EGFRm driven indication, all patients will be closely monitored over the first month on study to look for evidence of tumour flare. To overcome the concerns that arise from the non-clinical and clinical evidence presented above, this study includes the option for patients randomised to the savolitinib plus placebo arm to cross-over to receive savolitinib in combination with osimertinib following objective PD by RECIST 1.1 assessment. This will ensure that all patients enrolled may have the opportunity to receive the combination of savolitinib plus osimertinib.

4.3 Justification for Dose

CCI

[redacted]

4.3.1 Rationale for Endpoints

Objective response rate, PFS, DoR and percentage change from baseline in tumour size assessed by RECIST 1.1 using investigator assessment and OS are standard measures of clinical activity and are used to assess efficacy in solid tumour clinical studies.

The TATTON data indicate encouraging anti-tumour activity in patients with centrally confirmed MET amplified tumour status. This study is designed to allow further assessment of response in patients confirmed as MET amplified by FISH for the primary endpoint.

In 2 Phase III studies (AURA3 and FLAURA), a correlation was observed between clearance of plasma EGFRm after 3/6 weeks of osimertinib monotherapy and a numerical improvement in PFS (Shepherd et al 2018; Zhou et al 2019). As such, prevalence of plasma ctDNA clearance after 6 weeks of therapy is a secondary objective of this study.

Standard safety parameters (discontinuation rate due to AEs/SAEs, vital signs, clinical chemistry/haematology parameters and ECGs) will be used to assess the safety and tolerability of savolitinib in combination with osimertinib. To evaluate the safety and tolerability of savolitinib in combination with osimertinib, the proportion of patients discontinuing due to any AE and the proportion of patients discontinuing due to AE of hypersensitivity/anaphylaxis may be assessed.

Standard PK parameters will be used to evaluate the PK of osimertinib and savolitinib when given in combination and savolitinib alone when administered in combination with placebo in this population.

CCI [redacted]

4.4 End of Study Definition

A patient is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the SoAs (Table 1 and Table 2).

The end of the study is defined as the date of the last visit of the last patient in the study.

5 STUDY POPULATION

Prospective approval of CSP deviations to recruitment and enrolment criteria, also known as CSP waivers or exemptions, is not permitted.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be enrolled on the study. Under no circumstances can there be exceptions to

this rule. Patients who do not meet the entry requirements are screen failures, refer to Section 5.4.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.2.

5.1 Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

Informed Consent

1 Capable of giving signed informed consent as described in Appendix A, which includes compliance with the requirements and restrictions listed in the ICF and in this CSP.

2 Provision of signed and dated written ICF prior to any mandatory study specific procedures, sampling and analyses.

Age

3 Patients must be ≥ 18 years of age at the time of signing the informed consent (≥ 20 years of age in Japan). All genders are permitted.

Type of Patient and Disease Characteristics

4 Histologically or cytologically confirmed locally advanced or metastatic EGFRm+ NSCLC harbouring an EGFR mutation known to be associated with EGFR-TKI sensitivity and that is permitted in the osimertinib national label (such as exon 19 deletion and/or L858R), which is not amenable to curative therapy.

5 Documented radiologic PD following treatment with osimertinib (osimertinib does not need to be the most recent therapy).

6 Have MET amplification as determined by central MET FISH testing on tumour specimen collected following progression on prior osimertinib treatment.

7 Available FFPE tumour specimen for central MET FISH analysis or willingness to collect an additional specimen for central testing, which fulfils the following requirements:

- Obtained following progression on previous osimertinib therapy.
- Obtained within 2 years of submission for MET analysis.
- Sufficient specimen to meet the minimum specimen requirement defined in the current Laboratory Manual.

8 At least one 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 CT or MRI, which is suitable for accurate repeated measurements. If only one 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 specimen collection is performed.

9 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.
- No more than one prior line of chemotherapy regimen is acceptable.
- A chemotherapy regimen including a programmed cell death-1 or a programmed cell death ligand-1 agent is acceptable, provided it was not the most recent line of therapy.
- No more than 2 prior lines of therapy containing EGFR-TKI are acceptable.

10 Adequate haematological function defined as:
- Absolute neutrophil count ≥ 1500/μL
- Haemoglobin ≥ 9 g/dL (no transfusion in the past 2 weeks)
- Platelets ≥ 100000/μL (no transfusion in the past 10 days)

11 Adequate liver function defined as:
- ALT and AST ≤ 2.5 × the ULN with TBL ≤ ULN

  OR
- TBL > ULN to ≤ 1.5 × ULN with ALT and AST ≤ ULN

12 Adequate renal function defined as a creatinine < 1.5 times the institutional ULN OR a glomerular filtration rate ≥ 50 mL/min, as assessed using the standard methodology at the investigating centre (eg, Cockcroft-Gault, Modification of Diet in Renal Disease or Chronic Kidney Disease Epidemiology Collaboration formulae, ethylenediaminetetraacetic acid clearance or 24-hour urine collection). Confirmation of creatinine clearance is only required when creatinine is > 1.5 times ULN.

13 Adequate coagulation parameters, defined as INR < 1.5 × ULN and activated partial thromboplastin time < 1.5 × ULN unless patients are receiving therapeutic anti-coagulation which affects these parameters. Use of warfarin is not permitted in this study, but LMWH is allowed (Appendix J).

14 Patients with known tumour thrombus or deep vein thrombosis are eligible if clinically stable on LMWH for ≥ 2 weeks.

15 Eastern Cooperative Oncology Group/WHO performance status of 0 or 1 with no deterioration over the previous 2 weeks and a minimum life expectancy of 12 weeks.

16 Ability to swallow and retain oral medications.

17 Willingness and ability to comply with study and follow-up procedures.

Reproduction

18 Females of childbearing potential should be willing to use adequate contraceptive measures, should not be breastfeeding, and must have a negative pregnancy test if of childbearing potential, or must have evidence of non-childbearing potential by fulfilling one of the following criteria at screening:

- Post-menopausal is defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments.
- Women under the age of 50 years would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with luteinizing hormone and follicle stimulating hormone levels in the post-menopausal range for the institution.
- Women with documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.

Further information is available in Appendix G (Definition of WOCBP and Acceptable Contraceptive Methods).

19 Male patients with a female partner of childbearing potential should be willing to use barrier contraception during the study and for 6 months following discontinuation of study intervention. Patients should refrain from donating sperm from the start of dosing until 6 months after discontinuing study intervention.

5.2 Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Medical Conditions

1 Unresolved toxicities from any prior therapy greater than CTCAE Grade 1 at the time of starting study intervention with the exception of alopecia, haemoglobin ≥ 9 g/dL and Grade 2, prior platinum-therapy related neuropathy.

2 As judged by the investigator, active gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of oral therapy (eg, ulcerative disease, uncontrolled nausea, vomiting, diarrhoea Grade ≥ 2, malabsorption syndrome or previous significant bowel resection).

3 Any of the following cardiac diseases currently or within the last 6 months:

- Unstable angina pectoris
- Congestive heart failure (NYHA Grade ≥ 2)
- Acute myocardial infarction
- Stroke or transient ischemic attack

- Uncontrolled hypertension (BP ≥ 150/95 mmHg despite medical therapy).
- Mean resting corrected 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, congenital or familial long QT syndrome, family history of unexplained sudden death under 40 years of age in first-degree relatives, any concomitant medication known to prolong the QT interval and cause Torsade de Pointes, chronic hypokalaemia not correctable with supplements, or electrolyte abnormalities including:
  - Serum/plasma potassium < LLN
  - Serum/plasma magnesium < LLN
  - Serum/plasma calcium < LLN
- 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

4 Wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) administered ≤ 28 days or limited field radiation for palliation ≤ 7 days prior to starting study intervention or has not recovered from side effects of such therapy.

5 Major surgical procedures ≤ 28 days of beginning study intervention or minor surgical procedures ≤ 7 days. No waiting is required following port-a-cath placement.

6 As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases, including renal transplant or active bleeding diatheses, which in the investigator's opinion makes it undesirable for the patient to enter the study or which would jeopardise compliance with the CSP.

7 Active HBV (positive HBsAg result) or HCV. Viral testing is not required for assessment of eligibility for the study. Patients with a past or resolved HBV or HCV infection are eligible if:

- Negative for HBsAg and positive for hepatitis B core antibody or
- Positive for HBsAg, but for > 6 months have had normal transaminases and HBV DNA levels between 0 and 2000 IU/mL (inactive carrier state) and willing to start and maintain antiviral treatment for at least the duration of the study.
- 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.

8 Known serious active infection including, but not limited to, tuberculosis, or HIV (positive HIV 1/2 antibodies). Testing is not required for assessment of eligibility for the study.

9 Presence of other active cancers, or history of treatment for invasive cancer, within the last 5 years. Patients with Stage I cancer who have received definitive local treatment at least 3 years previously, and are considered unlikely to recur are eligible. All patients with previously treated in situ carcinoma (ie, non-invasive) are eligible, as are patients with history of non-melanoma skin cancer.

10 Spinal cord compression or brain metastases unless asymptomatic, stable and not requiring steroids for at least 2 weeks prior to start of study intervention.

11 Past medical history of ILD, drug-induced ILD, radiation pneumonitis, which required steroid treatment, or any evidence of clinically active ILD.

Prior/Concomitant Therapy

12 Prior or current treatment with a 3rd generation EGFR-TKI other than osimertinib.

13 Prior or current treatment with savolitinib or another MET inhibitor (for example, foretinib, crizotinib, cabozantinib, onartuzumab, capmatinib).

14 Patients who have received ≥ 4 lines of systemic therapy for NSCLC are not eligible.

15 Any cytotoxic chemotherapy, investigational agents or other anti-cancer drugs for the treatment of advanced NSCLC from a previous treatment regimen or clinical study within 14 days prior to the first dose of study intervention with the exception of monotherapy osimertinib which may continue uninterrupted during screening.

16 Patients currently receiving (or unable to stop use prior to receiving the first dose of study intervention) medications or herbal supplements known to be strong inducers of CYP3A4 or strong inhibitors of CYP1A2, or CYP3A4 substrates which have a narrow therapeutic range within 2 weeks of the first dose of study intervention (3 weeks for St John's Wort) will be excluded. All patients must try to avoid concomitant use of any medications, herbal supplements and/or ingestion of foods with known inducer effects on CYP3A4 during the study and for 3 months later the last dose intake.

Prior/Concurrent Clinical Study Experience

17 Participation in another clinical study with a cytotoxic, investigational product, or other anti-cancer drug for the treatment of advanced NSCLC if received study intervention from that study within 14 days of the first dose of study intervention.

18 Known hypersensitivity to the active or inactive excipients of osimertinib or savolitinib or drugs with a similar chemical structure or class.

Other Exclusions

19 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

20 Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.

21 Previous enrolment in the present study.

22 For women only - currently pregnant (confirmed with positive pregnancy test) or breast-feeding.

23 Patients unable to provide the required number of samples for MET analysis.

CCI

[redacted]

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Savolitinib should be taken within 15 minutes after the start of a meal. Osimertinib can be taken with water, with or without food. Osimertinib and savolitinib can be taken together.

On PK days, patients should come to the clinic fasted (the patient should not eat but may drink beforehand) where they will be given a moderate breakfast before dosing (the same breakfast should be given on all PK days).

5.3.2 Pregnancy and Contraception

Women of childbearing potential

Females of childbearing potential should use reliable methods of contraception from the time of screening until 6 weeks after discontinuing study intervention. Acceptable methods of contraception include full abstinence, tubal ligation, combined oral, transdermal or intra vaginal hormonal contraceptives, medroxyprogesterone injections (eg, Depo-provera), copper-banded intra-uterine devices, hormone impregnated intra-uterine systems and vasectomised partners. All methods of contraception (with the exception of total abstinence) should be used in combination with the use of a condom by their male sexual partner for intercourse.

Males

Male patients must use a condom during sexual intercourse with a female partner of childbearing potential during the study and for 24 weeks after discontinuing study

intervention.

Male patients should refrain from donating sperm from the start of dosing until 24 weeks after discontinuing study intervention.

5.3.3 Other Lifestyle Restrictions

For savolitinib, during the study therapy and for 4 weeks after the last dose of study intervention patients should be advised to avoid prolonged exposure to the sun, wear protective clothing, a hat and seek shade from the sun as far as possible; in addition sun protection factor 30+ sunscreen should be used. Exposure to other sources of ultraviolet light including sun beds and tanning booths, etc, should be avoided.

Patients should not donate blood or blood products during the study.

5.4 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, MET status information, eligibility criteria, and any SAEs.

Individuals who do not initially meet the criteria for participation in this study (for example, due to logistical constraints or slow recovery of side effects from previous treatment; ie, screen failures) may be rescreened. Rescreened patients retain the same patient number as for the initial screening. However, rescreening assessments should be documented so that its effect on study results, if any, can be assessed.

These patients should have failed inclusion/exclusion criteria and the reason for study withdrawal recorded in the eCRF.

Pre-screen failures are defined as patients who signed the pre-screening ICF but are not confirmed as MET amplified by central laboratory testing If the patient is subsequently pre-screened again the same patient number as for the initial pre-screening will be retained.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study patient according to the CSP.

6.1 Study Interventions Administered

6.1.1 Investigational Products

Refer to Table 5 for information regarding the study interventions.

Table 5 Investigational Products

Intervention name	Savolitinib	Osimertinib/Placebo
Type	Drug	Drug/Placebo
Dose Formulation	Tablet	Tablet
Dosage level	CCI savolitinib (CCI tablets CCI)	CCI osimertinib/placebo (CCI tablet CCI) CCI osimertinib/placebo tablets are available if a dose reduction is required
Route of administration	Oral	Oral
Dosing instructions	Savolitinib will be taken CCI within 15 minutes after the start of a meal except for the day on which PK samples are taken when savolitinib will be taken within 15 minutes after a meal prepared by the clinic. CCI Doses should not be missed. If a patient misses taking a scheduled dose, within a window of 12 hours, it is acceptable to take the dose. If it is more than 12 hours after the scheduled dose time, the missed dose should not be taken, and patients should be instructed to take the next dose at the next scheduled time. If a patient vomits after taking their study intervention, they should not make up for this dose, but should take the dose at the next scheduled time.	Osimertinib will be administered CCI with or without food except for the day on which PK samples are taken when osimertinib will be taken after a meal prepared by the clinic. CCI Doses should not be missed. If a patient misses taking a scheduled dose, within a window of 12 hours, it is acceptable to take the dose. If it is more than 12 hours after the scheduled dose time, the missed dose should not be taken, and patients should be instructed to take the next dose at the next scheduled time. If a patient vomits after taking their study intervention, they should not make up for this dose, but should take the dose at the next scheduled time.
Sourcing	AstraZeneca	AstraZeneca
Packaging and labelling	CCI	CCI
Current/former names	CCI	CCI

CCI CCI PK = Pharmacokinetics.

6.2 Preparation/Handling/Storage/Accountability of Interventions

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only patients enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3 Measures to Minimise Bias: Randomisation and Blinding

Patient eligibility will be established before treatment randomisation. Once the eligibility of a patient has been confirmed, the investigator (or nominated assistant) should contact the IVRS/IWRS Centralised Randomisation Centre for allocation of randomised therapy.

All patients will be centrally assigned to randomised study intervention using an IVRS/IWRS. Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information and directions for the IWRS will be provided to each site. Patients will be randomised in a 1:1 ratio with stratification according to the number of prior lines of therapy (ie, osimertinib monotherapy as first line or ≥ second line [which includes patients who received osimertinib monotherapy as first line therapy followed by chemotherapy or osimertinib monotherapy after chemotherapy]). If a patient withdraws from the study, then his/her enrolment/randomisation code cannot be re-used. Withdrawn patients will not be replaced.

It is recommended that patients commence study intervention as soon as possible after randomisation, and ideally within 3 days. Patients will complete treatments as specified above or until disease progression is confirmed, unacceptable toxicity occurs, withdrawal of consent, or another discontinuation criterion is met.

The IVRS/IWRS will provide to the investigator(s) or pharmacists the kit identification number to be allocated to the patient at the dispensing visit. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

The randomisation code can be broken after investigator-assessed PD per RECIST 1.1. Patients initially randomised to the savolitinib plus placebo arm may then be offered the opportunity to cross-over to receive savolitinib in combination with osimertinib. Once the investigator has documented progression in the eCRF, and obtained approval for unblinding from the study physician, the treatment code for a patient may be obtained from the IWRS via a dedicated option they may select in this situation. In all other circumstances the randomisation code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to the patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Randomisation codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

The IVRS/IWRS will be programmed with blind-breaking instructions. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the patient's condition (eg, antidote available), the investigator has the sole responsibility for determining if unblinding of a patients' intervention assignment is warranted. Patient safety must always be the first consideration in making such a determination. If a patient's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to the patient to the AstraZeneca staff. Additionally, patients with investigator-assessed objective PD may be unblinded.

Prior to CSP V3.0, the AstraZeneca study team was to be unblinded at the time of the primary analysis. Under CSP V3.0, following the early termination of study recruitment, an initial DCO will occur to allow an early review of the data. The study will be unblinded after data cleaning activities on this initial DCO data have been completed.

