Clinical Study Protocol	
Drug Substance	Osimertinib + savolitinib
Study Code	D5084C00007
Version	8.0
Date	24 May 2024

A Phase II Study Assessing the Efficacy of Osimertinib in Combination with Savolitinib in Patients with EGFRm+ and MET+, Locally Advanced or Metastatic Non-Small Cell Lung Cancer who have Progressed Following Treatment with Osimertinib (The SAVANNAH Study)

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Regulatory Agency Identifying Number(s):

EudraCT number: 2018-003012-51

EU CT number: 2024-512564-58-00

VERSION HISTORY

Version 8.0, 24 May 2024
This non-substantial amendment was done in order to include mandatory text for compliance with the EU CTR requirements and alignment with the latest CSP template; this applies to the Title page, Sections 4.4 (End of Study Definition), 6.1.1 (Investigational Products), 8.4.3 (Reporting of Overdose) and 8.4.4 (Medication Error, Drug Abuse, and Drug Misuse) and Appendices A 1 (Regulatory and Ethical Considerations), A 4 (Data Protection), A 6 (Dissemination of Clinical Study Data), A 7 (Data Quality Assurance) and B 8 (Medication Error, Drug Abuse, and Drug Misuse).

Version 7.0, 26 April 2022
Emerging data of the SAVANNAH study has shown encouraging efficacy signal in MET-amplified/overexpressed patients (FISH10+ and/or IHC90+). Cumulative evidence of efficacy, safety, PK and PK-PD has suggested that savolitinib 300 mg bid is the appropriate dosing regimen for further development. Therefore, the savolitinib 300 mg bid + osimertinib 80 mg od patient population is expanded to further assess efficacy and safety of savolitinib 300 mg bid in combination with osimertinib in patients with FISH10+ and/or IHC90+ status who have progressed following treatment with 1L osimertinib. As emerging pre-clinical data have suggested that the assessment of clinical efficacy of savolitinib monotherapy is warranted in patients with higher MET amplification/overexpression status, a savolitinib 300 mg bid monotherapy arm has been added to the study. Under CSP version 7.0, approximately CCI patients with MET amplification and/or overexpression (FISH10+ and/or IHC90+) who have progressed following 1L osimertinib therapy, will be randomised in a double-blinded manner and CCI ratio to receive savolitinib 300 mg bid in combination with osimertinib 80 mg od (CCI patients) or savolitinib 300 mg bid with placebo to osimertinib (CCI patients). Patients initially randomised to the savolitinib plus placebo arm will have the opportunity to cross over to the savolitinib plus osimertinib combination arm upon PD per RECIST 1.1. An IDMC will meet to assess the futility of the savolitinib 300 mg bid + placebo arm, and will also review the safety data of the randomised patients recruited under CSP version 7.0 for both arms (Sections 1.2, 9.6 and Appendix A 5). Primary and final analyses timing are adjusted to CCI and CCI months, respectively after the last patient under CSP version 7.0 has been randomised to achieve data maturity for newly

randomised patients (Sections 1.2, 4.1.1, and 9.5). The provision that additional OS follow up analyses may be performed was removed (Section 9.5).

Updates made throughout the protocol for MET amplified/overexpressed (FISH10 + and/or IHC90+) patients who will be randomised under CSP version 7.0, including removal of single arm from study title, numbers of patients planned and enrolled (Sections 1.2 and 4.1.1), schedules (including schedule added in Table 2) for patients who cross over), study schema (Section 1.3), additional primary and secondary objectives/endpoints for MET amplified/overexpressed (FISH10+ and/or IHC90+) populations (Sections 1.2 and 3), study design including rationale (Section 4), Inclusion Criterion (Section 5.1; no. 6), placebo/ unblinding added to study interventions (Section 6), discontinuation of study intervention (Section 7.1), addition of brain imaging at screening and further clarification on BICR (Sections 8.1.1 and 9.4.3), and statistical considerations including sample size, futility analysis, study populations, stratification factor, and study analyses (Section 8.7).

An additional primary objective/ endpoint was added to determine the ORR (by investigator assessment per RECIST 1.1) of savolitinib 300 mg bid in combination with osimertinib in patients with EGFRm+ and MET amplified/overexpressed (FISH10+ and/or IHC90+) who have progressed following treatment with 1L osimertinib. In addition, the following secondary investigator-assessed objectives were added: 1) To determine the efficacy (DoR, PFS, OS) of savolitinib (300 mg bid) in combination with osimertinib in MET amplified/overexpressed (FISH10 + and/or IHC90+) patients who have progressed following treatment with 1L osimertinib 2) To describe the difference in the efficacy of savolitinib (300 mg bid) in combination with osimertinib and savolitinib (300 mg bid) in combination with placebo in MET amplified/overexpressed patients (FISH10 + and/or IHC90+) who have progressed following treatment with1L osimertinib therapy under CSP version 7.0, and 3) To evaluate the safety of savolitinib + placebo. The remaining secondary objectives were modified as follows (1) To determine the efficacy of savolitinib (300 mg od and 600 mg od) in combination with osimertinib in MET-amplified/overexpressed (FISH10+ and/or IHC90+) patients following treatment with 1L osimertinib (2) To determine the efficacy of savolitinib (300 mg od, 300 mg bid, and 600 mg od) in combination with osimertinib in patients with MET amplified/overexpressed (FISH10+ and/or IHC90+) patients who have progressed following treatment of ≥ 2L osimertinib (3) To determine the efficacy of savolitinib (300 mg od, 300 mg bid, and 600 mg od) in combination with osimertinib in MET amplified/overexpressed (FISH5+ and/or IHC50+) patients who have progressed following osimertinib. A secondary objective was added to determine the efficacy in all patient populations by BICR. Biomarker cut-offs in objectives were clarified, and DoR, PFS, and OS were added as endpoints (Section 1.2 and Section 3). Exploratory objectives were added to assess the efficacy of savolitinib plus osimertinib and savolitinib plus placebo, respectively, on 1) CNS metastases in patients with CNS metastases at baseline and 2) the prevention of