The personnel analysing the PK samples will be unblinded to the investigational treatment for each patient.

Returned study intervention should not be re-dispensed to the patients.

6.4 Study Intervention Compliance

When patients self-administer study interventions at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by counting of returned tablets during the site visits and documented in the source documents and eCRF. Patients should return all unused medication and empty containers to the investigator.

Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of savolitinib and osimertinib/placebo tablets dispensed to and taken by each patient must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the patient is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

For patients continuing treatment with osimertinib during Screening, the date and time of administration of the last dose of osimertinib prior to Cycle 1 Day 1 (prior to PK sampling) should be recorded.

Medication other than that described in Appendix J, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

Guidance on medicines to avoid, medications that require close monitoring, and washout periods is provided in Appendix J and a list of medicines to avoid is kept up to date at the following: http://medicine.iupui.edu/clinpharm/ddis/main-table.

The use of medications listed in Table 6 is restricted, these medications are permitted with caution and careful monitoring of patients.

Table 6 Restricted Medications

Medication/class of drug	Usage (including limits for duration permitted and special situations in which it's allowed)
Statins	Discontinuation of statins is advised unless considered essential, in which case, the patients should be prescribed the lowest dose available and monitored for the effects of increased statin exposure.
Paracetamol	The administration of acetaminophen (paracetamol) to a patient is restricted to 3 g per day or the maximum dose approved locally (if less than 3 g/day) during the study.
Sensitive CYP2C8 substrates	Those drugs defined as sensitive CYP2C8 substrates (almost exclusively metabolised by CYP2C8, such as repaglinide and rosiglitazone) should be used with caution.
Drugs affected by P-glycoprotein	Drugs that are known to be affected by P-glycoprotein such as digoxin, quinidine, loperamide, ritonavir and saquinavir should be used with caution.
Metformin	Use with caution, monitor patients for the effect of increased metformin exposure.
Adefovir, lamivudine, and tenofovir	Use with caution, monitor patients for the effect of increased exposure.
Drugs whose disposition is dependent upon the BCRP	Patients taking concomitant medications whose disposition is dependent upon the BCRP and with a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving osimertinib. Patients taking rosuvastatin should have creatine phosphokinase levels monitored (due to BCRP-mediated increase in exposure). If the patient experiences any potentially relevant AEs suggestive of muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, rosuvastatin must be stopped and any appropriate further management should be taken.
Drugs prolonging QT interval	The concomitant administration of drugs known to prolong QT interval is restricted unless considered essential due to patient management, in which case, patients should be closely monitored with more frequent ECGs. Additional guidance on drugs known to prolong QT interval is provided in Appendix J. The following drugs are known to prolong QT interval or induce Torsades de Pointes and should not be combined with osimertinib: Clarithromycin, droperidol, erythromycin, procainamide, cisapride, disopyramide, dofetilide, domperidone, ibutilide, quinidine, sotalol, sparfloxacin, thioridazine, bepridil, chlorpromazine, halofantrine, haloperidol, mesoridazine, levomethadyl, methadone, pimozide, arsenic trioxide, pentamidine, amiodarone, chloroquine (Appendix J).

Table 6 Restricted Medications

Medication/class of drug	Usage (including limits for duration permitted and special situations in which it's allowed)
Drugs that may possibly prolong QT interval	The use of the following drugs is permitted (notwithstanding other exclusions and restrictions) provided the patient has been stable on therapy for the periods indicated: Alfuzosin, chloral hydrate, ciprofloxacin, dolasetron, foscarnet, galantamine, gemifloxacin, isridipine, ketoconazole, levofloxacin, mexiletine, nicardipine, octreotide, ofloxacin, ondansetron, quetiapine, ranolazine, telithromycin, tizanidine, vardenafil, venlafaxine, ziprasidone. Amantadine, amitriptyline, amoxapine, clozapine, doxepin, felbamate, flecainide, fluconazole, fosphenytoin, gatifloxacin, granisetron, imipramine, indapamide, lithium, moexipril/HCTZ, moxifloxacin, risperidone, roxithromycin, sertraline, trimethoprim-sulfa, trimipramine, voriconazole. Azithromycin, citalopram, clomipramine, itraconazole, nortriptyline, paroxetine, solifenacin, tacrolimus Fluoxetine, protriptyline, tamoxifen (Appendix J).

AE = Adverse event; BCRP = Breast cancer resistance protein; CYP = Cytochrome P450; ECG = Electrocardiogram.

6.5.1 Other Concomitant Treatment

Other medication other than that described above, including denosumab, corticosteroids and/or bisphosphonates for the treatment of bone metastases, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

Patients who have received prior treatment with IO therapies should be closely monitored for an appropriate period of time after the last dose of the IO treatment, in accordance with the respective IO label, as immune-mediated adverse reactions with the IO therapy may occur at any time during or after discontinuation of therapy. The stop date of the prior IO drug therapy should be captured in the eCRFs.

6.6 Dose Modification

Dose modifications of one or both agents are decided by the investigator (following discussion with AstraZeneca when needed) based on the type of AEs and the known adverse drug reactions for each drug. In case a dose reduction is necessary, the study interventions will be administered as follows:

Table 7 Dose Reduction for Savolitinib to Manage Adverse Events

Starting savolitinib dose	CCI
Reduced dose -1	CCI
Reduced dose -2	CCI

Note: Only 2 dose reductions of savolitinib are permitted.

Table 8 Dose Reduction for Osimertinib to Manage Adverse Events

Starting osimertinib dose	CCI
Reduced dose -1	CCI

For guidance on dose modifications for management of AEs for savolitinib and osimertinib, see Appendix I.

6.7 Intervention after the End of the Study

Patients receiving study intervention at the time of the final DCO will be able to continue to receive study intervention (ie, savolitinib plus osimertinib, savolitinib monotherapy, or osimertinib monotherapy [if savolitinib was stopped earlier]) as long as, in the opinion of the investigator, they are still receiving clinical benefit. Following the final DCO (9 months after the last patient has been randomised), the clinical study database will be closed to new data.

Patients who remain on study intervention after the final analysis will be monitored according to routine clinical practice as defined by the investigator. AstraZeneca will continue to supply study intervention after completion of this study while, in the opinion of the investigator, the patient is benefiting. In the event that product development reaches a point where alternative product supply options become available, then these alternative product supply options will be discussed by AstraZeneca with the investigator. AstraZeneca will work with the investigator to transition the patients to alternative supply, where possible.

Study intervention ongoing at the time of final analysis will be supplied to sites as per ongoing process. Placebo tablets will not be supplied after the final analysis but patients can continue on savolitinib monotherapy as long as, in the opinion of the investigator, they are still receiving clinical benefit and have not reported PD. Drug dispensation and reconciliation will be handled by site on each patient's visit. Paper form process will be used for SAE reporting, all SAEs, overdoses and pregnancies will be reported until 30 days after the last dose. The study will remain open until the last patient is treated. Last patient last visit will be defined as the last patient's treatment discontinuation.

In the event that a roll-over study is available at the time of the final DCO and database closure, patients currently receiving study treatment may be transitioned to such a study, and the current study participation would reach its end. The roll-over study would ensure treatment continuation with visits assessment per its protocol. Any patient that would be proposed to move to such study would be given a new ICF.

7 DISCONTINUATION OF STUDY INTERVENTION AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

It may be necessary for a patient to permanently discontinue (definitive discontinuation) study intervention. If study intervention is permanently discontinued, the patient will remain in the study to be evaluated for survival.

Patients may be discontinued from study intervention in the following situations. Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study.

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
- Adverse events.
- Severe non-compliance with the CSP.
- Disease progression as per RECIST 1.1; unless the patient is randomised to savolitinib plus placebo, when cross-over to savolitinib plus osimertinib may be permitted.

- Patients incorrectly initiated on study medication.
- Pregnancy.
- Specific stopping criteria, ie, ILD, acute anaphylaxis or QTcF interval prolongation with signs/symptoms of serious arrhythmia.

See the SoAs (Table 1 and Table 2) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Continuing on Monotherapy

If a patient discontinues osimertinib due to toxicity the patient may continue with savolitinib until progression.

If a patient discontinues savolitinib due to toxicity they may continue with osimertinib monotherapy until the Principal Investigator believes there is no further benefit (this may be beyond PD in the absence of clinical symptoms or signs indicating clinically significant PD; no decline in performance status; absence of rapid PD or threat to vital organs or critical anatomical sites [eg, central nervous system metastasis, respiratory failure due to tumour compression, spinal cord compression] requiring urgent alternative medical intervention; or no significant, unacceptable or irreversible toxicities related to study intervention), according to the SoAs (Table 1 and Table 2).

Following PD, patients may continue on osimertinib monotherapy and continue with all safety assessments as per the SoAs (Table 1 and Table 2). Savolitinib monotherapy (either if originally randomised to savolitinib plus placebo or after discontinuation of osimertinib if originally randomised to savolitinib plus osimertinib) post progression is not permitted.

7.1.1 Rechallenge

See guidance in Appendix I for circumstances under which a patient whose study intervention was temporarily interrupted due to an AE can restart treatment, and specifically additional precautions to be taken upon restarting savolitinib.

7.1.2 Procedures for Discontinuation of Study Intervention

The investigator should instruct the patient to contact the site before or at the time if any study intervention is stopped. A patient that decides to discontinue study intervention(s) will always be asked about the reason(s) and the presence of any AEs. The date of last intake of study intervention(s) should be documented in the eCRF. All study intervention(s) should be returned by the patient at their next on-site study visit or unscheduled visit. Patients permanently discontinuing study intervention should be given locally available standard of care therapy, at the discretion of the investigator.

Discontinuation of study intervention(s), for any reason, does not impact on the patient´s involvement in the study. The patient should continue attending subsequent study visits and data collection should continue according to the CSP. If the patient does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This could be a telephone contact with the patient, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

As a minimum, telephone contact should be made with the patient 28 days following the discontinuation of both study interventions to collect new AEs and follow up on any ongoing AEs and concomitant medications (including any subsequent cancer therapy, if appropriate). Refer to Section 8.3.2 for full details on AE recordings during follow-up.

7.2 Patient Withdrawal from the Study

- A patient may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons. This is expected to be uncommon.
- A patient who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician or information from medical records).
- At the time of withdrawal from the study, if possible, an Early Study Intervention Discontinuation visit should be conducted, as shown in the SoAs (Table 1 and Table 2). See the SoAs for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
  - The patient will discontinue the study intervention and be withdrawn from the study at that time.
- If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a patient withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the patient within legal and ethical boundaries for all patients randomised, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the patient will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoAs (Table 1 and Table 2). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoAs (Table 1 and Table 2), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the CSP-specified criteria and were performed within the time frame defined in the SoAs (Table 1 and Table 2).

8.1 Efficacy Assessments

8.1.1 CT and MRI Scans Tumour Assessments (RECIST 1.1)

The RECIST 1.1 guidelines for measurable, non-measurable, TLs and NTLs and the objective tumour response criteria are presented in Appendix H of this CSP.

Baseline tumour assessments should include CT/MRI of chest and abdomen (including liver and adrenal glands) and should be performed within 28 days of randomisation, and ideally as close as possible to the start of study intervention. At screening the MRI/CT scans will include brain imaging for all patients. Those determined to have brain metastases will have their brain rescanned at all subsequent tumour assessments. Any other regions suspected, or with known metastasis at baseline, will be assessed by imaging and recorded at baseline. The same imaging modality used for baseline tumour assessment should be used for each subsequent follow-up assessment throughout the study if possible. Further details of the CT and MRI acquisition parameters will be documented in a separate image acquisition guidelines document.

Follow-up assessments should be performed Q6W (± 7 days) after randomisation until Cycle 7 (up to 24 weeks), and then Q8W (± 7 days) until objective PD as defined by RECIST 1.1 even if a patient discontinues treatment prior to progression (unless they withdraw consent). For patients who cross-over based on confirmed objective disease progression during the initial randomised treatment period (including patients who have already crossed over based on confirmed PD prior to CSP Version 3.0), 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 after study unblinding and who have not objectively progressed during the initial randomised treatment period. Patients who cross-over after study unblinding, who have no objective progression during initial randomisation period, and who discontinue study intervention 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.

It is important to follow the assessment schedule as closely as possible. 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. Patients will be evaluated until objective radiological PD by RECIST 1.1 as per the SoAs (Table 1 and Table 2).

Categorisation of objective tumour response at each visit will be based on the RECIST 1.1

guidelines for response: CR, PR, SD, NE and PD.

Target lesion progression will be calculated in comparison to when the tumour burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, SD, NE) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

If the investigator is in doubt as to whether progression has occurred, particularly with response to NTLs or the appearance of a new lesion, it is advisable to continue treatment and reassess the patient's status at the next scheduled assessment or sooner if clinically indicated.

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

If repeated scans confirm progression, then the date of the initial scan should be declared as the date of progression.

All CT/MRI scans and all imaging assessments performed for RECIST 1.1 tumour assessment will be reviewed at site. All images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed CRO to enable BICR up to the point of the final analysis (the earlier of 18 months after the last patient is randomised or when 70% of patients have progressed or died). Guidelines for image acquisition, de-identification, storage at the investigative site as source data, and transfer to the imaging CRO will be provided in a separate document. Further details of the BICR will be documented in the Independent Review Charter (also referred to as "Imaging Charter"). Results of the independent reviews will not be communicated to investigators, and results of investigator RECIST 1.1 assessments will not be shared with the central reviewers. The management of patients will be based wholly upon the results of the RECIST 1.1 assessment conducted by the investigator.

Following investigator-assessed PD, in patients who cross-over from savolitinib plus placebo to receive the combination of savolitinib and osimertinib, secondary ORR, PFS, DoR and change in tumour size assessments will be performed by the investigator using imaging assessments per RECIST 1.1 (see Section 9.4.2.3). These local-practice scans should not be sent to the appointed CRO for BICR.

8.1.2 Survival Follow-up

Patients who have discontinued study intervention will be followed up for survival status Q12W until death, withdrawal of consent or the end of the study, ie, at the time of final analysis. Survival information may be obtained via telephone contact with the patient,

patient's family or by contact with the patient's current physician. In addition to the survival status, the assessment of anti-cancer and surgical treatments are also required.

Patients should be contacted in the week following the DCOs for the final analysis to provide complete survival data.

For patients who have not actively withdrawn consent, the status of those ongoing, withdrawn (from the study), and "lost to follow-up" at the time of the first analysis should be obtained by the site personnel by checking the patients notes, hospital records, contacting the patients 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.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoAs (Table 1 and Table 2).

8.2.1 Physical Examinations

A complete physical examination will be performed and include assessments of the following; general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, muscular-skeletal (including spine and extremities) and neurological systems.

Physical examination will be performed at timelines as specified in the SoAs (Table 1 and Table 2), investigators should pay special attention to clinical signs related to previous serious illnesses, new or worsening abnormalities may qualify as AEs, see Section 8.3.4 for details.

8.2.2 Vital Signs

Vital signs (heart rate, BP, temperature, and respiration rate) will be performed as specified in the SoAs (Table 1 and Table 2) and as clinically indicated. Height will be assessed at the screening visit only. Weight will be assessed at the screening visit, Day 1 of each cycle for the first 6 cycles, Q8W from Cycle 7 onwards, and more frequently if clinically indicated. If a patient crosses over to savolitinib plus osimertinib they will continue to have follow-up assessments in line with these timings relative to randomisation, although they will be reported with a new baseline of the progression scan on randomised treatment (see Section 8.1.1).

- Temperature, pulse rate and BP will be assessed.
- Blood pressure and pulse measurements will be assessed in the semi-supine position with a completely automated device. Manual techniques will only be used if an automated device is not available.

- Vital sign measurements should be preceded by at least 10 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones).
- Measurements will be taken in a semi-supine position after 10 minutes rest and will include temperature, systolic and diastolic BP and pulse.

Any changes in vital signs should be recorded as an AE, if applicable.

8.2.3 Electrocardiograms

The QTCF evaluations will be done based on triplicate 12-lead ECGs as indicated in the SoAs (Table 1 and Table 2). Twelve-lead ECGs (triplicate) will be obtained after the patient has been rested in a supine position for at least 5 minutes. The investigator or designated physician will review the 12-lead ECGs. Electrocardiograms will be recorded at 25 mm/sec. All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal/not clinically significantly abnormal.

Triplicate ECGs will be required on Cycle 3 Day 1 collected pre-dose, and at 1, 3, 4, and 6 hours post-dose, on randomised treatment and again on cross-over treatment (Cycle 3 Day 1 on cross-over being relative to first dose of osimertinib), to coincide with collection of blood samples for assessment of PK of osimertinib and savolitinib at this visit.

If there is a clinically significant abnormal ECG finding, the investigator will record it as an AE on the eCRF. The original ECG traces must be stored in the patient's medical record as source data. A 28-day follow-up assessment will be required if an on-treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality.