CNS metastases in patients without CNS metastases at baseline (Section 3). Statistical considerations in Section 9 including hypotheses, sample size, populations, and efficacy endpoint analyses updated accordingly.

As the dosing regimen of 300 mg bid for savolitinib has been selected for further evaluation, the previously planned IA3 was removed. A futility analysis for the savolitinib 300 mg bid + placebo arm was added (Sections 1.2, 4.1.1 and 9.5).

Program-wide measures to mitigate and manage the risk of drug-induced liver injury were added based on FDA feedback and hepatic safety knowledge group review including the introduction of an Independent Hepatic Assessment Committee (Sections 1.2, 9.6 and Appendix A 5), exclusion of patients with serious/chronic liver disease (exclusion criterion 12), updates to drug-related hepatotoxicity management guidelines (Appendix I 3.3.1), and guidance on patients with HBV infection updated (Exclusion Criterion 7 clarified and Appendix I 2 [new]).

Clarified the use of direct oral anticoagulants and warfarin as treatment for cancer-related thromboembolism (Inclusion criterion 14 and Section 6.5).

Safety data for osimertinib updated (Section 2.3.1) and guidelines added for the management of aplastic anaemia, a newly classified adverse drug reaction, osimertinib-related QTc prolongation, and dose adjustments for adverse reactions based on a review of all available safety data and subsequent investigator's brochure update (Appendix I 1).

List of restricted medications updated based on latest in vitro and in vivo data on drug-drug interactions (Section 6.5).

Dose modifications for savolitinib updated based on latest safety data (Appendix I 3) and guidance regarding potential interactions of savolitinib with concomitant medications updated based on latest drug-drug interaction data (Appendix J), including new appendix (Appendix J 4 [new]) on medicines whose exposures may be affected by savolitinib that AstraZeneca strongly recommend are not combined with savolitinib and guideline added for the management of overlapping toxicities between osimertinib and savolitinib (Appendix I 3.5 [new]).

New sections added for further clarity including benefit of treatment (Section 2.3.2), rescue medicine (6.5.1), follow-up post treatment discontinuation (Section 7.1.3) follow up for survival (Section 7.1.4), and ECOG performance status (Section 8.2.7).

Added a column to SoAs to clarify that blood sample for biomarker analyses and optional tumour biopsy are to be taken at disease progression (Section 1.1). PK sampling for

patients with abnormal LFTs removed from discontinuation visit (Sections 1.1, 8.5.1, and I 3.3). Clarified process in the event that product development reaches a point where alternative supply options become available (Section 6.7). Additional clarifications added for the handling of human biological samples (Section 8.5), biomarkers (Section 8.6), and optional genomics (Section 8.7). Additional minor changes include removal of duplicate text from synopsis and body, shortening of synopsis, alignment of headings with latest template, and references moved to the end of the document. Maximum blood collected (Section 8) was removed to align with template (reported in ICF).

Version 6.0, 22 February 2021
Enrolment of new patients to the 300 mg bid and 600 mg od dosing regimens is restricted to post 1L osimertinib patients only. See Sections 1.1, 1.2, 1.3, 2, 4.1, 4.2.1, and 5.1 (Inclusion criteria 5 and 9), and 9.2. Enrolment of new patients to the 300 mg bid and 600 mg od dosing regimens is restricted to central MET FISH+ patients only. See Sections 1.1, 1.2, 1.3, 2, 4.1, 4.2.1, 5.1 (Inclusion criteria 5 and 6), 5.4, 6.3, 8.6, and 9. Interim analysis 2 data are summarised, see Sections 1.2 and 2. Analysis of secondary and exploratory objectives/endpoints by centrally confirmed IHC and FISH patient populations is removed, with the exception of the analysis of ORR in the 300 mg od dosing regimen. These analyses will be performed as sub-group analyses. See Sections 1.2, 3, and 9.4.3.3. Due to the introduction of the 300 mg bid regimen under CSP version 5.0 it is anticipated that the original plan for primary analysis of ORR and the final analysis could both occur before the end of the recruitment to the 300 mg bid and 600 mg od regimens. Therefore, the primary analysis and final analysis will be combined and performed when all patients (including 300 mg bid and 600 mg od regimens) have had the opportunity to be followed for approximately [redacted] months. See Sections 1.2, 4.1, 9.2 and 9.5.