8.2.4 Multi-gated Acquisition/Echocardiogram

An ECHO or MUGA scan to assess left ventricle ejection fraction will be conducted during the main study screening period, Q12W (± 2 weeks) relative to randomisation, and at the end of treatment as indicated in the SoAs (Table 1 and Table 2). If a patient crosses over to savolitinib plus osimertinib they will continue to have follow-up assessments in line with these timings relative to randomisation, although they will be reported with a new baseline of the progression scan on randomised treatment (see Section 8.1.1). The modality of the cardiac function assessments must be consistent within a patient, ie, if ECHO is used for the screening assessment then ECHOs should also be done for subsequent testing. The patients should also be examined using the same machine and operator whenever possible, and quantitative measurements should be taken. A 28-day follow-up assessment will be required if an on-treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality.

8.2.5 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation and urinalysis will be taken at the visits indicated in the SoAs (Table 1 and Table 2). All CSP-required safety laboratory assessments, as defined in Table 9, will be performed in a licensed local clinical laboratory according to local standard procedures.

The investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at the centre as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.5.

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

The clinical chemistry (including LFTs), haematology and urinalysis will be performed at a local laboratory at or near to the investigator site. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site.

The following laboratory variables will be measured.

Table 9 Laboratory Safety Variables

Clinical chemistry	Haematology	Urinalysis (Dipstick) [a]
S/P – Albumin	B – Haematocrit	U – Blood
S/P – ALP [b]	B – Haemoglobin	U – Glucose
S/P – ALT [b]	B – Leucocyte cell count	U – Ketones
S/P – Amylase	B – Platelet count	U – Leukocyte esterase
S/P – AST [b]	B – Red blood cell count	U – Protein
S/P – Bilirubin, total [b]	B - Reticulocytes	
S/P – Calcium, total	B – Absolute leucocyte differential count: B – Neutrophil count B – Lymphocyte count B – Eosinophil count	
S/P – Creatinine		
S/P – Glucose		
S/P – Magnesium		
S/P – Sodium		
S/P – Potassium		
S/P – Total protein		
S/P – Blood urea nitrogen or urea		
S/P – Lactate dehydrogenase		

[a] If 3 + or greater proteinuria is identified by dipstick assessment, a 24-hours urine collection for formal quantification of the level of protein excretion should be performed

[b] Designates tests that are considered LFTs and are to be done weekly for the first 10 weeks relative to randomisation, then Day 1 of every subsequent cycle and at progression.

ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; B = Blood; LFT = Liver function test; P = Plasma; S = Serum; U = Urine.

Note: In case a patient shows an AST **or** ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN please refer to Appendix E "Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law", for further instructions.

8.2.6 Serum of Urine Pregnancy Test

A pregnancy test on urine or blood sample will be performed for pre-menopausal WOCBP, at the study screening visit, and prior to the first dose of study intervention on Cycle 1 Day 1, Day 1 of every cycle, and at treatment discontinuation. Tests will be performed by the institutional laboratory. If results are positive the patient is ineligible/must be discontinued from the study. In the event of a suspected pregnancy during the study, the test should be repeated and if positive, the patient will be discontinued from study intervention immediately.

8.3 Adverse Events and Serious Adverse Events

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

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorised representative).

The investigator and any designees are responsible for detecting, documenting and recording events that meet the definition of an AE.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse Events and SAEs will be collected from time of signature of the main study ICF throughout the treatment period and including the follow-up period. The follow-up period is defined as 28 ± 7 days after study intervention is discontinued.

Procedure-related AEs and SAEs for those patients who provide a new tumour biopsy occurring up to and including 21 days after the new tumour biopsy procedure will be captured. This procedure may be performed prior to signing the main study ICF.

If the investigator becomes aware of a SAE with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical study in a patient treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor.

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the patient's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.2.1 Adverse Event Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- The maximum on-treatment CTCAE grade (according to CTCAE Version 5.0)
- Whether the AE is serious or not
- Investigator causality rating against the study interventions (yes or no)
- Action taken with regard to study interventions
- Outcome.

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

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.3.3 Causality Collection

The investigator should assess causal relationship between study intervention and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the study intervention?'

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

A guide to the interpretation of the causality question is found in Appendix B to the CSP.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study site staff: "Have you had any health problems since the previous visit/you were last asked?" or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the CSP-mandated laboratory tests, ECGs, and vital signs will be summarised in the CSR.

Deterioration as compared with baseline in CSP-mandated laboratory values, ECGs and vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention, or are considered to be

clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

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

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.6 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of HL.

8.3.7 Disease Progression

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

8.3.8 Disease Under Study

Symptoms of disease under study are those that might be expected to occur as a direct result of locally advanced or metastatic NSCLC. Events which are unequivocally due to disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the study intervention.

8.3.9 New Cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New cancers are those that are not the primary reason for the

administration of the study intervention and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer.

8.3.10 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the study intervention, or to the study procedure(s). All SAEs will be recorded in the eCRF.

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

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

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

Once the investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the investigator/study site staff how to proceed.

For further guidance on the definition of a SAE, see Appendix B of the CSP. Section 5.4 of the osimertinib and savolitinib IBs provides information related to the emerging safety profile of both study interventions.

8.3.11 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study patient has received any study intervention

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.11.1 Maternal Exposure

If a patient becomes pregnant during the course of the study, study intervention should be discontinued immediately.

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

If any pregnancy occurs in the course of the study or within 6 weeks of the last dose of study intervention, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within one or 5 calendar days for SAEs (see Section 8.3.1) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

8.3.11.2 Paternal Exposure

Male patients should refrain from fathering a child or donating sperm during the study and 6 months following the last dose.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality), occurring from the date of the first dose until 6 months after the last dose and as indicated by previous studies (pre-clinical and clinical) should, if possible, be followed up and documented in the Pregnancy Report Form.

To capture information about a pregnancy from the partner of a male patient, the male patient's partner's consent must be obtained to collect information related to the pregnancy and outcome; the male patient should not be asked to provide this information. A consent form

specific to this situation must be used. The outcome of any conception occurring from the date of the first dose until 4 months after dosing ends should be followed up and documented.

8.3.12 Medication Error

If a medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within one day, ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within one (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error (see Section 8.3.1) and within 30 days for all other medication errors.

The definition of a Medication Error can be found in Appendix B.

8.4 Overdose

A maximum tolerated dose has not been established for osimertinib or savolitinib, therefore an overdose is any dose which exceeds the daily dose that is defined in this CSP.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site, within one or 5 calendar days for overdoses associated with an SAE (see Section 8.3.1) and within 30 days for all other overdoses.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Sample see Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in

line with consent and local requirements, after which they will be destroyed/repatriated.

- Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - Pharmacokinetic samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

8.5.1 Pharmacokinetics

- Plasma samples will be collected for measurement of plasma concentrations of osimertinib, savolitinib and their metabolites as specified in the SoAs (Table 1 and Table 2) and Table 10.
- Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.
- Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Table 10 Pharmacokinetic Sampling Schedule

Cycle number	Sampling point [a]
Cycle 1, Day 1	Pre-dose, and 1 and 3 hours post-dose
Cycle 2, Day 1	Pre-dose, and 1 and 3 hours post-dose
Cycle 3, Day 1	Pre-dose, and 1, 3, 4, and 6 hours post-dose [b]
Cycle 6, Day 1	Pre-dose
Discontinuation	Discontinuation PK samples will be collected as soon as feasible if a patient discontinues due to an AE reaction.

[a] Samples may be collected at additional timepoints.
[b] Triplicate ECGs to be collected at these timepoints as described in Section 8.2.3.
PK sample collection windows are: Pre-dose, up to 2 hours pre-dose; 1 hour post-dose, ± 5 minutes; 3 hours post-dose, ± 10 minutes; 4 hours and 6 hours post-dose, ± 30 minutes.
PK samples are collected for both treatment periods. Timings are relative to the start of study intervention ie, randomised treatment or cross-over.
AE = Adverse event; ECG = Electrocardiogram; PK = Pharmacokinetics.

On PK days patients should come to the clinic fasted where they will first be given a moderate breakfast (the same breakfast should be given on all PK days) and will administer the

savolitinib and osimertinib/placebo dose at the same time. Fasting state will be collected in the eCRF. Pre-dose PK sample may be drawn up to 2 hours pre-dose (before or after breakfast).

Samples will be used to analyse the PK of savolitinib, osimertinib and their metabolites and appropriate PK parameters will be determined and summarised. Summary concentrations for appropriate PK parameters will be reported in the CSR separately for randomised and cross-over treatment. The concentration data from this study may be combined with data from other studies in a population PK analysis and, if conducted, will be reported separately from the CSR.

Any changes in the timing or addition of time points for any planned study assessments for individual patients must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, and may not constitute a CSP amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF and CSP.

8.5.1.1 Determination of Drug Concentration

Samples for determination of individual drug and/or metabolite concentrations in plasma will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

8.5.2 Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

8.5.3 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of Mandatory Samples for Biomarker Analysis

By consenting to participate in the study the patient consents to participate in the mandatory research components of the study. The following samples for biomarker research are required and will be collected from all patients in this study as specified in the SoAs (Table 1 and Table 2):

- Tumour specimen, taken following progression on prior treatment with osimertinib, will be required at Pre-screening to assess eligibility. The MET amplification status of the patients' tumour specimen by FISH will be determined at a central laboratory. This analysis is required to investigate the presence of MET gene amplification that is needed to include the patient in the study. CCI [redacted] Tumour sample requirements for biomarker testing will be defined in the supporting Laboratory Manual.
  - Sampling should be undertaken by experienced physicians in appropriate medical facilities in accordance with standard clinical practice for patients with advanced NSCLC.
  - Patients will only undergo tumour specimen collection when the risks are considered medically acceptable by their caring physicians. Where possible, high-risk sites (such as brain, pancreas, etc) should be avoided.
  - Supported by NCCN/European Society for Medical Oncology guidelines, tumour re-biopsy at PD is an option for standard clinical practice at many sites in order to evaluate the appropriate therapeutic options, including in the event of alternative mechanisms of resistance to EGFR-TKI treatment.
- Blood samples will be collected at Pre-Screening and Screening to analyse plasma biomarkers. CCI [redacted]

CCI [redacted]

As the rate of clearance of ctDNA after 6-weeks of therapy is a secondary endpoint, these data will be presented in the CSR. The results of the other exploratory research may be reported separately from the CSR.

The results of this exploratory research may be pooled with data from other studies with the study interventions to generate hypotheses to be tested in future studies.

8.6.2 CCI [redacted]

CCI [redacted]

CCI

8.6.3 CCI

CCI

CCI

8.7 CCI

CCI

CCI

CCI

8.8 Medical Resource Utilisation and Health Economics

Medical resource utilisation and health economics are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary objective of this study is to assess the ORR of savolitinib in combination with osimertinib versus savolitinib in combination with placebo in patients with EGFRm+, MET amplified locally advanced or metastatic NSCLC who have progressed on previous osimertinib therapy. The null hypothesis is that there is no difference between treatment groups on ORR based on investigator assessment per RECIST 1.1 when all patients have had the opportunity to be treated for 6 months. The alternative hypothesis is that there is a difference between treatment groups in this regard.

9.2 Sample Size Determination

Prior to CSP V3.0, approximately 200 patients were planned to be screened to achieve 56 patients randomly assigned to study intervention, with the primary analysis to occur 6 months after the last patient was randomised. With 56 patients (28 per arm) planned, CCI [redacted]. At least half of the patients in the study (28 patients) will be second-line patients who were treated with osimertinib in the first-line setting.

Under CSP V3.0, the planned number of randomised patients will not be met. This is a result of the decision by AstraZeneca to terminate study recruitment early.

9.3 Populations for Analyses

The following populations are defined:

Table 11 Populations for Analysis

Population/Analysis set	Description
Full Analysis Set	The FAS will include all randomised patients with treatment groups assigned in accordance with the randomisation, regardless of the treatment actually received. Patients who are randomised but did not subsequently receive treatment will be included in the FAS. The analysis of data using the FAS therefore follows the principles of intention to treat. The FAS will be the primary population for reporting efficacy data and to summarise baseline characteristics.
Safety Analysis Set	The SAS will consist of all randomised patients who received any amount of study intervention. If a patient receives any amount of an experimental therapy, they will be summarised in the treatment group corresponding to the first experimental treatment they received. The SAS will be used as the primary population for reporting safety data
Cross-over Analysis Set	The Cross-over Analysis Set will consist of all patients who crossed over to savolitinib plus osimertinib who have received at least one dose of savolitinib plus osimertinib. It will be used as the population for reporting the efficacy and safety data for patients who crossed over to treatment with savolitinib plus osimertinib following objective progression on savolitinib plus placebo.
PK Analysis Set	All patients who receive at least 1 dose of savolitinib or osimertinib as per the CSP, for whom there are at least one reportable PK concentration will be included in the PK Analysis Set.
Interim Futility Analysis Set	The Interim Futility Analysis Set will include the patients who have had the opportunity to be treated for 2 RECIST post baseline scans (12 weeks). This analysis set will only be used for the interim futility analysis.

CSP = Clinical Study Protocol; FAS = Full Analysis Set; PK = Pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumours; SAS = Safety Analysis Set.

9.4 Statistical Analyses

Under CSP V3.0, the SAP will be finalised prior to the unblinding of the study that is to occur following early study recruitment termination, for the purpose of an early review of the study data by AstraZeneca.

The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

Descriptive statistics will be used for all variables as appropriate and will be presented by treatment arm. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarised by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment arm.

Results of all statistical analyses will be presented using a 95% CI and p-value, unless otherwise stated.

Additional subgroup analyses of efficacy and safety may be performed and will be specified in the SAP.

Depending on the extent of any impact, summaries of data relating to patients diagnosed with COVID-19, and impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued study intervention, and other protocol deviations) may be generated. More detail will be provided in the SAP.

Baseline for patients on randomised 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 visit prior to randomisation. 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.

Efficacy data will be summarised and analysed on the FAS, safety data will be summarised on the SAS and PK data will be summarised on the PK Analysis Set.

Baseline for ORR, PFS, DoR and tumour size assessments of patients who cross-over to savolitinib plus osimertinib from savolitinib plus placebo will be the progression scan on savolitinib plus placebo, acquired within 28 days of the start of treatment in the cross-over period. CCI [redacted] Baseline for safety assessments of patients who cross-over to savolitinib plus osimertinib from savolitinib plus placebo will be set as the last assessment prior to first dose of osimertinib.

A Cross-over Analysis Set is included for patients randomised to savolitinib plus placebo who cross-over to savolitinib plus osimertinib upon objective PD per RECIST 1.1.

9.4.1.1 Stratification Factors

The stratification in the statistical analyses will be based on the values entered in the IWRS at randomisation, even if it is subsequently discovered that these values were incorrect. If there

are any patients who were mis-stratified, a sensitivity analysis on the primary endpoint may be carried out using the correct baseline data collected in the eCRF.

9.4.1.2 Multiplicity Strategy for Primary and Key Secondary Endpoints

Prior to CSP V3.0, the primary analysis was to occur 6 months after the last patient was randomised. This will be based on a comparison of the primary endpoint (ie, ORR) between treatment groups and will be tested at the 2-sided 5% significance level.

CCI [redacted] the secondary efficacy endpoints will be tested at a 2-sided significance level of 5%. There will be no adjustment for multiplicity as the study is not designed to support labelling claims on any of the endpoints.

Final analysis was to be performed after the earlier of 18 months after the last patient was randomised or when 70% of the patients have progressed or died due to any cause. CCI [redacted]

Under CSP V3.0, as a result of AstraZeneca's decision to terminate study recruitment early, there will be no primary analysis at the originally planned timepoint. Following early termination of study recruitment, an initial DCO will occur to allow an early review of data by AstraZeneca. A final DCO will occur 9 months after the last patient has been randomised, after which the final analysis will be performed. CCI [redacted]

9.4.2 Efficacy

Investigator RECIST Based Assessments

From the investigators review of the imaging scans, the RECIST tumour response data will be used to determine each patient's visit response according to RECIST 1.1. It will be used to determine the endpoints of ORR, PFS, DoR and tumour size change.

At each tumour assessment, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD or PD 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, 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).

Investigator-assessment of PD per RECIST 1.1 of patients receiving savolitinib plus placebo is required prior to cross-over to savolitinib plus osimertinib.

Please refer to Appendix H for the definitions of CR, PR, SD, PD and NE.

Central Review of RECIST 1.1 Based Assessments

The 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. Blinded independent central review data will be used to determine endpoints: ORR and PFS as a sensitivity analysis.

Further details of the BICR will be documented in the BICR charter.

9.4.2.1 Analysis of Primary Endpoint

Objective response rate by investigator assessment in accordance with RECIST 1.1 is the primary endpoint for this study.

The ORR is defined as the proportion of patients with an investigator-assessed response of CR or PR by RECIST 1.1.

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 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.

The ORR will be analysed using a logistic regression model adjusting for the stratification used in the randomisation. The results of the analysis will be presented in terms of an odds ratio (an odds ratio greater than 1 will favour savolitinib in combination with osimertinib versus savolitinib in combination with placebo) together with its associated profile likelihood 95% CI and p-value (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model).

If there are not enough responses for a meaningful analysis using logistic regression then a CMH test will be presented.

Summaries will be produced that present the number and percentage of patients in each treatment group with a tumour response (CR/PR).

A sensitivity analysis of the ORR will be performed based on the BICR assessment of disease progression by RECIST 1.1. Further sensitivity analyses will be described in the SAP.

Summaries will be produced that present the number and percentage of patients in each treatment group with a tumour response (CR/PR). Summaries will also be produced for ORR per BICR.

Subgroup Analysis

Subgroup analyses will be conducted comparing ORR between the treatment arms in each stratum used in the randomisation. If there are sufficient patients in each stratum, a logistic regression comparing treatments may be used to compare treatments. The results of the analysis will be presented in terms of an odds ratio in analogy with the primary logistic regression described above. If there are not enough responses for meaningful subgroup analysis using logistic regression, then a CMH test may be used instead. Objective response rate within each stratum will be presented with a two-sided 95% CI using the Clopper-Pearson method.

The odds ratios and associated two-sided 95% profile likelihood CIs will be summarised and presented on a forest plot, along with the results of the overall primary analysis.

No adjustment to the significance level for testing of subgroups will be made since the subgroup analyses CCI [redacted] may only be supportive of the primary analysis of ORR.

9.4.2.2 Analysis of Secondary Efficacy Endpoints

Progression-free Survival

Progression-free survival is defined as the time from randomisation until the date of objective disease progression per RECIST 1.1 as assessed by the investigator or death due to any cause regardless of whether the patient withdraws from therapy or receives another anti-cancer therapy prior to progression. 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 assessment. 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: in such a case, the death date will be used as the event date.

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

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

- 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.

Prior to CSP V3.0, the primary analysis of PFS was to occur 6 months after the last patient was randomised. A final analysis was to occur after the earlier of 18 months after the last patient was randomised or when 70% of patients had progressed or died. Under CSP V3.0, as a result of AstraZeneca's decision to terminate study recruitment early, there will be no primary analysis at the originally planned timepoint. Following early termination of study recruitment, an initial DCO will occur to allow an early review of data by AstraZeneca. The study will be unblinded after completion of data cleaning activities on this initial DCO data, and patients on savolitinib monotherapy (savolitinib plus placebo) will be given the opportunity to cross-over to the savolitinib plus osimertinib arm. If the investigator believes patients are gaining clinical benefit and patients have not reported PD, patients may continue to receive savolitinib monotherapy. All patients will be followed until the final analysis. A final DCO will occur 9 months after the last patient has been randomised, after which the final analysis will be performed. CCI [redacted]

Progression-free survival based on investigator assessment will be analysed using a stratified log-rank test adjusting for the same factors as for ORR for generation of the p-value. The effect of treatment will be estimated by the HR together with its corresponding 95% CI for the FAS. An HR less than 1 will favour savolitinib plus osimertinib. The HR and its CI will be estimated from a stratified 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.

Kaplan-Meier plots of PFS will be presented by treatment arm. Summaries of the number and percentage of patients experiencing a PFS event, and the type of event (RECIST 1.1 or death) will be provided along with summaries of PFS (n, events, medians, quartiles, proportion progression free at 3, 6, 9, and 12 months and corresponding 95% CIs) by treatment group.

The assumption of proportionality will be assessed. Proportional hazards will be tested firstly by examining plots of complementary log-log (event times) versus log (time) and, if these raise concerns, by fitting a time dependent covariate (adding a treatment-by-time or treatment-by-ln[time] interaction term) to assess the extent to which this represents random variation. If a lack of proportionality is evident, the variation in treatment effect can be described by presenting piecewise HR calculated over distinct time-periods for example 0 to 6 months, 6 to 12 months etc. In such circumstances, the HR from the primary analysis can still be meaningfully interpreted as an average HR over time unless there is extensive crossing of the survival curves. If lack of proportionality is found this may be a result of a treatment-by-covariate interaction, which will be investigated.

The treatment status at progression of patients at the time of analysis will be summarised. This will include the number (%) of patients study intervention prior to progression, the number

(%) of patients who have not progressed and were on treatment or discontinued treatment. This will also provide distribution of number of days prior to progression for the patients who have discontinued treatment.

Sensitivity Analysis

Progression-free survival defined by the BICR in the FAS will be analysed as described for the investigator-assessed PFS endpoint (see above). Further sensitivity analyses will be described in the SAP.

Duration of Response

The DoR is defined as the time from the date of first documented response until date of documented progression or death in the absence of PD (ie, 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 response of CR or PR.

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

If there are sufficient numbers of responders, and sufficient numbers of responses that have progressed by the point of the analysis, Kaplan-Meier plots of DoR in the responding patient will be produced and appropriate descriptive summary statistics will be presented (n, number of responses that have progressed, median, quartile, minimum and maximum DoR) by treatment group without any formal comparison or p-value attached.

Percentage Change from Baseline in Tumour Size

Tumour size assessment is defined as the percentage change in TLs at 12 weeks per RECIST 1.1. Absolute change and percentage change from baseline in TL's tumour size at 12 weeks will be based on RECIST TLs measurements taken at baseline and at Week 12. Tumour size is the sum of the longest diameters of the TLs. Baseline for RECIST is defined as the last evaluable assessment prior to randomisation.

The percentage change in TL tumour size at Week 12 will be obtained for each patient by taking the difference between the sum of the TLs at Week 12 and the sum of the TLs at baseline divided by the sum of the TLs at baseline times 100 (ie, [Week 12 - baseline] / baseline × 100).

The absolute change in TL tumour size at Week 12 will be obtained for each patient by the difference between the sum of the TL at Week 12 and the sum of the TL at baseline.

The absolute change in TL tumour size from baseline and percentage change in TL tumour

size from baseline will be summarised using descriptive statistics by randomised treatment group. Best percentage change will also be summarised.

The effect of study interventions on absolute and percentage change in TL tumour size will be estimated from an ANCOVA model including a term for treatment, the absolute (percentage) change in Week 12 value, a covariate for baseline TL tumour size, stratification used in randomisation, and a covariate for the time from the baseline scan to randomisation. The number of patients, unadjusted mean and least-squares means for each treatment group should be presented, together with the difference in least-squares means, 95% CI and corresponding p-value.

Handling of missing data will be described in the SAP.

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 actual change and the percentage change from baseline in tumour size for each patient over time may be produced.

Model checking diagnostics for the ANCOVA will be described in the SAP. If ANCOVA is deemed not to be appropriate, non-parametric techniques will be used. Further details in this regard will be described in the SAP.

Overall Survival

Overall survival is defined as the time from randomisation until death due to any cause, regardless of whether the patient withdraws from randomised therapy or receives another anticancer therapy. 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.

Note: Patients will be contacted for survival follow-up Q12W until death, withdrawal of consent, or the end of the study ie, at the time of final analysis, defined as the earlier of 18 months after the last patient is randomised or when 70% of patients have progressed or died. Patients should be contacted in the week after DCO for each analysis to establish survival status. 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 the DCO.

Overall survival will be analysed as described for the investigator-assessed PFS endpoint (mentioned earlier in this section). CCI [redacted] Further details will be provided in the SAP.

Summaries of OS (n, events, medians, quartiles, proportion alive at 3, 6, 9 and 12 months and corresponding 95% CIs) and a Kaplan-Meier plot will be provided.

9.4.2.3 Analysis of Efficacy Endpoints of the Cross-over Analysis Set

For the Cross-over Analysis Set, efficacy endpoints include ORR, PFS, DoR, tumour size assessment[CCI]. Details of the baseline for these endpoints are given in Section 9.4.1. These endpoints will only be summarised descriptively (Section 9.4.2.2).

Listings, and possibly summaries of the above endpoints depending on the number of patients, will be presented for patients who cross-over from savolitinib plus placebo to savolitinib plus osimertinib, presenting data from the baseline of their second phase onwards (see Section 9.4.1).

Further details of how the data for these patients will be presented will be described in the SAP.

9.4.2.4 Exploratory Endpoints

Statistical analysis of the exploratory endpoints will be summarised in the SAP.

9.4.3 Safety

Safety and tolerability will be assessed in terms of AEs, SAEs, discontinuation rate due to AEs, deaths, laboratory data, vital signs, ECHO data, ECG data and ECOG performance status. All safety analyses will be performed on the SAS. Data will also be presented separately for patients who crossed over to savolitinib plus osimertinib upon investigator-assessed PD per RECIST 1.1 on savolitinib plus placebo. Safety data will be presented using descriptive statistics unless otherwise specified.

Adverse events will be coded using the most recent version of MedDRA that have been released for execution at AstraZeneca. Adverse events will be graded according to the National Cancer Institute CTCAE (Version 5.0).

The number of patients experiencing each AE will be summarised by the MedDRA system organ class, preferred term and treatment group. The number and percentage of patients with AEs in different categories (eg, causally related, CTCAE Grade ≥ 3 etc) will be summarised, and events in each category will be further summarised by MedDRA system organ class, preferred term and treatment group. If there are sufficient SAEs, they will be summarised separately. Further details will be provided in the SAP.

Adverse events occurring prior to the start of study intervention, treatment-emergent AEs and post-treatment emergent AEs will be presented separately. Adverse events occurring in the savolitinib in combination with placebo group will be split into 2 presentations based on whether they occurred before or after the crossover into the savolitinib in combination with osimertinib group.

Any AE occurring before the first dose of study intervention will be included in the data

listings but will not be included in the summary tables of AEs. Adverse event summary tables will include only treatment-emergent AEs. The following events are considered treatment emergent:

- Adverse events with an onset date on or after the first dose of randomised study intervention and within the safety follow-up period (28 days [± 7 days] after last dose of all study intervention). Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of all study intervention) will be flagged in the data listings.
- Worsening of pre-existing events on or after the first dose of study intervention and within the safety follow-up period.

Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of all study intervention) will be flagged in the data listings, but not included in the summaries.

An overview of AEs will present for each treatment group the number and percentage of patients with any AE, AEs with outcome of death, SAEs, and AEs leading to discontinuation of study intervention, as well as AEs leading to study intervention dose interruptions, and AEs leading to study intervention dose reduction as well as the number of individual occurrences in those categories.

Separate AE tables will be provided taken into consideration relationship as assessed by the investigator, CTCAE grade, seriousness, death and events leading to discontinuation of study intervention for the first 6 weeks and at any time as well as other action taken related to study intervention.

An additional table will present number and percentage of patients with most common AEs. Most common (eg, frequency of $> x\%$, $\geq x\%$) will be defined in the SAP.

In accordance with the requirements of the FDA, a separate table will present non-serious AEs occurring in more than 5% of patients in any treatment group.

Key patient information will be presented for patients with AEs with outcome of death, SAEs, and AEs leading to discontinuation of study intervention.

An AE listing for the SAS will cover details for each individual AE; an AE listing for patients who were not exposed to study intervention is presented separately.

Full details of AE analyses will be provided in the SAP.

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review

the list of AEs that were not reported as SAEs or 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 AEs and reported as such in the CSR. A similar review of laboratory/vital signs (pulse and BP)/ECG data will be performed for identification of other significant AEs. 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. Tables and figures for potential Hy's Law cases will be produced.

Duration of exposure will be summarised. The number and percentage of patients with at least one dose interruption/dose delay and at least one dose reduction will also be summarised separately for the first 6 weeks and at any time.

Details of any deaths will be listed for all patients.

Graphical presentations of safety data will be prepared as is deemed appropriate.

Other safety data including physical examinations, clinical haematology, chemistry, urinalysis, vital signs and ECGs will be summarised using descriptive statistics. For all laboratory variables, which are included in the current version of CTCAE, the CTCAE grade will be calculated. The analysis will be performed based on the SAS for the overall population and the Cross-over Analysis Set.

A frequency table presents number of patients reporting at least one treatment emergent changes in laboratory parameters. For all laboratory variables, which are included in the current version of CTCAE, the CTCAE grade will be calculated.

Details of vital sign and laboratory analyses will be provided in the SAP.

9.4.4 Pharmacokinetic Analyses

Pharmacokinetic analyses of the plasma concentration data for savolitinib, osimertinib and their metabolites (M2 and M3 for savolitinib; AZ5104 for osimertinib) will be performed by CPQP, AstraZeneca or a delegate on behalf of CPQP. The actual sampling times will be used in the parameter.

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

- After single dosing: C_{1h} and C_{3h} post-dose.
- After multiple dosing: $C_{pre\text{-}dose}$, and at C_{1h}, and C_{3h}, post-dose. Appropriate PK parameters such as AUC_{ss}, C_{ssmax}, T_{ssmax}, CL_{ss}/F at Cycle 3, Day 1 may also be calculated for savolitinib, osimertinib and their metabolites. These parameters may be presented

separately for savolitinib plus osimertinib, savolitinib plus placebo and for patients who crossed over.

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

Where possible, the appropriate PK parameters will also be determined for the metabolites of savolitinib and osimertinib. The concentration data from this study may be combined with other studies to perform population PK analysis and if conducted, will be reported separately from the CSR.

9.4.5 Other Analyses

Biomarker analyses for the CSR will be described in the SAP.

Circulating-tumour DNA dynamics will be evaluated as a surrogate marker of clinical efficacy. For the secondary objective, the prevalence of ctDNA clearance of 6 weeks treatment with savolitinib and osimertinib will be determined.

The percentage change in EGFR mutation ctDNA allele frequencies at Week 6 will be obtained for each patient taking 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 (ie, [Week 6 baseline]/baseline × 100). Patients with undetectable EGFR mutations at baseline will be excluded from this analysis. Samples with undetectable EGFR mutations will be interpreted as 0% allele frequency so that the % change is 100%.

The absolute change in ctDNA at Week 6 will be obtained for each patient by the difference between the EGFR mutation ctDNA allele frequencies at Week 6 and at baseline.

Patients with detectable EGFR mutations at baseline and available data at 6-weeks will also be categorised into the following groups: (1) ctDNA clearance: defined by a 100% change in EGFR mutations in ctDNA (ie, undetectable at Week 6) and (2) ctDNA non-clearance: defined by a percent change in EGFR mutations in ctDNA less than 100% (ie, detectable at Week 6). Patients with undetectable EGFR mutations at baseline will be categorised as "uninformative."

Handling of missing data will be described in the SAP.

The percentage change and absolute change at Week 6 in ctDNA from baseline will be summarised using descriptive statistics. Descriptive summaries showing the actual change and the percentage change from baseline in tumour size for each patient over time may be produced. Summary statistics of the categorised ctDNA groups will also be produced. Analysis will also be presented for patients in the Cross-over Analysis Set.

Waterfall plots showing the percentage change at Week 6 will be produced for the FAS and Cross-over Analysis Set. Spider plots showing the actual change and the percentage change from baseline in tumour size for each patient over time may be produced.

CCI

CCI

CCI

9.5 Interim Analyses

Prior to CSP V3.0, a non-comparative interim futility analysis for the savolitinib plus placebo arm was planned to occur after 20 patients overall (10 per arm) had the opportunity to be treated for 2 RECIST post-baseline scans (12 weeks). The outcome of the interim futility analysis was to be as follows:

- Stop further enrolment into the study if no responses are observed
- If true rate = 5%, there is a 59.9% probability of observing no responses.
- If true rate = 10%, there is a 34.9% probability of observing no responses.
- If true rate = 43%, there is a 0.4% probability of observing no responses.

Recruitment was to continue during the interim futility analysis.

If the decision was made by the IDMC that the study was futile, no new patients were to be enrolled into the study and all randomised patients were to be unblinded and those randomised to savolitinib plus placebo were to be given the opportunity to cross-over to savolitinib plus osimertinib (see Section 4.1.2).

The SAP will describe the planned analyses in greater detail.

Under CSP V3.0, as a result of AstraZeneca's decision to terminate study recruitment early, the planned interim futility analysis will not be performed and there will be no requirement for data review by the IDMC. Alternatively, following the termination of study recruitment, an initial DCO will occur to allow an early review of the data by AstraZeneca. The study will be unblinded after completion of data cleaning activities on the initial DCO data, and patients on savolitinib monotherapy (savolitinib plus placebo) will be given the opportunity to cross-over to the savolitinib plus osimertinib arm. If the investigator believes patients are gaining clinical benefit and patients have not reported PD, patients may continue to receive savolitinib monotherapy. All patients will be followed until the final analysis.

9.6 Data Monitoring Committees

9.6.1 Independent Data Monitoring Committee

Prior to CSP V3.0, an IDMC for the randomised period was planned to be utilised for this study to monitor efficacy. For details on the IDMC, refer to Appendix A 5. Under CSP V3.0, the planned interim futility analysis will not be performed and hence an IDMC review will not be required. This is a result of the decision by AstraZeneca to terminate study recruitment early.

9.6.2 Independent Hepatic Assessment Committee (I-HAC)

A program-wide I-HAC will review safety data related to hepatic events as per case definition of drug-induced liver injury (Aithal et al 2011).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the CSP and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The CSP, CSP amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the CSP will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those utilising medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorised representative and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Patients or their legally authorised representative (defined as any individual person, judicial body or other body of individuals who are legally authorised under state and federal law to consent to research participation on behalf of a designated person) will be required to sign a statement of informed consent that meets the requirements of Title 21 of the Code of Federal Regulations part 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the patient or the patient's legally authorised representative.