The timing of additional OS follow-up analyses is amended to be until [redacted] % of the patients treated with the 300 mg bid and 600 mg od dosing regimens have died due to any cause, see Section 9.5. It is clarified that in order to assess the safety and tolerability of the 300 mg bid and 600 mg od dosing regimens, safety data reviews will be performed on an ongoing basis, as appropriate. See Sections 1.2, 4.1, 9.2 and 9.5. Inclusion criterion 18 is refined to reflect current osimertinib PSSR language for females of childbearing potential, see Section 5.1. This is also implemented in Section 5.3.2. The exclusion criteria are updated to clarify that exclusion criteria 12 and 24 were removed due to duplication of information with other criteria, and exclusion criterion 18 was removed because warfarin has been removed from restrictions in the savolitinib PSSR, see Section 5.2. Exclusion criterion 15 (*Patients who have received ≥4 lines of systemic therapy for NSCLC are not eligible*) is removed, as the allowed prior lines of therapy are detailed under the inclusion criteria, see Section 5.2. The requirement to flag and follow-up patient compliance below 85% is deleted. See Section 8.1.2. Additionally, text was clarified and administrative (typographical and formatting) changes were implemented where necessary.

Version 5.0, 30 October 2020
The definition of MET+ is replaced by MET-amplified/overexpressed; applicable throughout the CSP. The terminology regarding tumour ‘biopsy/tissue’ collection is widened to ‘tumour sample’ to include cytology samples in addition to FFPE cell blocks. See Sections 1.1, 4.1, 5.1, 8.3.2, and 8.6. Footnote ‘n’ of the Schedule of Activities is amended to more clearly reflect the timing of RECIST 1.1 tumour assessment for patients who discontinue study drug for reasons other than disease progression, see Section 1.1.

International Co-ordinating Investigator details are updated to reflect current status, see Section 1.2.

To better characterise benefit-risk at different doses of savolitinib in combination with osimertinib, 2 alternative dosing regimens are included; savolitinib **300 mg bid** plus osimertinib 80 mg od is added, and the savolitinib **600 mg od** plus osimertinib 80 mg od is re-introduced. Enrolment to the savolitinib 300 mg od plus osimertinib 80 mg od regimen will be stopped upon implementation of this amendment. Rationale is included in Sections 1.2, 2, and 4.3.

Sample size determination, patient numbers and randomisation (CCI to 300 mg bid:600 mg od) are summarised in Sections 1.2, 4.1, 6.3, and 9.2. Dosage formulation and dosing instructions are updated in Section 6.1.1. Dose reductions are introduced for the 300 mg bid regimen in Section 6.6.

The primary objective and endpoint (ORR in all patients population) is updated to clarify that this will only be assessed for the savolitinib 300 mg od plus osimertinib 80 mg od dosing regimen. See Sections 1.2, 3, 4.1, and 9.4.3.1.

The first secondary objective and endpoint (ORR in centrally confirmed by FISH and centrally confirmed by IHC populations) is updated to clarify that this will only be assessed for the savolitinib 300 mg od plus osimertinib 80 mg od dosing regimen. See Sections 1.2, 3, and 9.4.3.2.

A new secondary objective and endpoint is included to assess the efficacy of savolitinib 300 mg bid and 600 mg od regimens (ORR in all patients population). See Sections 1.2, 3, and 9.4.3.2.

The estimated date of last patient completed is extended to Q4 2022, see Section 1.2.

In order to reduce heterogenicity and provide data in a more matched population to a potential future phase 3 study, for patients enrolled after this amendment, only 1 or 2 prior lines of therapy are allowed, see Sections 1.2 and 4.1.

The description of interim analysis 1 is amended for clarification to read "An interim analysis is planned after the CCI centrally confirmed FISH+ patient treated at 300 mg od savolitinib dose (approximately CCI overall) has had the opportunity of being treated for 2 RECIST post-baseline scans (12 weeks) **or** the CCI patient treated with osimertinib (80 mg od) and savolitinib (300 mg od) has had the opportunity to be treated for 6 weeks, whichever is the later." See Sections 1.2, 4.1, 9.2, and 9.5.

A third interim analysis is introduced after approximately CCI patients (CCI patients each regimen) treated with osimertinib (80 mg od) and savolitinib (300 mg bid) / savolitinib (600 mg od) have had the opportunity to be treated for 2 RECIST post-baseline scans (12 weeks). To assess the early safety and tolerability of the 300 mg bid and 600 mg od savolitinib regimens, a safety data review will be performed after CCI since the first patient is dosed with 300 mg bid savolitinib regimen. See Sections 1.2, 4.1, 9.2, and 9.5.

The study schema is updated to reflect the changes to the study design, see Figure 1.

Updates to important identified and potential risks in line with the savolitinib investigator's brochure (2020): CCI , see Section 2.3.

The final analysis will occur after the earlier of CCI months after the last patient on the study was enrolled, or when CCI % of the patients have progressed or died due to any cause. See Section 4.1.

Inclusion criterion 5 is amended to specify the required documented radiologic disease progression in the 300 mg bid and 600 mg od regimens, see Section 5.1.

Inclusion criterion 9 is amended to specify the allowed prior lines of therapy in the 300 mg bid and 600 mg od regimens, see Section 5.1.

Inclusion criterion 12 is updated to align with the current savolitinib PSSR (addition of 'serum' as shown: *Adequate renal function defined as a **serum** creatinine <1.5 times the institutional ULN OR a glomerular filtration rate ≥50 mL/min…*), see Section 5.1.

Inclusion criterion 13 is updated to remove reference to use of warfarin being disallowed, as warfarin has been removed from restrictions in the savolitinib PSSR, see Section 5.1. Exclusion criterion 18 (now 17; exclusion of warfarin use) is also deleted in line with this change, see Section 5.2.