A patient who is rescreened is not required to sign another ICF if the rescreening occurs within the screening window.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory CCI [redacted] human biological samples. The investigator or authorised designee will explain to each patient the objectives of the analysis to be done on the samples CCI [redacted]. CCI [redacted]

If a patient declines to participate in any voluntary exploratory CCI [redacted] research component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be

excluded from other aspects of the study.

If a patient's partner becomes pregnant during or within 6 months after the study, the partner is asked to sign the "Adult Study Informed Consent Form for Pregnant Partners of Study Patients" and provide information about the pregnancy accordingly.

A 4 Data Protection

- Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the patient in the informed consent.
- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

Prior to CSP V3.0, the IDMC was to meet for the planned interim futility analysis to provide a recommendation for the continuation of this study based on efficacy observed. For further information, refer to the IDMC charter. Under CSP V3.0, no interim futility analysis will be performed and hence no IDMC review will be required. This is a result of the decision by AstraZeneca to terminate study recruitment early.

A program-wide I-HAC will review safety data related to hepatic events as per case definition of drug-induced liver injury (Aithal et al 2011).

A 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 7 Data Quality Assurance

- All patient data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved CSP and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 10 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Source Data Verification Plan.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of

patients.

The first act of recruitment is the first patient consented and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the CSP, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

Patients from terminated sites will have the opportunity to be transferred to another site to continue the study, if feasible.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multi-centre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An AE is 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. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

B 2 Definitions of Serious Adverse Events

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical treatment to prevent one of the outcomes listed above.

Adverse Events for **malignant tumours** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **Non-Serious** AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-Serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumour event in question is a new

malignant tumour (ie, it is *not* the tumour for which entry into the study is a criterion and that is being treated by the study intervention under study and is not the development of new or progression of existing metastasis to the tumour under study). Malignant tumours that – as part of normal, if rare, progression – undergo transformation (eg, Richter's transformation of B cell chronic lymphocytic leukaemia into diffuse large B cell lymphoma) should not be considered a new malignant tumour.

Life threatening

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

Hospitalisation

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

Important medical event or medical treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the patient or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

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

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

Intensity rating scale:

The grading scales found in the revised National Cancer Institute CTCAE latest version will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

B 3 A Guide to Interpreting the Causality Question

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

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

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

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

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

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

B 4 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study intervention that either causes harm to the patient or has the potential to cause harm to the patient.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or patient.

Medication error includes situations where an error:

- occurred
- was identified and intercepted before the patient received the drug
- did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong patient received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to patient (excluding IVRS/IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Patient accidentally missed drug dose(s) eg, forgot to take medication

- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

The investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

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

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

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

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that patient, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action documented and study site notified.

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A pathogens are eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900:

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

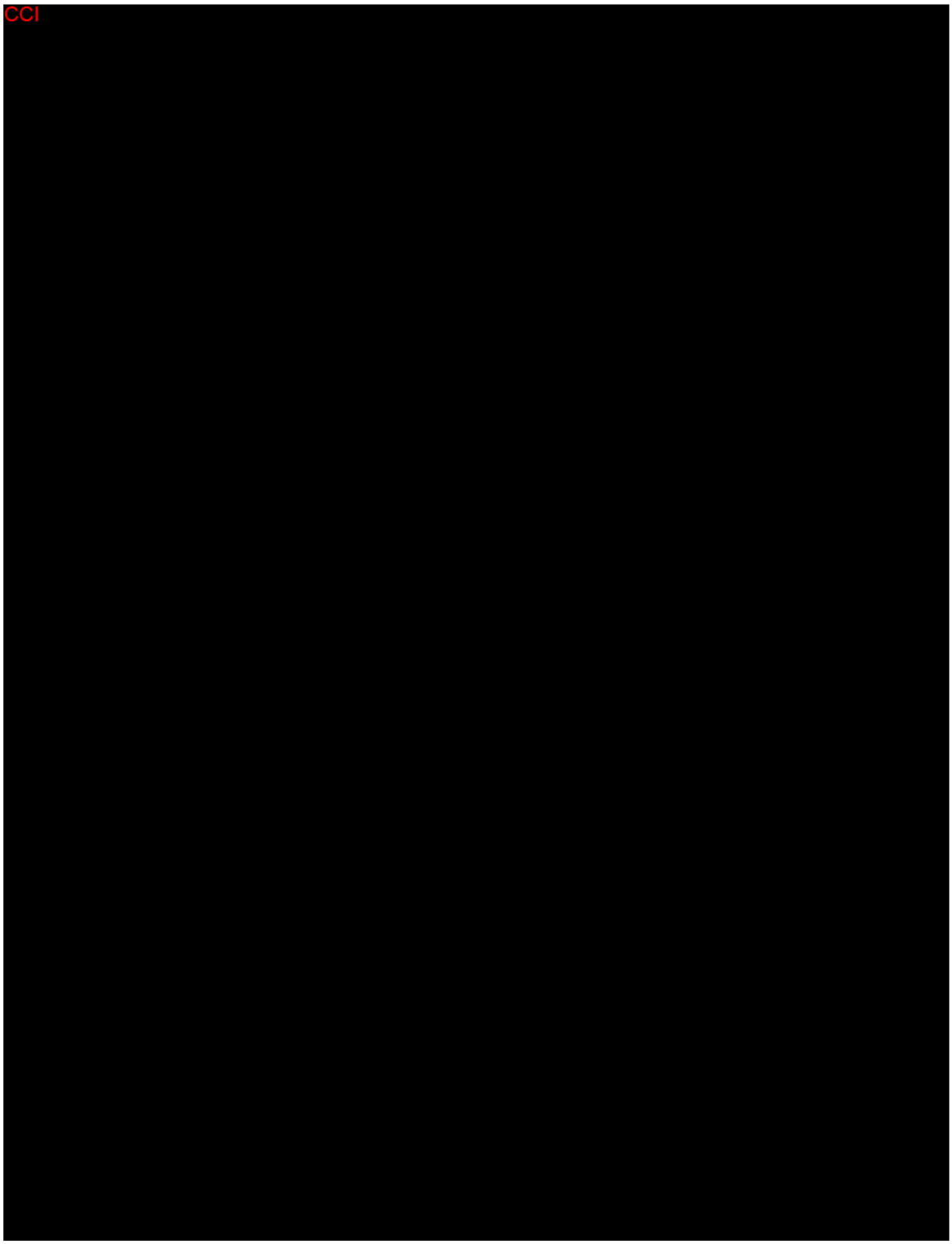
Appendix D [redacted]

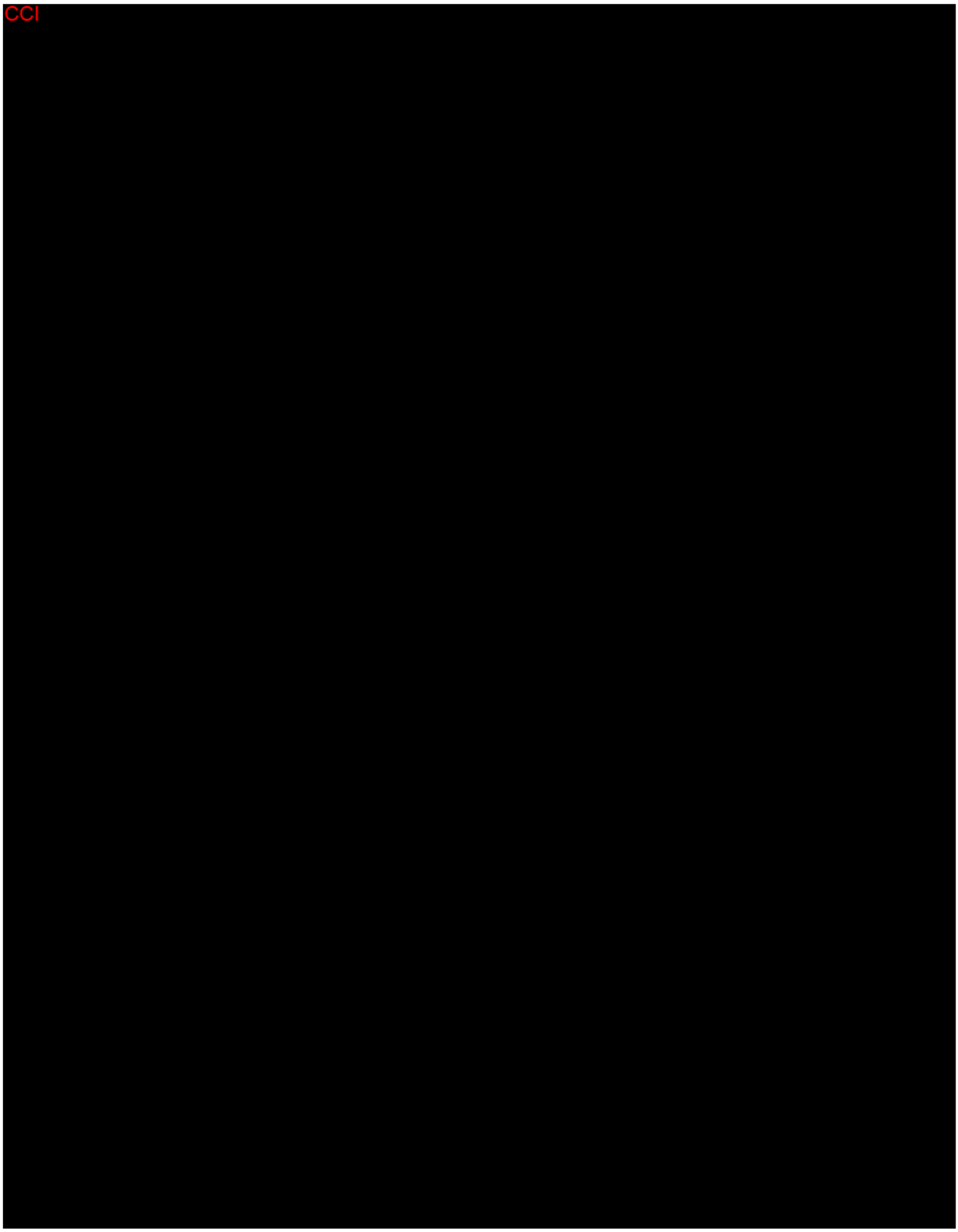
D 1 [redacted]

[redacted]

D 2 [redacted]

[redacted]


CCI


CCI

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

E 1 Introduction

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

During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the study intervention.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law

Aspartate aminotransferase or ALT $\geq 3 \times$ ULN **together with** TBL $\geq 2 \times$ ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

Hy's Law

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

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

E 3 Identification of Potential Hy's Law Cases

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

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

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

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Section E 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria Not Met

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

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

E 4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study intervention (See Section E 6)
- Notify the AstraZeneca representative who will then inform the central Study Team

- Within one day of PHL criteria being met, the investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For patients that met PHL criteria prior to starting study intervention, the investigator is not required to submit a PHL SAE unless there is a significant change in the patient's condition
- The Study Physician contacts the investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up (including any further laboratory testing) and the continuous review of data
- Subsequent to this contact the investigator will:
  - Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician.
  - Complete the three Liver eCRF Modules as information becomes available.

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

E 5 Review and Assessment of Potential Hy's Law Cases

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

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the study intervention, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

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

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

whether the AE meets the criteria for an SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

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

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

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to study intervention and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Intervention

This section is applicable to patients with liver metastases who meet PHL criteria on study intervention, having previously met PHL criteria at a study visit prior to starting study intervention.

At the first on-study intervention occurrence of PHL criteria being met the investigator will determine if there has been a **significant change** in the patients' condition compared with the last visit where PHL criteria were met.

- If there is no significant change no action is required
- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Section E 4.2.

E 7 Actions Required for Repeat Episodes of Potential Hy's Law

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

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

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

> Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study eg, chronic or progressing malignant disease, severe infection or liver disease or did the patient meet PHL criteria prior to starting study intervention and at their first on-study intervention visit as described in Section E 6 of this Appendix?

If **No**: follow the process described in Section E 4.2 for reporting PHL as an SAE.

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

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section E 4.2 for reporting PHL as an SAE

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

E 8 References

Aithal et al, 2011
Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther. 2011;89(6):806-15.

FDA Guidance for Industry, July 2009
FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'. Available from; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation. Accessed 06 April 2020.

Appendix F New York Heart Association classification of heart disease

F 1 NYHA Classification of Heart Disease

NYHA class	Symptoms
I	No symptoms and no limitation in ordinary physical activity, eg, shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, eg, walking short distances (20 to 100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

F 2 References

New York Heart Association 1994
The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th edition. Boston, MA: Little, Brown & Co; 1994. p. 253-6.

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

Definition of Women of Childbearing Potential

Women of Childbearing Potential:

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

Women NOT of Childbearing Potential:

Women who are permanently or surgically sterilised or post-menopausal (definitions below): Permanent sterilisation includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal occlusion. Tubal occlusion is considered a highly effective method of birth control but does not absolutely exclude possibility of pregnancy. (The term occlusion refers to both occluding and ligating techniques that do not physically remove the oviducts).

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

Acceptable contraception methods

Highly effective method of birth control is defined in Note 3 in ICH Guidance M3 (Nonclinical Safety Studies for the conduct of Human Clinical trials for Pharmaceuticals) as one that results in a low failure rate (eg, less than 1 percent per year) when used consistently and correctly.

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

Acceptable contraception methods are:

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

Unacceptable contraception methods

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

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

Appendix H Guidelines for Evaluation of Objective Tumour Response using RECIST 1.1 Criteria

H 1 Introduction

This appendix details the implementation of RECIST 1.1 guidelines (Eisenhauer et al 2009). Investigator assessments will use the RECIST 1.1 guidelines described in this Appendix.

H 2 Imaging Modalities and Acquisition Specifications for RECIST 1.1

A summary of the imaging modalities that can be used for tumour assessment of TLs, NTLs, and NLs is provided in Table H1.

Table H1 Summary of Imaging Modalities for Tumour Assessment

Target lesions	Non-target lesions	New lesions
CT	CT	CT
MRI	MRI	MRI
	Plain X-ray	Plain X-ray
	Chest X-ray	Chest X-ray
		Bone scan (Scintigraphy)
		FDG-PET/CT

CT = Computed tomography; FDG-PET/CT = Fluorodeoxyglucose-positron emission tomography/CT; MRI = Magnetic resonance imaging.

H 2.1 CT and MRI

Computed tomography with IV contrast is the preferred imaging modality (although MRI with IV contrast is acceptable if CT is contraindicated) to generate reproducible anatomical images for tumour assessments (ie, for measurement of TLs, assessment of NTLs, and identification of NLs). It is essential that the same correct imaging modality, image acquisition parameters (eg, anatomic coverage, imaging sequences, etc), imaging facility, tumour assessor (eg, radiologist), and method of tumour assessment (eg, RECIST 1.1) are used consistently for each patient throughout the study. The use of the same scanner for serial scans is recommended, if possible. It is important to follow the image collection/tumour assessment schedule as closely as possible (refer to the SoAs; Table 1 and Table 2), and this on-study imaging schedule MUST be followed regardless of any delays in dosing or missed imaging visits. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the patient has not progressed, every attempt should be made to perform the subsequent scan acquisitions at the next scheduled imaging visit.

Due to its inherent rapid acquisition (seconds), CT is the imaging modality of choice. Body

scans should be performed with breath-hold scanning techniques, if possible. Therefore, CT of the chest is recommended over MRI due to significant motion artefacts (eg, heart, major blood vessels, breathing) associated with MRI. Magnetic resonance imaging has excellent contrast and spatial and temporal resolutions; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline, and the lesions should be measured/assessed on the same pulse sequence. In general, local oncology diagnostic imaging parameters are applied for scan acquisition.

The most critical CT and MRI image acquisition parameters for optimal tumour evaluation are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

a. Anatomic coverage: Optimal anatomic coverage for most solid tumours is the chest-abdomen (and often pelvis). Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

Required anatomical regions to be imaged for assessment of tumour burden (TLs and/or NTLs) at baseline and follow-up visits vary according to the study, and these timepoints are specified in the SoAs (Table 1 and Table 2). Examples include the following:

- IV contrast-enhanced CT of chest-abdomen (including the entire liver and both adrenal glands) (-pelvis)
- Non-contrast CT of chest and IV contrast-enhanced abdomen (including the entire liver and both adrenal glands) (-pelvis)
- IV contrast-enhanced MRI (preferred) or CT of the brain

For chest-abdomen (-pelvis) imaging, the following are scanning options in decreasing order of preference, with additional options (2 to 4) for consideration when patients have sensitivity to IV contrast or have compromised renal function:

1 Chest-abdomen (-pelvis) CT with IV CT contrast (most preferred)
2 Chest CT without IV-contrast + abdomen (-pelvis) MRI with IV MRI contrast, if CT IV contrast (iodine based) is medically contraindicated at any time during the study
3 Chest-abdomen (-pelvis) CT without IV contrast, if both IV CT and MRI contrast are medically contraindicated or the patient has compromised renal function

4 Chest-abdomen (-pelvis) MRI with IV MRI contrast, if CT cannot be performed at any time during the study

b. IV contrast administration: Optimal visualisation and measurement of metastases in solid tumours require consistent administration (dose and rate) of IV contrast as well as timing of scanning. An adequate volume of a suitable contrast agent should be given so that the tumour lesions are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. Oral contrast is recommended to help visualise and differentiate structures in the abdomen and pelvis.

c. Slice thickness and reconstruction interval: It is recommended that extracranial CT or MRI scans be acquired/reconstructed as contiguous (no gap) slices with ≤ 5-mm thickness throughout the entire anatomic region of interest for optimal lesion measurements. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses > 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

For CT scans, all window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study.