Inclusion criterion 18 is refined to reflect current savolitinib PSSR language for females of childbearing potential, see Section 5.1.

Exclusion criterion 12 (*Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values: Absolute neutrophil count <1.5 x 109/L; Platelet count <100 x 109/L; Haemoglobin <90 g/L*) is deleted as it was a duplication with inclusion criterion 10, see Section 5.2.

Exclusion criterion 17 (now 16) is amended to remove 'strong inhibitors of CY3A4' and 'CYP3A4 substrate which have a narrow therapeutic range', in alignment with current savolitinib PSSR, see Section 5.2.

Exclusion criterion 24 (*For women only - currently pregnant (confirmed with positive pregnancy test) or breast feeding*) is deleted as it was a duplication with inclusion criterion 18, see Section 5.2.

It is clarified that it was originally planned to treat approximately CCI patients with osimertinib 80 mg od plus savolitinib 300 mg od, to achieve the required CCI centrally confirmed MET-amplified/overexpressed by FISH **and/or** IHC patients. Clarification on the updated patient numbers to now treat CCI patients. See Sections 1.2 and 4.1.

For patients receiving savolitinib 300 mg bid, it is specified that a pre-dose meal will be provided if the second dose of the day is given in the clinic, see Section 5.3.1. It is additionally clarified that for this regimen on PK sampling days, samples will be collected after the first dose of the day, see Sections 1.1 and 8.5.1.

The requirement to abstain from eating/drinking grapefruit and Seville oranges products is removed per the current PSSR, see Section 5.3.1.

It is clarified that male patients should use a condom during the study and for 5 elimination half-lives afterwards (48 hours after last dose of savolitinib) with all sexual partners (if the partner is not of childbearing potential), see Section 5.3.2.

Statins are removed from the list of restricted medications, in-line with the current savolitinib PSSR, see Section 6.5.

Use of paper backups for PRO questionnaires is introduced in case of issues with the ePRO, see Section 8.1.2.5.

Adverse events of special interest for savolitinib and osimertinib are summarised in a new section, see Section 8.3.13.

Additional PK parameters are included following multiple dosing for the 300 mg bid dose regimen, see Section 9.4.5.

Language is included relating to the COVID-19 pandemic '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.' See Section 9.4.

The requirement to prepare 2 CSRs is removed in-line with changes to the study design and planned analyses (Section 9.5). Hydroxychloroquine is added to Table 24 Drugs with a known risk of Torsades de Pointes (TdP), for clarification should it be used during the study to treat COVID-19, see Table 29. Appendix A 9 (study and site closure) and Appendix E (Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law) are updated in-line with the current late oncology CSP template.

Version 4.0, 22 Jan 2020
The patient population for assessment of the primary objective of efficacy is broadened to include all patients treated with at least one dose of study drug and not just those patients centrally confirmed as MET+ by the FISH test (MET amplified), 1.2 Synopsis, 9.4.3.1, 9.4.1.2, 9.4.1.3. Correspondingly, the patient population for assessment of the secondary objective of efficacy is changed from all patients to include those patients centrally confirmed as MET+ by the FISH test as an additional population to those patients centrally confirmed as MET+ by IHC (MET overexpression). There is no resulting change in the number of patients because the study has been sized to ensure there are sufficient patients in each of the diagnostic populations, see Section 4.1, 4.2.2, 9.2. The existing "first" interim analysis is changed to be planned after the CCI patient treated with osimertinib and savolitinib (300 mg) have had the opportunity to be treated for 2 post-baseline RECIST scans (12 weeks) and the CCI patient treated with osimertinib (80 mg) and savolitinib (300 mg) has had the opportunity to be treated for 6 weeks, whichever is the later, see Section 1.2 Synopsis Statistical Methods, Section 4.1, 9.2, 9.3, 9.5. A second interim analysis is introduced after the CCI patients treated with osimertinib and savolitinib (starting dose of 300 mg) in the second line setting have had the opportunity to be treated for 2 RECIST post-baseline scans (12 weeks), 1.2 Synopsis Statistical Methods, Section 4.1, 9.2, 9.3, 9.5. Additional safety analysis set 2 added to table of populations for analyses in Section 9.3 for interim analyses. Clarification of the wording of the note below Inclusion criterion 6 in Section 5.1 to ensure it is clear that for those patients enroled based on a pre-existing MET+ by NGS (MET amplification) result, the central MET testing required for the SAVANNAH study are not required before the start of treatment. The subsequent central MET testing will determine in which diagnostic populations these patients will be included. The rationale for allowing

enrolment of patients with a pre-existing MET amplification result by NGS testing has been added to the Study Design in section 4.1.

References to "local" NGS testing are changed to "pre-existing" NGS testing in order to make clear that this result must have been obtained prior to obtaining consent for pre-screening and screening for the SAVANNAH study. Also to make clear that the NGS testing laboratory approved by AstraZeneca as being suitable to assess eligibility for the SAVANNAH study, may be local to the participating investigational site or may be external to the site. This change is made to Inclusion criterion 6 in Section 5.1 and throughout. Simplification of the reference to acceptance criteria in section 4.1 to allow flexibility in these requirements which are assessed by the Sponsor. N.B. This testing is not an alternative to the central MET testing by FISH and IHC required for all patients and is not performed as part of the SAVANNAH study. It is in addition to the central testing and is intended to allow a patient already known to be MET+ by NGS to start treatment without delay in the best interests of the patient.

The study rationale in Section 2.1 is corrected to refer to overexpression in addition to amplification of the MET receptor tyrosine kinase as a mechanism for resistance to EGFR-TKIs. Clarification made that this study will explore overcoming MET-mediated osimertinib resistance.

Tumour imaging to assess efficacy is required every 6 weeks (±7 days). Clarification added to the Schedule of Assessments in section 1.1 Table 1, that this timing is relative to the first dose of treatment and not relative to the previous tumour imaging, also Section H 3.1.

Further guidance on performance of ePRO assessments is added to Table 1 Schedule of activities to footnote o and to section 8.1.2.5. The Screening timepoint is optional and offers the site and the patient an opportunity to prepare for the mandatory baseline ePROs before dosing on Cycle 1 Day 1 when the patient will take the device home. The Screening timepoint also serves as a back-up to ensure a baseline is recorded.

The ctDNA clearance secondary objective is corrected to determining the prevalence rather than rate of ctDNA clearance after osimertinib and savolitinib treatment in Section 1.2, Section 3 and Section 9.4.6 to more accurately reflect the endpoint of total clearance in EGFR mutations at 6-weeks after therapy initiation.

Patients should come to the clinic fasted and be given a moderate breakfast at the clinic. Clarification added to Section 5.3.1 and 8.5.1 that the pre-dose PK sample may be drawn before dosing, either before or after this moderate breakfast. Also clarified that fasted means the patient should not eat but may drink beforehand, Section 5.3.1.

Information to be collected for screen failure patients will include MET status information, added to list of minimal information in Section 5.4. Acknowledgement that SAEs will be reported according to local regulations added to Section 8.3.2. Guidance introduced to Appendix I Dose modification for the management of AEs for osimertinib management for erythema multiforme and Stevens-Johnson syndrome Section I 1.4. Clarification to dose modification due to drug-related hepatotoxicity to withhold dosing if ALT or AST 3 x ULN and concurrent total bilirubin should be above 1.5 x ULN rather than 1.5 x ULN, Section I 3.3.1. Guidance on concomitant therapy in Section 6.5 Table 4 Prohibited Medications relating to savolitinib is removed and introduced into Appendix J (J 6) to provide consolidated guidance for the combination treatment of osimertinib and savolitinib in the same part of the protocol (updates to J 1 and Table 26 in relation to osimertinib or savolitinib treatment and Table 27 and J 5 in relation to savolitinib treatment). Additions to J 3 'Medicines whose exposures may be affected by osimertinib' that AstraZeneca considers may be allowed with caution of P-gp substrate, fexofenadine, aliskerin, dabigatran etixelate and digoxin.

Version 3.0, 31 May 2019
All patients will be assigned to 300 mg od savolitinib flat dosing (see Figure 1) replacing the previous weight-based dosing regimen where patients were assigned to either 300mg od or 600 mg od savolitinib dependent upon their weight at Screening. Rationale for this change is described in sections 1.2, 2, 0, 4.3 and in a revised study design schema in section 1.3 Figure 1, and revised layout of Table 9 showing savolitinib dose reductions. Preliminary review of emerging clinical data from the Phase I TATTON study carried out by the Sponsor indicated that there was an improvement in overall safety profile with no apparent reduction in objective response rate between weight-based savolitinib dosing (TATTON Part B) and 300 mg dose (TATTON Part D) in combination with osimertinib 80mg QD. Patients who commenced study treatment at 600 mg savolitinib can choose to either continue at this dose or change to 300 mg (no subsequent re-escalation will be permitted after changing to 300 mg dose). The primary and secondary variables will be summarised only on patients treated at 300 mg od savolitinib and not on patients treated at 600 mg od savolitinib. The interim, primary and final analyses triggers will be based on the number of patients treated at 300 mg savolitinib

section 9.5, 1.2, 3. The approximate study population of 172 patients refers only to patients treated at 300 mg savolitinib (see section 1.2, 9.2), patients treated at 600 mg savolitinib will be in addition. Statistical analyses will be presented by the assigned starting dose (see Section 9.4).

The proportion of patients treated on this study in the second line setting will be increased from a third to a half (see section 1.2).

Patients may be repeatedly pre-screened. If the patient has received EGFR-TKI therapy in the interval since initial pre-screening, then a new blood sample for ctDNA analysis for diagnostic development is requested, see section 1.1 Table 1 footnote b.

The minimum requirement for tumour tissue for central MET testing has been reduced from 12 to 10 slides. This is documented in the Central Laboratory Manual in detail. Reference to the approximate number of slides required is revised from 12-22 to 10-20 slides in footnote c of Table 1 Schedule of Activities.

Introduction of sequence of ECGs and extension to existing PK sampling timepoints on Cycle 3 Day 1 to evaluate QTc interval around the time for savolitinib and osimertinib maximum concentration. Triplicate ECGs and blood samples for PK assessment of osimertinib and savolitinib will be required Pre-dose (a blood sample for PK assessment is already required Pre-dose), and at the following new sample timepoints at 1 hour (h), 3 h, 4h, and 6 h post-dose shown in Table 1 footnote p, Table 13 and section 9.4.5.

Statement added to section 8.5.1 that actual date, time and amount of the last doses of IP prior to each PK sample will be recorded.

Simplification of description of planned evaluation of PK of both IPs (section 9.4.5 and section 8.6, and removal of section 9.4.3.1 which gave details of population analysis of PK/ pharmacodynamic variables) because these analyses will be reported separately from the main CSR in Bioanalytical reports and do not require this level of detail in the CSP.