H 2.1.1 Brain MRI

It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. For optimal brain scan acquisition however, the recommended MRI sequences include a T1-weighted scan (≤ 1.5mm slice thickness) before gadolinium contrast administration as well as an identical T1 sequence after contrast administration. Fluid-attenuation inversion-recovery, diffusion-weighted and T2-weighted sequences can help in the identification and assessment of brain metastases.

H 2.2 Chest X-rays

Chest X-ray assessments will not be used for assessment of TLs. Chest X-rays can, however, be used to assess NTLs and to identify the presence of NLs. However, there is preference that a higher resolution modality, such as CT, be used to confirm the presence of NLs.

H 2.3 Plain X-ray

Plain X-ray may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.

H 2.4 Isotopic Bone Scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI or X-ray at baseline should be recorded as NTLs and followed by the same method as per baseline assessment.

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions may be recorded in case positive hot-spots appear on a bone scan that were not present on a previous bone scan; however, a newly observed equivocal hot-spot on a bone scan that cannot be verified with correlative imaging (CT, MRI, or X-ray) of the same anatomical region shall not be the only trigger for a PD assessment at that time point.

H 2.5 FDG-PET

^{18}F-Fluorodeoxyglucose positron emission tomography/CT scans may be used as a method for identifying NLs for RECIST 1.1 assessments according with the following algorithm: NLs will be recorded where there is positive ^{18}F-Fluorodeoxyglucose uptake which is not present on the baseline or prior FDG-PET scan or when its location corresponds to NL on a companion CT/MRI that has been collected close in time to the FDG-PET scan. A positive FDG-PET scan lesion should be reported only when an uptake (eg, standardised uptake values) greater than twice that of the surrounding tissue or liver is observed. The PET portion of the PET/CT introduces additional data that may bias an investigator if it is not routinely or serially performed. Therefore, if there is no baseline or prior FDG-PET scan available for comparison, and no evidence of NLs on companion CT/MRI scans, then follow-up CT/MRI assessments should continue as per the regular imaging schedule to verify the unequivocal presence of NLs.

At present, low-dose or attenuation correction CT portions of a combined FDG-PET/CT scan are of limited use in anatomically based efficacy assessments, and it is therefore suggested that they should not substitute for dedicated diagnostic contrast-enhanced CT scans for tumour measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed, as part of a PET/CT examination, is of identical diagnostic quality (with IV contrast) to a dedicated diagnostic CT scan, then the CT portion of the PET/CT can be used for RECIST 1.1 tumour assessments. Caution that this is not recommended because the PET portion of the CT introduces additional (PET) data that may bias an investigator if it is not routinely or serially recorded.

H 2.6 Ultrasound

Ultrasound examination will not be used for RECIST 1.1 assessment of tumours as it is not a reproducible method (operator dependent), is subjective in interpretation, and may not provide an accurate assessment of the true tumour size. Tumours identified by ultrasound will need to

be assessed by correlative CT or MRI anatomical scan.

H 2.7 Other Tumour Assessments

H 2.7.1 Clinical Examination

Clinical examination of skin/surface lesions (by visual inspection or manual palpation) will not be used for RECIST 1.1 assessments. Tumours identified by clinical examination will need to be assessed by correlative CT or MRI anatomical scans.

H 2.7.2 Endoscopy and Laparoscopy

Endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour measurements.

H 2.7.3 Histology and Cytology

Histology or tumour markers on tumour biopsy samples will not be used as part of the tumour response assessments per RECIST 1.1. Results of cytological examination for the neoplastic origin of any effusion (eg, ascites, pericardial effusion, and pleural effusion) that appears or worsens during the study will not be used as part of the tumour response assessment as per RECIST 1.1. Furthermore, an overall assessment of CR (all other disease disappears/reverts to normal) would be changed to PR if an effusion remains present radiologically.

H 2.8 Measurability of Tumour Lesions at Baseline

H 2.8.1 RECIST 1.1 Measurable Lesions at Baseline

A tumour lesion that can be accurately measured at baseline as ≥ 10 mm in the longest diameter for non-nodal lesions or ≥ 15 mm in short axis diameter for lymph node lesions with IV contrast-enhanced CT or MRI and that is suitable for accurate repeated measurements. The short axis is defined as the longest in-plane axis perpendicular to the long axis.

H 2.8.2 Non-measurable Lesions at Baseline

- Truly non-measurable lesions include the following:
  - Bone lesions (see exception below for soft tissue component)
  - Leptomeningeal disease
  - Ascites, pleural effusion, or pericardial effusion
  - Inflammatory breast disease
  - Lymphangitic involvement of skin or lung
- All other lesions, including small lesions, ie, longest diameter < 10 mm or pathological lymph nodes with ≥ 10-mm to < 15-mm short axis diameter at baseline. Please note that

lymph nodes with < 10-mm short axis diameter are considered non-pathological and should not be recorded or followed as NTLs.

- Previously irradiated lesions. Localised post-radiation changes that affect lesion size may occur. Therefore, lesions that have been previously irradiated are typically considered non-measurable and as assessed as NTL.
- Brain metastases should be assessed as NTLs.

H 2.8.3 Special Considerations Regarding Lesion Measurability at Baseline

- Bone lesions
  - Bone scan, PET scan, or plain X-ray are not considered adequate imaging techniques to measure bone lesions; however, these techniques can be used to confirm the presence or disappearance of bone lesions.
  - Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability.
  - Blastic lesions are considered non-measurable.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected over cystic lesions as TLs.

H 2.8.4 RECIST 1.1 TL Selection at Baseline

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes collectively considered as a single organ), representative of all lesions involved, should be identified as TLs at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. 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 that can be measured reproducibly, should be selected.

Lymph nodes, in any location (local/regional and distant), are collectively considered as a single organ, with a maximum of 2 lymph nodes as TLs. A bilateral organ (eg, adrenal glands), a segmented organ (eg, liver), or a multilobed organ (eg, lung) is each considered as a single organ.

The site and location of each TL should be documented as well as the longest axis diameter for non-nodal lesions (or short axis diameter for lymph nodes). All measurements should be

recorded in whole (integer) millimetres and calculated values should be rounded to whole numbers. At baseline, the sum of the diameters for all TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits, the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

Special Cases for TL Assessment at Baseline:

- For TLs measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis diameter.
- When lymph nodes are coalesced and no longer separable in a conglomerate mass, the maximal short axis diameter of the coalesced mass should be recorded. Non-nodal lesions that coalesce should similarly be assessed by the longest axis diameter.
- Tumour lesions selected for fresh screening biopsy or FNA FFPE cell block should not be selected as TLs, unless imaging occurred at least approximately 2 weeks after biopsy, allowing time for healing.
- If the CT/MRI slice thickness used is > 5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as a NL.

H 2.8.5 RECIST 1.1 NTL Selection at Baseline

All other lesions, including non-measurable lesions and surplus measurable lesions, not recorded as TLs should be identified as NTLs at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

H 2.9 Evaluation of Tumour Response and Progression

H 2.9.1 RECIST 1.1 TL Assessment at Follow-up

This section defines the criteria used to determine objective tumour visit response for RECIST 1.1-defined TLs. The imaging modality, location, and scan date of each TL identified previously at baseline should be documented at follow-up visits with the long axis diameter for non-nodal lesions or short axis diameter for lymph node lesions. All measurements should be recorded in whole millimetres. The sum of the diameters for all TLs at each follow-up visit will be compared to the baseline sum of diameters (for response or SD) or to the smallest prior (nadir) sum of diameters (for progression).

Special Cases for TL Assessment at Follow-up

- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as an NL.
- If a TL splits into 2 or more parts, the sum of the diameters of those parts should be recorded.
- If 2 or more TLs merge, then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s). If the merged TLs are non-nodal lesions, record the long axis diameter of the merged lesion. If pathologic lymph nodes coalesce and are no longer individually separable within a conglomerate mass, the maximal short axis diameter is recorded.
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion. The choice of "Too large to measure" in the case report form will trigger an overall visit response of PD.
- When a TL has had an unscheduled, non-protocol intervention, the following apply:
  - Target lesion intervention may include radiotherapy, embolisation, excisional biopsy, surgery, etc, that is not a part of study intervention and might adversely affect the size of that TL
  - If an Intervention on a TL is ticked in the CRF, the diameter of the lesion is still recorded (0 mm if no longer present) and is included in the sum of diameters.
  - If a TL Intervention is ticked, the intervention must be reported for all subsequent assessments of that TL.
  - If a TL has an Intervention, the only overall visit responses allowed to be recorded by the investigator are NE or PD, with PD if the sum of diameters exceeds a 20% increase and at least a 5 mm absolute increase in the visit sum of diameters compared to the previous minimum (nadir) sum of diameters.
  - No visit with a recorded Target lesion intervention can be used as the minimum (nadir) sum of diameters.

Table H2 RECIST Evaluation of Target Lesions

Complete response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis diameter to < 10 mm.
Partial response (PR)	At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters.
Stable disease (SD)	Neither sufficient decrease in the sum of diameters to qualify for PR nor sufficient increase to qualify for PD.
Progression of disease (PD)	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest previous sum of diameters (nadir)—This includes the baseline sum if that is the smallest on study. In addition to the relative increase of 20%, the sum must demonstrate an absolute increase of at least 5 mm from nadir.
Not evaluable (NE)	Only relevant if any of the TLs at follow-up were not assessed or NE (eg missing anatomy) or had a lesion intervention at this visit. Note: If the sum of diameters meets the PD criteria, PD overrides NE as a TL response.
Not applicable (NA)	Only relevant if no TLs present at baseline.

CR = Complete response; NA = Not applicable; NE = Not evaluable; PD = Progression of disease; PR = Partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SD = Stable disease; TL = Target lesion.

H 2.9.2 RECIST 1.1 NTL Assessment at Follow-up

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. At each visit an overall assessment of the NTL response should be recorded by the investigator.

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 presence of SD or PR in TLs, the overall tumour burden has increased sufficiently to merit unequivocal progression by NTLs. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

Table H3 RECIST 1.1 Evaluation of Non-target Lesions

Complete response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non CR/Non PD	Persistence of 1 or more NTLs.
Progressive Disease (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in 1 lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not evaluable (NE)	Only relevant when 1 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 no NTLs present at baseline.

CR = Complete response; NA = Not applicable; NE = Not evaluable; NTL = Non-target lesion;
PD = Progression of disease; RECIST = Response Evaluation Criteria in Solid Tumours; TL = Target lesion.

H 2.9.3 RECIST 1.1 NL Identification at Follow-up

Details, including the imaging modality, the date of scan, and the location of any NLs will also be recorded in the CRF. The presence of one or more NLs is assessed as progression. The finding of an NL should be unequivocal, ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour. If an NL is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the previously (pre-existing) new lesion has been assessed as unequivocal at a follow-up visit, and then the progression date should be declared using the date of the initial scan when the NL first appeared.

A lesion identified at a follow-up assessment in an anatomical location that was not scanned at baseline is considered an NL and will indicate PD.

H 2.9.4 RECIST 1.1 Evaluation of Overall Visit Response at Follow-up

Derivation of overall visit response as a result of the combined assessment of TLs, NTLs, and NLs uses the algorithm shown in Table H4.

Table H4 RECIST 1.1 Overall Visit Response

Target lesions	Non-target lesions	New lesions	Overall visit response
CR	CR	No	CR
CR	NA	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE or NA	No	PR
SD	Non-PD or NE or NA	No	SD
NE	Non-PD or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note: An overall assessment of CR (all other disease disappears/reverts to normal) would be changed to PR if ascites remains present radiologically.
CR = Complete response; NA = Not applicable (only relevant if there were no non-target lesions at baseline, however at least one target lesion is an entry criterion for the study); NE = Not evaluable; PD = Progression of disease; PR = Partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SD = Stable disease.

The following overall visit responses are possible depending on the extent of tumour disease at baseline:

- For patients with TLs (at baseline): CR, PR, SD, PD, or NE
- For patients with NTLs only (at baseline): CR, Non-CR/Non-PD, PD, or NE
- For patients with no disease at baseline: NED (available as an option in the eCRF), PD, or NE

H 2.9.5 Central Imaging

Images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed imaging CRO for quality control, storage, and for BICR. Guidelines for image acquisition, de-identification, storage of digital copies at the investigative site (as source documents), and transfer to the imaging CRO will be provided in a separate document. Electronic image transfer from the sites to the imaging CRO is strongly encouraged. A BICR of images will be performed at the discretion of AstraZeneca. Results of these independent reviews will not be communicated to investigators, and results of investigator RECIST 1.1 assessments will not be shared with the central reviewers. The management of patients will be based in part upon the results of the RECIST 1.1 assessment conducted by the investigator. Further details of the BICR will be documented in the Independent Review Charter.

H 3 References

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

Appendix I Dose Modifications for the Management of Adverse Events

I 1 Management of Study Treatment-related Toxicities

The patient will be continuously evaluated for AEs during the study. AEs are to be assessed according to the NCI CTCAE Version 5.0. The investigator should attribute the AE to a specific drug or to the combination if it is not possible to assign the AE to a specific study intervention. This is to guide dose modifications that may lead to a treatment hold, dose reduction and/or discontinuation of a specific study intervention. If there are multiple or overlapping toxicities or where the relationship is not clear, the investigator should consult with the AstraZeneca Study Team.

Dose modification guidelines for toxicities related to osimertinib and savolitinib are shown in Table I1 and toxicities that require permanent discontinuation of study treatment are shown in Table I2.

Table I1 Study Treatment Dose Modification Instructions for Toxicities Related to Osimertinib and/or Savolitinib (excluding toxicities that require specific management guidelines)

CTCAE Grade [a]	Instructions for osimertinib	Instructions for savolitinib
Grade 2 or lower	Continue and treat with supportive measures (as per local practice)	Continue and treat with supportive measures (as per local practice)
Grade 3	Withhold osimertinib for up to 3 weeks If the AE improves to ≤ Grade 2 after withholding of osimertinib for up to 3 weeks, osimertinib may be restarted at the same dose CCI or a lower dose CCI. If the AE does not improve to ≤Grade 2 after withholding for up to 3 weeks, permanently discontinue osimertinib. See also toxicity specific guidance.	Withhold savolitinib Savolitinib may be restarted at the same dose or consider a dose reduction upon recovery of the AE to ≤ Grade 2 within 7 days [b] Savolitinib should be permanently discontinued if the AE does not recover to ≤Grade 2 within 7 days. If this is a recurrence of the same Grade 3 toxicity, resume dosing at one reduced dose level (maximum of 2 dose reductions) as clinically appropriate upon recovery of the AE to ≤ Grade 2 within 7 days [b]
Grade 4	Permanently discontinue if related to osimertinib.	Withhold savolitinib and discuss with the AstraZeneca Study Team. Continuation of savolitinib depends on whether the AE is reversible or manageable with a dose reduction. If it is not expected that the AE is manageable or reversible with a dose reduction, discontinue savolitinib.

CTCAE Grade [a]	Instructions for osimertinib	Instructions for savolitinib
		If this is a recurrence of the same Grade 4 toxicity, permanently discontinue savolitinib.

[a] AEs need to be assessed according to the NCI CTCAE Version 5.0.
[b] Resumption of savolitinib must follow the specific restart guidelines if the event is a constellation of pyrexia, skin reactions, myalgia, arthralgia or hypersensitivity, see Section I 3.3

Note: For instructions regarding any AE that requires permanent discontinuation see Table I2. For instructions on dose reduction for osimertinib, see Table I4; for instructions on dose reductions for savolitinib, see Table I5. If the study intervention has been reduced to the lowest dose level in the protocol, the patient will be permanently discontinued from the study intervention.
AE = Adverse event; CTCAE = Common Technology Criteria for Adverse Events; NCI = National Cancer Institute.

Table I2 Toxicities that Require Permanent Discontinuation of Study Treatment

Toxicity	Instructions for osimertinib	Instructions for savolitinib
Pulmonary: Interstitial lung disease or pneumonitis	Permanently discontinue osimertinib	Not applicable
Cardiovascular: QTc interval prolongation with signs/symptoms of serious arrythmia	Permanently discontinue Osimertinib	Permanently discontinue savolitinib
Symptomatic congestive heart failure	Permanently discontinue osimertinib	Not applicable
Hepatic	Not applicable	See Section I 3.2 for drug-related hepatotoxicity meeting the criteria for discontinuation
Dermatological	Withhold osimertinib for suspected cases of SJS or EMM. Permanently discontinue osimertinib for confirmed cases of SJS or EMM.	Discontinue in the case of confirmed or suspected SJS
Acute hypersensitivity	Not applicable	Discontinue in the case of acute hypersensitivity

EMM = Erythema Multiforme Major; QTc = corrected QT interval; SJS = Stevens-Johnson syndrome.

Patients experiencing ILD will not be permitted to restart osimertinib. Patients experiencing QTc prolongation with signs/symptoms of serious arrhythmia will not be permitted to restart study treatment.

I 1.1 Guidelines for the Management of Overlapping Toxicities Between Osimertinib and Savolitinib

QTc Prolongation

QTc prolongation is a recognised toxicity of osimertinib and savolitinib; management of this toxicity is summarised in Table I3.

Table I3 Management of QTc Prolongation

CTCAE Grade	Instructions for osimertinib	Instructions for savolitinib	Further investigation required
CTCAE Grade 1 or Grade 2	No action required	No action required	Review concomitant treatments and co-morbidities for risks of QT prolongation or risk for TdP [a]
CTCAE Grade 3 (QTc interval > 500 msec or > 60 msec change from baseline on at least 2 separate ECGs)	Withhold osimertinib until QTcF interval is < 481 msec, or has recovered to baseline if baseline QTc was > 481 msec, within 21 days of interruption. Then restart osimertinib at a reduced dose CCI CCI at the discretion of the investigator, to allow for situations where causality in relation to osimertinib may be difficult to determine.	Withhold savolitinib until QTcF interval is < 481 msec. If the QTcF resolves to < 481 msec in 21 days, restart savolitinib at a reduced dose.	Review concomitant treatments and co-morbidities for risks of QT prolongation or risk for TdP [a] Consult with cardiologist to validate ECG finding. Ensure cardiac surveillance and take actions in accordance with clinical standards. Regular ECGs performed until resolution to QTcF < 481 msec.
	If the QTcF does not resolve to < 481 msec in 21 days, discontinue osimertinib.	If the QTcF does not resolve to < 481 msec in 21 days, discontinue savolitinib.	Consult with a cardiologist for further management as clinically indicated.
CTCAE Grade 4 (TdP; polymorphic ventricular tachycardia; signs and symptoms of serious arrhythmia)	Discontinue osimertinib	Discontinue savolitinib	Consult with a cardiologist for further management as clinically indicated.

[a] For guidance regarding potential interactions with concomitant medications known to prolong the QT interval, see Section J 5.

CTCAE = Common Terminology Criteria for Adverse Events; ECG = Electrocardiogram; QTc = corrected QT interval; QTcF = QT interval calculated using Fridericia's correction; TdP = Torsades de Pointes.

In light of the potential for QT changes associated with osimertinib, and in accordance with GCP, it is recommended that correction of clinically significant electrolyte abnormalities (hypokalaemia, hypomagnesaemia, hypocalcaemia) to within normal ranges takes place prior to first dose and is monitored during treatment with osimertinib.

The QTc interval prolongation potential of savolitinib 600 mg was assessed in a thorough QT study in healthy volunteers. Analysis of the data showed that it was a positive study, as the upper bounds of the 2-sided 90% CI for the mean ΔΔQTcF were up to 13.6 msec and 14 msec, at 4 hours and 5 hours, respectively. QTcF will be assessed frequently on triplicate ECG assessments performed at regular intervals throughout the study according to the SoA.

Erythema Multiforme and Stevens-Johnson Syndrome

Case reports of EM (including Erythema Multiforme Major [EMM]) and SJS have been uncommonly and rarely reported, respectively, in association with osimertinib treatment. Before initiating treatment, patients should be advised of signs and symptoms of EM/EMM and SJS. If signs and symptoms suggestive of EM/EMM develop, close patient monitoring and drug interruption or discontinuation of osimertinib should be considered. If signs and symptoms suggestive of SJS appear, osimertinib should be interrupted or discontinued immediately.

A case of SJS has been reported in temporal association with savolitinib. Patients who show symptoms or signs suggesting emerging SJS while on study treatment (eg, progressive skin rash often with blisters or mucosal lesions) must discontinue savolitinib immediately and receive appropriate treatment. If emerging SJS is suspected, re-challenge with savolitinib must be avoided.

I 2 Osimertinib Dose Modification and Guidance

Osimertinib management should be in accordance with the local label in the first instance.

If a patient experiences a CTCAE Grade 3 and/or unacceptable toxicity (excluding ILD, QTc prolongation, keratitis, and EMM/SJS) including a DLT not attributable to the disease or disease-related processes under investigation, dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines.

If a toxicity (excluding ILD, QTc prolongation, keratitis, and EMM/SJS) resolves or reverts to ≤ CTCAE Grade 2 within 3 weeks of onset, treatment with osimertinib may be restarted at the same dose [redacted] or a lower dose [redacted] using the rules below for dose modifications (Table I4) and with discussion and agreement with the AstraZeneca Study Team Physician as needed. There will be no individual modifications to dose regimen in response to toxicity, only potential dose reduction or dose interruption.

If the toxicity (excluding ILD, QTc prolongation, keratitis, and EMM/SJS) does not resolve to ≤ CTCAE Grade 2 after 3 weeks of withholding osimertinib, then the patient should be withdrawn from the study and observed until resolution of the toxicity (Table I1).

Table I4 Dose Reduction for Osimertinib to Manage Adverse Events

	Starting osimertinib dose CCI
Reduced dose -1	CCI

On resolution of toxicity within 3 weeks:

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

I 2.1 ILD/Pneumonitis-like Toxicity

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormality suggestive of ILD is observed, an interruption in osimertinib dosing is recommended, and the AstraZeneca study team should be informed. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic oedema or pulmonary haemorrhage. The results of full diagnostic workup (including high resolution CT, blood and sputum culture, haematological parameters) will be captured by eCRF. All image data should be provided to AstraZeneca. In the presence of confirmatory high resolution CT scans where other causes of respiratory symptoms have been excluded, a diagnosis of ILD should be considered and osimertinib permanently discontinued.

I 2.2 Keratitis

Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.

I 2.3 Changes in Cardiac Contractility

Based on the available clinical study data, a causal relationship between effects on changes in cardiac contractility and osimertinib has not been established. In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including an assessment of LVEF at baseline and during treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.

I 3 Savolitinib Dose Modification and Guidance

I 3.1 Savolitinib Dose Modification and Guidance

Substantial acute toxicities should be managed as medically indicated and with temporary suspension of savolitinib, as appropriate unless due to suspected hypersensitivity (see Section I 3.3).

Dose reductions or holds are allowed as clinically indicated by the treating physician and in line with Table I5 and Table I1. For each patient, a maximum of 2 dose reductions of savolitinib will be allowed. No dose re-escalations are allowed. Guidance on dose level reduction is presented in Table I5.

Table I5 Dose Reduction for Savolitinib Adverse Events

	Starting savolitinib dose CCI
Reduced dose -1	CCI
Reduced dose -2	CCI

Note: Only 2 dose reductions of savolitinib are permitted.

I 3.2 Hepatotoxicity Management Guideline

- Promptly evaluate patients with elevated LFTs during treatment with savolitinib for alternative aetiologies and PHL criteria, and discontinue potential contributing concomitant medications or alternative causal agents, as well as anti-coagulants, if appropriate.
- Ensure a PK sample is collected as soon as feasible when the patient discontinues due to an AE reaction (see Table 1, Table 2 and Section 8.5).
- If a patient discontinues due to LFT abnormality, LFT monitoring should continue until resolved to Grade 1 or baseline or an apparent plateau has been reached.

I 3.2.1 Dose Modification Due to Drug-related Hepatotoxicity

- Discontinue drug if:
  - ALT or AST > 8 × ULN with TBL elevation above baseline or ULN, or
  - ALT or AST > 5 × ULN for up to one week (< 7 days) with TBL elevation above baseline or ULN, following immediate withholding of drug. Repeat LFT testing within 2 to 3 days and at least twice a week until improvement to Grade 1 or baseline.
  - ALT or AST > 3 × ULN and (TBL >2 × ULN or INR>1.5 if not on anticoagulants that elevate the INR), or

  - AST or ALT > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia > 5%
- Withhold dosing if ALT or AST > 5 × ULN for > 2 weeks or 8 × ULN without TBL elevation above baseline or ULN, repeat LFT testing twice a week for one week:
  - If improved to Grade 1 or baseline in one week, resume at reduced dose with LFT testing twice a week for 6 weeks
  - If not, discontinue
- Withhold dosing if ALT or AST > 3 × ULN and concurrent TBL > 1.5 × ULN, repeat LFT testing twice a week for one week:
  - If both ALT/AST and TBL improved to Grade 1 or baseline in one week, resume at reduced dose with LFT testing twice a week for 6 weeks
  - If not, discontinue
- Withhold dosing if ALT or AST > 3 × ULN and concurrent TBL > 1 × ULN to 1.5 × ULN, repeat LFT testing twice a week for one week,
  - If both ALT/AST and TBL improved to normal range (< Grade 1) or baseline in one week, resume at same dose with LFT testing twice a week for 6 weeks
  - If not, resume at reduced dose
- Continue dosing if ALT or AST > 3 × ULN without TBL elevation above baseline or ULN, repeat LFT testing every week
  - If ALT or AST trending upward, withhold dosing and repeat LFT twice a week for one week
  - If improve to Grade 1 or baseline in one week, resume at same dose with LFT testing every week for 6 weeks
  - If improve to Grade 1 or baseline in 2 weeks, resume at reduced dose with LFT testing every week for 6 weeks
  - If not, discontinue
- Discontinue for recurrent ALT or AST > 5 × ULN
- Discontinue for recurrent ALT or AST > 3 × ULN and TBL > 1.5 × ULN
- Withhold dosing for recurrent ALT or AST > 3 × ULN without TBL elevation above baseline or ULN, repeat LFT testing twice a week for one week
  - If improve to Grade 1 or baseline in one week, resume at reduced dose with LFT testing every week for 6 weeks; if not, discontinue

I 3.3 Guidance for Management of Savolitinib Specific Toxicities

Hypersensitivity: Hypersensitivity, which may manifest as a constellation of symptoms such as but not limited to pyrexia, allergic skin reaction, increased liver enzymes, cytopenia, or myalgia and/or arthralgia has been reported after savolitinib dosing. These reactions have occurred within days to weeks after the first dose but the majority of reactions have occurred in the first six weeks of therapy. Patients with suspected savolitinib-related hypersensitivity (excluding confirmed infective aetiology), may be managed with corticosteroids, antihistamines and antipyretics (doses and duration of treatment according to local practice at the discretion of the investigator). Dose interruption with savolitinib should be avoided, if possible. Some patients who experienced the initial hypersensitivity reaction also reported severe acute hypersensitivity reactions, including anaphylaxis, upon restarting savolitinib treatment following a short period of interruption.

Restarting savolitinib: acute hypersensitivity including anaphylaxis has been observed in a number of patients mostly upon savolitinib restart. If interruption of savolitinib occurs in the first 6 weeks of savolitinib due to savolitinib-related general toxicities, or specific hypersensitivity toxicities occur at any time, dosing with savolitinib may be resumed but at a reduced dose, only after consultation with and approval from the study physician and with the following management:

- Treatment:
  - Pre-treatment with systemic corticosteroids must be started at least 24 hours before the restart of savolitinib;
  - Pre-treatment with antipyretics and antihistamines on the day of restart of savolitinib;
  - Doses of antihistamines, corticosteroids and antipyretics should be according to labelling instructions/product information.
  - These medications must be continued daily until discontinuation of savolitinib, but doses of steroids may subsequently be tapered according to local practice

- Intense medical monitoring (restart at the institution);
  - The restart of savolitinib must be performed in the hospital/institution where the clinical study is carried out with medical equipment readily available for resuscitation and management of anaphylaxis
  - Vital status recording (BP, temperature, respiratory rate, heart rate, etc) before administration of savolitinib, every 15 minutes after savolitinib dosing for the first hour, every 30 minutes for the next hour and hourly for a total of at least 4 hours and
  - Patient must be observed in the clinic for 24 hours before discharge.

- Should the symptoms recur, or an acute anaphylactic reaction occurs, immediate intervention must be instituted for appropriate management of event and savolitinib must be permanently discontinued.

Any recommendations regarding hypersensitivity management or pre-treatment should be used as guidelines only. Final decisions concerning management of individual patients reside with the investigator or the treating physician.

Appendix J Guidance Regarding Potential Interactions with Concomitant Medications

The use of any natural/herbal products or other "folk remedies" should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements and all other concomitant medications must be recorded in the eCRF.

J 1 Drugs Inducing CYP3A4 Metabolism that AstraZeneca Strongly Recommend are not Combined with Osimertinib or Savolitinib

Osimertinib and savolitinib are metabolised by CYP3A4 and CYP3A5 enzymes.

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

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

Table J1 Drugs Inducing CYP3A4

Contraindicated drugs	Withdrawal period prior to osimertinib or savolitinib start
Avasimibe, carbamazepine, mitotane, phenobarbital (phenobarbitone), phenytoin, rifampicin, rifabutin, rifapentin St John's Wort	3 weeks
Enzalutamide	5 weeks

CYP = Cytochrome P450.

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

J 2 Drugs Inhibiting CYP1A2 Metabolism that AstraZeneca Strongly Recommend are not Combined with Savolitinib

Table J2 Drugs Inhibiting CYP1A2

Contraindicated drugs	Withdrawal period prior to savolitinib start
Ciprofloxacin, Enoxacin, Clinafloxacin Fluvoxamine	2 weeks

CYP = Cytochrome P450.

This list is not intended to be exhaustive, and a similar restriction will apply to other agents

that are known to strongly inhibit CYP1A2 activity. Appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue.

Savolitinib is a weak inhibitor of Organic Anion Transporter Protein B1 and B3, and BCRP. The use of statins should be avoided as far as possible and if considered necessary, the patients should be given the lowest available dose and closely monitored for the effects of increased statin exposure.

J 3 Medicines whose Exposures may be Affected by Osimertinib that AstraZeneca Considers may be Allowed with Caution

Osimertinib may increase the concentrations of sensitive BCRP or P-gp substrate (concentrations of sensitive BCRP substrate, rosuvastatin or P-gp substrate, fexofenadine is increased).

Table J3 Exposure, Pharmacological Action and Toxicity may be Increased or Decreased by Osimertinib

Warning of possible interaction	Advice
Rosuvastatin Sulfasalazine Doxorubicin Daunorubicin Topotecan Aliskiren Dabigatran etixelate Digoxin	Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with osimertinib.

J 4 Medicines whose Exposures may be Affected by Savolitinib that AstraZeneca Strongly Recommend are not Combined with Savolitinib

Cytochrome P450 3A4 substrates which have a narrow therapeutic range must not be taken within 2 weeks of the first dose of savolitinib treatment (3 weeks for St John's Wort) and for 3 weeks after the last dose of savolitinib.

Patients are not permitted to receive warfarin when patients are treated with savolitinib. Low molecular weight heparin is allowed.

Any cytotoxic chemotherapy, investigational agents or other anti-cancer drugs for the treatment of advanced NSCLC from a previous treatment regimen or clinical study within 14 days of the first dose of savolitinib.

J 5 Drugs that may Prolong QT Interval

The drugs listed in this section are taken from information provided by The Arizona Center for Education and Research on Therapeutics on the CredibleMeds® website: https://www.crediblemeds.org. The website categorises drugs based on the risk of inducing TdP.

During screening, the drugs that patients are currently receiving (prescribed and non-prescription) should be checked against the Arizona Center website above. In addition, drugs intended for use following study intervention initiation should be checked against the website.

J 5.1 Drugs with a Known Risk of TdP

The following drugs prolong QT interval and are clearly associated with a known risk of TdP even when taken as recommended. These drugs must have been discontinued prior to the start of administration of study intervention, in accordance with guidance provided in Table J4 and should not be co-administered with savolitinib or osimertinib and for a period of two weeks after discontinuing study intervention.

The list of drugs may not be exhaustive and is subject to change as new information becomes available. As such, investigators are recommended to search the Arizona Center website to confirm the most up to date information. Recommended withdrawal periods following cessation of treatment with these agents are provided in Table J4.

Table J4 Drugs with a Known Risk of TdP

Contraindicated drugs	Withdrawal period prior to osimertinib and/or savolitinib start [b]
Aclarubicin, anagrelide, ciprofloxacin, clarithromycin, cocaine, droperidol, erythromycin, levofloxacin, ondansetron, papaverine hydrochloride, procainamide, sulpiride, sultopride, terfenadine, terlipressin.	2 days
Cilostazol, cisapride, disopyramide, dofetilide, domperidone, flecainide, gatifloxacin, grepafloxacin, ibutilide, moxifloxacin, oxaliplatin, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sparfloxacin, thioridazine	7 days
Azithromycin, bepridil, citalopram, chlorpromazine, dronedarone, escitalopram, fluconazole, halofantrine, haloperidol, levomepromazine, levosulpiride, mesoridazine	14 days
Donepezil, terodiline	3 weeks
Levomethadyl, methadone, pimozide	4 weeks
Arsenic trioxide [a], ibogaine	6 weeks
Pentamidine	8 weeks
Astemizole, probucol, vandetanib	4 months
Amiodarone, chloroquine	1 year

[a] Estimated value as pharmacokinetics of arsenic trioxide has not been studied.
[b] Values determined from comprehensive review (internal to AstraZeneca) of each compound's PK half-life and determination of the wash-out period.
This list should be checked against the full and most current list presented in the CredibleMeds® website (https://www.crediblemeds.org/).
PK = pharmacokinetic; TdP = Torsades de Pointes.