Window for electronic clinical outcome assessments (eCOA) questionnaires reduced from ±5 days to ±2 days relative to the first dose of treatment in Cycles 1 and 2 (28 day cycle). The increase to a ±5 day window for these assessments was an error in the previous CSP version 2.0; see Table 1.

Inclusion criterion 4 amended to allow rare EGFR mutations known to be associated with EGFR-TKI sensitivity if permitted in the osimertinib national label in section 5.1.

Statements added clarify that viral screening is not required to diagnose hepatitis B or hepatitis C virus infection or serious active infection eg, tuberculosis or human

immunodeficiency virus, for the assessment of eligibility for the study, section 5.2 Exclusion criteria 7 and 8. Criteria to allow inclusion of patients with a past or resolved HBV or HCV infection are already provided. Clarification added to section 5.4 Screen failures to define Pre-screen failures. Dose modification to osimertinib for cardiac adverse reactions are removed from Table 9. More detailed guidance provided in Table 1 for management of missed/late doses of osimertinib and savolitinib. If a daily dose of either IP is more than 12 hours late this is considered a missed dose and should not be taken. If a patient vomits after taking a dose a repeat dose should not be taken. Correction of the requirement for reporting AEs and SAEs during Pre-screening, prior to provision of a patient's consent to the main study in section 8.3.2. Only procedure-related AEs and SAEs for those patients who provide a new tumour biopsy occurring within 21 days after the procedure require reporting. This was the intended meaning of the previous version of the CSP and so the revised wording is to clarify the reporting requirements. Usage guidance for drugs that prolong QT interval has been consolidated into one entry in Table 7 Restricted medications as an administrative change. Guidance for the management of QTc prolongation for osimertinib and savolitinib are shown side by side in a revised Table 12 Dose modifications for QTc prolongation in section 8.4.5.2 Management of savolitinib-related toxicities. Assessment of causality is not required in order to implement these dose modifications. Details of management of these adverse reactions has been removed from Table 11 and direction to Table 12 added to section 8.4.5.1.

Version 2.0, 20 February 2019
Correction to the note to Inclusion criterion 6 that local NGS testing requirements are not provided in the Central Laboratory Manual (these requirements are added to the CSP in this revision to Inclusion criterion 7). Statement added to the inclusion criterion that if performed this local NGS testing must be pre-approved by the Sponsor. Inclusion criterion 7 in section 5.1 requires patients to have available tissue from a biopsy for MET analysis or willingness to collect additional tissue for central testing obtained following progression on therapy. In this revision, the requirements for this available tissue are added to this inclusion criterion to reflect the importance of provision of this tumour

tissue and to ensure compliance with requirements already described in current Central Laboratory Manual and guidance in this CSP as follows: Tissue must be collected following progression on osimertinib therapy; obtained within 2 years of submission for MET analysis; and sufficient to meet the minimum tissue requirement defined in the current Central Laboratory Manual. The exact number of slides of tissue is not described in the CSP as this is subject to change. The Sponsor will continue to seek to minimise the amount of tissue requested during the study and this requirement will be documented in the Central Laboratory Manual and supporting instructions provided to sites.

Introduction of ±7 day window for collection of blood samples for plasma for ctDNA analyses scheduled to be collected on the day of every RECIST 1.1 scan to offer flexibility for site staff and patients in Table 1, and footnote h. Addition of the purpose of ctDNA sampling (in Table 1 and footnotes b and h) to differentiate between use of ctDNA to support potential development of MET clinical diagnostic collected at Pre-screening and Screening for all patients and ctDNA sampling to measure clearance of EGFR mutation alleles and for exploratory analysis collected for eligible patients at baseline, weekly during Cycle 1 of treatment, Cycle 2 Day 1, at every RECIST 1.1 scan and treatment discontinuation to explore response to study treatment. In section 8.6, clarification that blood rather than plasma samples are requested for circulating DNA/RNA for consistency with Table 1, and clarification that the baseline sample will be collected prior to the first dose.

Demography and Medical/Surgical history are requested at Pre-screening in order to allow collection of relevant information to support development of clinical diagnostic of either FISH and/or IHC MET testing, see Table 1. Demography is removed from the Screening assessments as this information will not change. Medical/surgical history should be reviewed again at Screening to assess the patient's eligibility for the trial.

Clarification of the two types of tumour biopsy tissue collected in footnote j of Table 1. Tumour biopsy tissue is required for all patients for submission to the central MET testing laboratory collected after progression on previous osimertinib therapy. Collection of a new tumour biopsy is requested following disease progression on study treatment to look at possible resistance mechanisms for savolitinib; collection and provision of this biopsy is optional.

Addition of collection of blood samples for PK analyses on Cycle 1 Day 1 and Cycle 2 Day 1 to Table 1 to match existing description of PK sampling schedule in section 8.5.1 and Table 13.

Introduction of acceptable time windows around the preferred timing of collection of blood samples for PK analyses to inform clinical staff scheduling and collecting these samples;

Pre-dose, up to 2 hours pre-dose; 1 hour post-dose, ±5 minutes; 3 hours post-dose, ±10 minutes to Table 1.