J 5.2 Other TdP Risk Categories

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

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

J 5.3 Guidance Regardless of TdP Risk Category

During study intervention and for a period of 2 weeks after discontinuing study intervention if it is considered essential for patient management to co-administer drugs known to prolong QTc interval, regardless of TdP risk category, close monitoring of ECGs and electrolytes is recommended.

J 5.4 Drugs that may Possibly Prolong QT Interval

The use of the following drugs is permitted (notwithstanding other exclusions and restrictions) provided the patient has been stable on therapy for the periods indicated.

Table J5 Drugs that may Prolong QT Interval

Drug	Minimum treatment period on medication prior to osimertinib start
Alfuzosin, chloral hydrate, ciprofloxacin, dolasetron, foscarnet, galantamine, gemifloxacin, isridipine, ketoconazole, levofloxacin, mexiletine, nicardipine, octreotide, ofloxacin, ondansetron, quetiapine, ranolazine, telithromycin, tizanidine, vardenafil, venlafaxine, ziprasidone	2 days
Amantadine, amitriptyline, amoxapine, clozapine, doxepin, felbamate, flecainide, fluconazole, fosphenytoin, gatifloxacin, granisetron, imipramine, indapamide, lithium, moexipril/HCTZ, moxifloxacin, risperidone, roxithromycin, sertraline, trimethoprim-sulfa, trimipramine, voriconazole	7 days
Azithromycin, citalopram, clomipramine, itraconazole, nortriptyline, paroxetine, solifenacin, tacrolimus	14 days
Fluoxetine	5 weeks
Protriptyline	6 weeks
Tamoxifen	8 weeks

J 6 References

The Arizona Center for Education and Research on Therapeutics on the CredibleMeds® website
Available at URL: https://www.crediblemeds.org. Accessed on 06 April 2020.

Appendix K Abbreviations

Abbreviation or special term	Explanation
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC_{ss}	Area under the plasma concentration-time curve at steady state
B	Blood
BCRP	Breast cancer resistance protein
BICR	Blinded independent central review
BP	Blood pressure
C_{1h}	Plasma concentration at 1 hour
C_{3h}	Plasma concentration at 3 hours
CEP7	Centromeric portion of chromosome 7
CI	Confidence interval
CL_{ss}/F	Apparent clearance at steady state
CMH	Cochran–Mantel–Haenszel
COVID-19	Coronavirus 2019
$C_{pre\text{-}dose}$	Plasma concentration pre-dose
CPQP	Clinical Pharmacology and Quantitative Pharmacology
CR	Complete response
CRO	Contract Research Organisation
CSP	Clinical Study Protocol
CSR	Clinical Study Report
C_{ssmax}	Maximum plasma concentration at steady state
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumour DNA
CYP	Cytochrome P450
DCO	Data cut-off
DILI	Drug induced liver injury
DoR	Duration of response
ECG	Electrocardiogram

Abbreviation or special term	Explanation
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EGFRm	Epidermal growth factor receptor mutation
EGFRm+	Epidermal growth factor receptor mutation positive
EM	Erythema multiforme
EMM	Erythema Multiforme Major
FAS	Full Analysis Set
FDA	US Food and Drug Administration
FDG-PET	Fluorodeoxyglucose-positron emission tomography
FFPE	Formalin-Fixed, Paraffin-Embedded
FISH	Fluorescence in situ hybridisation
FNA	Fine needle aspiration
GCP	Good Clinical Practice
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDPE	High-density polyethylene
HGF	Hepatocyte growth factor
HIV	Human immunodeficiency virus
HL	Hy's Law
CCI	CCI
HR	Hazard ratio
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
I-HAC	Independent Hepatic Assessment Committee
ILD	Interstitial lung disease
INR	International Normalisation Ratio
IO	Immune-oncology

Abbreviation or special term	Explanation
IRB	Institutional Review Board
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LFT	Liver function test
LLN	Lower limit of normal
LMWH	Low molecular weight heparin
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MET	Hepatocyte growth factor receptor
MRI	Magnetic resonance imaging
MUGA	Multi-gated acquisition
NCCN	National Comprehensive Cancer Network
NE	Not evaluable
NL	New lesions
NSCLC	Non-small cell lung cancer
NTL	Non-target lesions
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
P	Plasma
PD	Progression of disease
PFS	Progression-free survival
PHL	Potential Hy's law
PK	Pharmacokinetics
PR	Partial response
Q6/8/12W	Every 6/8/12 weeks
QTc	Corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumours
CCI	CCI
S	Serum
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set

Abbreviation or special term	Explanation
SD	Stable disease
SJS	Stevens-Johnson syndrome
SoAs	Schedule of activities
TBL	Total bilirubin
TdP	Torsades de Pointes
TKI	Tyrosine kinase inhibitor
TL	Target lesions
T_{ssmax}	Time of maximum plasma concentration at steady state
U	Urine
ULN	Upper limit of normal
WHO	World Health Organization
WOCBP	Women of childbearing potential

Appendix L Summary of Changes

L 1 Amendment 1 (28 May 2021)

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Appendix I: Dose Modifications for the Management of Adverse Events	Dose modification guidelines for osimertinib and savolitinib were updated. The main changes included addition of Table I1 (Study Treatment Dose Modification Instructions for Toxicities Related to Osimertinib and/or Savoltinib (excluding toxicities that require specific management guidelines), Table I2 (Toxicities that Require Permanent Discontinuation of Study Treatment), and Table I3 (Management of QTc Prolongation). Table I1 was created by combining information in previous Tables I2 and I4. Contents in previous Table I2 and Sections I2.4 are merged into new Table I2. Contents of previous Table I5 and Section I1.2 were merged to create new Table I3.	Dose modification guidelines updated in response to the FDA information request and in line with the prescribing label for osimertinib.	Substantial
Appendix I: Dose Modifications for the Management of Adverse Events	Instruction for recurrent Grade 3 savolitinib-related toxicities that resolved to baseline within 14 days of onset was removed.	Updated in line with most recent PSSR.	Substantial

11 REFERENCES

Aithal et al 2011
Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther. 2011;89(6):806-15.

Ballard et al 2016
Ballard P, Yates JW, Yang Z, Kim DW, Yang JC, Cantarini M, et al. Preclinical comparison of osimertinib with other EGFR-TKIs in EGFR-mutant NSCLC brain metastases models, and early evidence of clinical brain metastases activity. Clin Cancer Res. 2016;22(20):5130-40.

Bean et al 2007
Bean J, Brennan C, Shih JY, Riely G, Viale A, Wang L, et al. MET amplification occurs with or without T790 mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib. Proc Natl Acad Sci USA. 2007;104(52):20932–7.

Becker et al 2011
Becker A, Crombag L, Heideman DAM, Thunnissen FB, van Wijk AW, Postmus PE et al. Retreatment with erlotinib: Regain of TKI sensitivity following a drug holiday for patients with NSCLC who initially responded to EGFR-TKI treatment. European Journal of Cancer 2011;47(17):2603-6.

Camidge et al 2014
Camidge DR, Pao W, Sequist LV. Acquired resistance to TKIs in solid tumours: learning from lung cancer. Nat Rev Clin Oncol. 2014;11(8):473–81.

Chaft et al 2011
Chaft JE, Oxnard GR, Sima CS, Kris MG, Miller VA, Riely GJ. Disease flare after tyrosine kinase inhibitor discontinuation in patients with EGFR-mutant lung cancer and acquired resistance to erlotinib or gefitinib: implications for clinical trial design. Clin Cancer Res. 2011;17(19):6298-303.

Chen et al 2013
Chen HJ, Yan HH, Yang JJ, Chen ZH, Su J, Zhang XC, et al. Disease flare after EGFR tyrosine kinase inhibitor cessation predicts poor survival in patients with non-small cell lung cancer. Pathol Oncol Res. 2013;19(4):833-8.

Chong and Jänne 2013
Chong CR and Jänne PA. The quest to overcome resistance to EGFR-targeted therapies in cancer. Nat Med. 2013;19(11):1389-1400.

Choueiri et al 2017
Choueiri TK, Halabi S, Sanford BL, Hahn O, Michaelson MD, Walsh MK, et al. Cabozantinib

versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: The Alliance A031203 CABOSUN Trial. J Clin Oncol. 2017;35(6):591-7.

Cross et al 2014
Cross DA, Ashton SE, Ghiorghiu S, Eberlein C, Nebhan CA, Spitzler PJ, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer Discov. 2014:4(9);1046-61.

Eder et al 2009
Eder JP, Vande Woude GF, Boerner SA, LoRusso PM. Novel therapeutic inhibitors of the c-Met signaling pathway in cancer. Clin Cancer Res. 2009;15(7):2207-14.

Engelman et al 2007
Engelman JA, Zejnullahu K, MitsudomiT, Song Y, Hyland C, Park JO, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science. 2007;316(5827):1039-43.

GLOBOCAN 2018
Available from URL: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed 06 April 2020.

Gridelli et al 2012
Gridelli C, Ciardiello F, Gallo C, Feld R, Butts C, Gebbia V, et al. First-line erlotinib followed by second-line cisplatin-gemcitabine chemotherapy in advanced non-small-cell lung cancer: the TORCH randomized trial. J Clin Oncol. 2012;30(4):3002-11.

Henry et al 2016
Henry RE, Barry ER, Castriotta L, Ladd B, Markovets A, Beran G, et al. Acquired savolitinib resistance in non-small cell lung cancer arises via multiple mechanisms that converge on MET-independent mTOR and MYC activation. Oncotarget. 2016;7(36):57651-70.

Jänne et al 2015
Jänne PA, Felip E, Kim D-W, John T, Haggstrom DE, Ahn M-J, et al. Characterization of the activity of AZD9291 in patients (pts) with T790M 'negative' advanced non-small cell lung cancer (aNSCLC). [abstract]. In: Proceedings of the AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics; 2015 Nov 5-9; Boston, MA. Philadelphia (PA): AACR; Mol Cancer Ther 2015;14(12 Suppl 2):Abstract nr B105. Available from URL: https://mct.aacrjournals.org/content/14/12_Supplement_2/B105. Accessed 06 April 2020.

Jia et al 2014
Jia H, Dai G, Weng J, Zhang Z, Wang Q, Zhou F, et al. Discovery of (S)-1-(1-(Imidazo[1,2-

a]pyridin-6-yl)ethyl)-6-(1-methyl-1H-pyrazol-4-yl)-1H-[1,2,3]triazolo[4,5-b]pyrazine (volitinib) as a highly potent and selective mesenchymal-epithelial transition factor (c-Met) inhibitor in clinical development for treatment of cancer. J Med Chem. 2014;57(18):7577-89.

Keedy et al 2011
Keedy VL, Temin S, Somerfield MR, Beasley MB, Johnson DH, McShane LM, et al. American Society of Clinical Oncology provisional clinical opinion: epidermal growth factor receptor (EGFR) mutation testing for patients with advanced non-small-cell lung cancer considering first-line EGFR tyrosine kinase inhibitor therapy. J Clin Oncol. 2011;29(15):2121-7.

Langer et al 2013
Langer CJ, Mok T, Postmus PE. Targeted agents in the third-/fourth-line treatment of patients with advanced (stage III/IV) non-small cell lung cancer (NSCLC). Cancer Treat Rev. 2013;39(3):252-60.

Leighl and Curigliano 2014
Leighl NB, Curigliano G. Early-stage lung cancer--what do the experts recommend? Ann Oncol. 2014;25(8):1451-3.

Masters et al 2015
Masters GA, Temin S, Azzoli CG, Giaccone G, Baker S Jr, Brahmer JR, Ellis PM, Gajra A, Rackear N, Schiller JH, Smith TJ, Strawn JR, Trent D, Johnson DH; American Society of Clinical Oncology Clinical Practice. Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2015;33(30):3488-515.

Mok et al 2016
Mok TS, Wu Y-L, Ahn M-J, Garassino MC, Kim HR, Ramalingam SS, Shepherd FA, He Y, Akamatsu H, Theelen WS, Lee CK, Sebastian M, Templeton A, Mann H, Marotti M, Ghiorghiu S, Papadimitrakopoulou VA; AURA3 Investigators. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med. 2017;376(7):629-40.

Mok et al 2017
Mok TSK, Kim SW, Wu YL, Nakagawa K, Yang JJ, Ahn MJ, et al. Gefitinib Plus Chemotherapy Versus Chemotherapy in Epidermal Growth Factor Receptor Mutation-Positive Non-Small-Cell Lung Cancer Resistant to First-Line Gefitinib (IMPRESS): Overall Survival and Biomarker Analyses. J Clin Oncol. 2017;35(36):4027-34.

NCCN 2020
National Comprehensive Cancer Network Guidelines for Treatment of Cancer by Site. 2020. Available from URL: https://www.nccn.org/professionals/physician_gls/default.aspx#nscl.

Ohashi et al 2012
Ohashi K, Sequist LV, Arcila ME, Moran T, Chmielecki J, Lin Y, et al. Lung cancers with acquired resistance to EGFR inhibitors occasionally harbor BRAF gene mutations but lack mutations in KRAS, NRAS, or MEK1. Proc Nat Acad USA 2012;109(31):E2127-33.

Oxnard et al 2020
Oxnard GR, Yang JC, Yu H, Kim SW, Saka H, Horn L, et al. TATTON: a multi-arm phase Ib trial of osimertinib combined with selumetinib, savolitinib, or durvalumab in EGFR-mutant lung cancer. Ann Oncol. 2020;31(4):507-16.

Park et al 2012
Park S, Choi YL, Sung CO, An J, Seo J, Ahn MJ, et al. High MET copy number and MET overexpression: poor outcome in non-small cell lung cancer patients. Histol Histopathol. 2012;27(2):197–207.

Piotrowska et al 2017
Piotrowska Z, Thress KS, Mooradian M, Suk Heist R, Azzoli CG, Temel JS, et al. MET amplification (amp) as a resistance mechanism to osimertinib [abstract]. J Clin Oncol 2017;35(15 suppl):9020. Available from URL: https://ascopubs.org/doi/10.1200/JCO.2017.35.15_suppl.9020. Accessed 07 April 2020.

Pisters and Le Chevalier 2005
Pisters KM, Le Chevalier T. Adjuvant chemotherapy in completely resected non-small-cell lung cancer. J Clin Oncol. 2005;23(14):3270-8.

Ramalingam et al 2018
Ramalingam SS, Yang JC, Lee CK, Kurata T, Kim DW, John T, et al. Osimertinib as first line treatment of EGFR mutation-positive advanced non-small-cell lung cancer. J Clin Oncol. 2018;36(9):841-9

Reck et al 2014
Reck M, Popat S, Reinmuth N, De Ruysscher D, Kerr KM, Peters S; ESMO Guidelines Working Group. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;Suppl 3;iii27-39.

Schmidt et al 1997
Schmidt L, Duh FM, Chen F, Kishida T, Glenn G, Choyke P, et al. Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas. Nat Genet. 1997;16(1):68-73.

Sequist et al 2011
Sequist LV, Waltman BA, Dias-Santagata D, Digumarthy S, Turke AB, Fidias P, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci Transl Med. 2011;3(75):75ra26.

Sequist et al 2020
Sequist LV, Han JY, Ahn MJ, Cho BC, Yu H, Kim SW, et al. Osimertinib plus savolitinib in patients with EGFR mutation-positive, MET-amplified, non-small-cell lung cancer after progression on EGFR tyrosine kinase inhibitors: interim results from a multicentre, open-label, phase 1b study. Lancet Oncol. 2020;21(3):373-86.

Shepherd et al 2018
Shepherd FA, Papadimitrakopoulou V, Mok T, Wu Y-L, Han J-Y, Ahn M-J, et al. Early clearance of plasma EGFR mutations as a predictor of response to osimertinib in the AURA3 trial. J Clin Oncol 2018;36(15 suppl):9027.

Soria et al 2015
Soria JC, Wu YL, Nakagawa K, Kim SW, Yang JJ, Ahn MJ, et al. Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial. Lancet Oncol. 2015;16(8):990-8.

Soria et al 2018
Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med. 2018;378(2):113-25.

Travis et al 2011
Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol. 2011;6(2):244-85.

Zhou et al 2019
Zhou C, Imamura F, Cheng Y, Okamoto I, Cho BC, Lin MC, et al. Early clearance of plasma EGFR mutations as a predictor of response to osimertinib and comparator EGFR-TKIs in the FLAURA trial [abstract]. J Clin Oncol. 2019;37(15 suppl):9020. Available from URL: https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.9020 Accessed 07 April 2020.

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: d5084c00009-csp-v3		
Document Title:	D5084C00009 Clinical Study Protocol version 3	
Document ID:	CCI [redacted]	
Version Label:	3.0 CURRENT LATEST APPROVED	
Server Date (dd-MMM-yyyy HH:mm 'UTC'Z)	**Signed by**	**Meaning of Signature**
09-May-2022 21:37 UTC	PPD	Content Approval
10-May-2022 15:50 UTC	PPD	Content Approval
09-May-2022 18:27 UTC	PPD	Content Approval

CCI [redacted]