Window for electronic clinical outcome assessments (eCOA) questionnaires increased from ±2 or ±3 days to ±5 days relative to the first dose of treatment in Cycles 1 and 2 (28 day cycle) for ease of scheduling for the patient; see Table 1 footnote c) and section 4.1 Overall design: clarification of the timing of when to provide tumour tissue for central MET testing for those minority of patients enrolled with MET+ tumour tested by local NGS as being as soon as possible during Pre-screening, Screening or early during study treatment.

Addition of serum samples to types of biological samples to be collected and stored for companion diagnostic development and exploratory analyses in the Exploratory objective, section 1.2. Addition of circulating tumour protein in addition to DNA or RNA in the corresponding exploratory study endpoint/variable.

Introductory paragraph to Section 3 Objectives and Endpoints wording adjusted to make clear that patients included in the “All patients” population includes all patients, including those centrally confirmed as MET+ by either FISH and/or IHC.

Section 4.1 Criteria for local NGS MET test to be used for assessment of patient eligibility require completion of the local NGS testing laboratory questionnaire to obtain Sponsor approval with reference to the Sponsor acceptance criteria. These criteria are not described in the Central Laboratory Manual and so this reference has been removed. Clarification that a pre-existing local NGS test result is for assessment of MET testing of tumour for the purpose of assessment of eligibility. Guidance that sites must provide the minimum required tumour tissue samples for central confirmation of MET status by central FISH and IHC testing as defined in the Central Laboratory Manual as soon as possible during Pre-screening, Screening or early during study treatment. This central testing is required to allow determination of the study populations for each patient according to MET status by central FISH, central IHC and/or all patients.

Section 7.3 Guidance on withdrawal of a patient from the study has been corrected by removal of the following statement "Personal information and samples that have already been collected prior to withdrawal will still be used as intended in the CSP.” in order to align with the options for withdrawal of consent available to a patient. The guidance included earlier in this section covers the intent of this statement “the sponsor may retain and continue to use any data collected before the consent is withdrawn”. The patient may explicitly choose to withdraw his/her consent for future use or genetic testing of samples already provided. The patient may choose to withdraw consent for the use of their personal data.

Section 8.2.1 Table 10 clarification that either blood urea nitrogen (BUN), also known as urea nitrogen, or urea clinical chemistry parameters can be collected as part of routine safety blood tests. Previously the list of required parameters included Blood urea nitrogen and urea nitrogen listed separately which describe the same test but did not include urea. Either blood urea nitrogen or urea are permitted to accommodate those tests available at the local analysing laboratory.

Section 8.3.2 Time period and frequency for collecting AE and SAE information previously referred to Appendix B for details of the time period for SAE reporting, procedures for completing and transmitting SAE reports. This reference is incorrect. This information is provided in section 8.4.1 Reporting of serious adverse events and so these incorrect references to Appendix B have been corrected to refer to section 8.4.1.

Section 8.4.5.2 Management of savolitinb-related toxicities – additional requirement for French sites only for clinical monitoring of savolitinib-related QTc prolongation NCI CTCAE Grade 3. The patient must remain hospitalised with continuous cardiac monitoring (ECG) until specialist advice is obtained by a cardiologist.

Section 8.7 (optional genomics initiative sample) – details of tube to be used removed (standard 6 ml EDTA tube). This level of detail is provided in the Central Laboratory Manual which is open to revision and is not required within the clinical study protocol.

The Sponsor management team will actively assess the safety and tolerability of the study treatment through continuous safety monitoring starting after the first 15 patients have had the opportunity to be treated for at least 6 weeks; see description in section 8.2 and section 9.5, also introduced in section 1.2. Intent to evaluate safety and tolerability of the study treatment by continuous monitoring of key patient information by the Sponsor (included in Section 8.2) is replaced with a more detailed proposal in planned statistical analyses in Section 9.2 of possible evaluation criteria of safety and tolerability of the study treatment at the planned interim analysis for assessment of efficacy. At the interim analysis (CCI) it may be considered futile to continue the study if there is CCI % probability for the discontinuation due to any AE rate to be below the target value (CCI %). Additionally, once the first 15 patients have had the opportunity to be treated for at least 6 weeks a predictive power calculation will be used to assess the chance of observing a discontinuation due to any AE rate of CCI % or less and a discontinuation due to a hypersensitivity/anaphylaxis AE rate of CCI % or less.

Section 4.2.2 addition of possible assessment of the proportion of patients discontinuing study treatment due to any AE and the proportion of patients discontinuing due to AE of hypersensitivity/anaphylaxis to evaluate the safety and tolerability of savolitinib in

combination with osimertinib to the listing of standard safety parameters under rationale for study endpoints.

Appendix I 3.4 recommendations for clinical management of hypersensitivity revised following review by the Sponsor of reported safety information for patients treated with the combination of savolitinib with osimertinib on the Phase I TATTON study. Investigators are recommended to continue treatment with savolitinib through initial mild symptoms of potential hypersensitivity with optimal supportive care rather than mandating immediate dose interruption and subsequent rechallenge. The rationale for this change in management is the Sponsor's observation that the majority of severe acute hypersensitivity reactions, including in some cases anaphylaxis, occurred following dose interruption and rechallenge.

If savolitinib dosing is interrupted, intense medical monitoring for restart at the institution is required with medical equipment readily available for resuscitation and management of anaphylaxis, vital status recording before and for at least 4 hours after dosing, 24 hour observation in the clinic prior to discharge. Should symptoms of potential hypersensitivity recur, or an acute anaphylactic reaction occur, immediate intervention must be instituted for appropriate management of the event and savolitinib must be permanently discontinued. These recommendations are guidelines only and final decisions concerning management of individual patients reside with the investigator or the treating physician. Clarification in the Benefit/risk assessment in Section 2.3 that these toxicity management guidelines apply to patients who experience hypersensitivity or pyrexia.

Clarification that Appendix I 3.2 Dose modification guidelines due to savolitinib-related toxicity apply to general toxicities. Restart of savolitinib dosing following dosing hold due to NCI CTCAE Grade 3 or recurrence of Grade 3 toxicity must follow the specific restart guidelines if the event includes symptoms of pyrexia, skin reactions, myalgia, arthralgia, or hypersensitivity, as per section I 3.4, added as footnote b to Table 23 for NCI CTCAEs of Grade 3 or recurrence of Grade 3 toxicities.

Criteria to discontinue savolitinib dosing due to drug-related hepatotoxicity have been revised in Appendix I 3.3.1 to clarify elevated ALT or AST >8 x ULN with total bilirubin elevation above baseline or ULN; or ALT or AST >5 x ULN for >2 weeks with total bilirubin elevation above baseline or ULN. Dosing should be withheld if ALT or AST >5 x ULN for >2 weeks or 8 x ULN without total bilirubin elevation above baseline or ULN. Dosing should be withheld if ALT or AST >3 x ULN and concurrent total bilirubin 1.5 x ULN. Dosing should be discontinued for recurrent ALT or AST >3 x ULN rather than >3 to 5 x ULN; for total bilirubin >1.5 x ULN rather than >1.5 to 2 x ULN; withheld for recurrent ALT or AST >3 rather than >3 to 5 x ULN without total bilirubin elevation above baseline or ULN.

Appendix I 1 provides osimertinib dose modification and guidance: - An opening statement has been introduced that clinical management should be in accordance with the local label in the first instance which takes precedence over the management guidance provided in this CSP and the osimertinib investigator's brochure. - Dose adjustment information for cardiac adverse reactions to osimertinib in Table 11 are revised for QTcF interval greater than 500msec on at least 2 separate ECGs. Osimertinib should be withheld until QTcF interval is <481msec or recovery to baseline if baseline QTCF is >481 msec within 3 weeks of onset. Dosing can be restarted at a reduced dose (40mg) or at the same dose (80mg) at the discretion of the Investigator (also included in section I 1.2.) - The footnote to Table 11 has been updated to refer to NCI CTCAE version 5.0 in line with the rest of the CSP. - Addition of guidance for investigators to correct clinically significant electrolyte abnormalities to within normal ranges prior to first dose and during study treatment (see section I 1.2 QTcF prolongation). Aclarubicin added to list of Drugs inducing Torsades de Pointes in J 5.1 Table 29.
Version 1.0, 20 August 2018
Initial creation

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.

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1.1 Schedule of activities (SoA)

The schedule of activities (SoA) at screening, treatment period, discontinuation, follow-up period and progression is shown in Table 1. The SoA for patients who cross over to savolitinib 300 mg bid plus osimertinib from the savolitinib 300 mg bid plus placebo arm is shown in Table 2.

Schedule of activities (SoA) for allocated / randomised treatment

Table 1 Schedule of Activities for allocated / randomised treatment

Visit	Pre-screening	Screening	Treatment Period						Follow-up[a]				Details in CSP section
			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]	Progression Follow-up[c]	Survival Follow up	
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	**NA**		**1**	**8**	**15**	**22**	**1**	**1**					
Visit window			**±1 day**				**±3 days**	**±3 days**	**Within 7 days of the final dose of the last IP**	**±7 days**	**±7 days**	**± 7 days**	
Informed consent for MET status testing	X												5.1
Retrieve or collect tumour tissue for MET status testing	X[e]												5.1 and 8.6
Blood sample for ctDNA for diagnostic development)[d]	X	X											8.6
Confirm tumour harbours EGFRm (exon 19 deletion and/or L858R)	X[f]												5.1
Informed consent for main study		X											5.1
Inclusion/exclusion criteria		X											5.1 and 5.2

Visit	Pre-screening	Screening	Treatment Period						Follow-up[a]				Details in CSP section
			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]	Progression Follow-up[c]	Survival Follow up	
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	**NA**		**1**	**8**	**15**	**22**	**1**	**1**					
Visit window			**±1 day**				**±3 days**	**±3 days**	**Within 7 days of the final dose of the last IP**	**±7 days**	**±7 days**	**± 7 days**	
Routine clinical procedures													
Demography	X												5.1
Physical examination		X	X	X	X	X	Every visit		X				8.2.2
Height		X											8.2.3
Weight		X[g]	X				Day 1 of every cycle	Every 8 weeks	X				8.2.3
Medical/surgical history and comorbid conditions	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			8.2.3
Triplicate ECG		X	X	X	X	X	Day 1 of every cycle Cycle 3 Day 1[t]		X	X[h]			8.2.4
MUGA/ECHO		X	Q12W (±2 weeks) relative to randomisation (patients recruited under CSP v7.0) or first dose of study drug (patients recruited prior to CSP v7.0)						X	X[h]			8.2.5
Concomitant medication and procedures		X	At every visit and may be conducted by phone if not tied to a clinic visit						X	X			6.5

Visit	Pre-screening	Screening	Treatment Period						Follow-up[a]				Details in CSP section
			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]	Progression Follow-up[c]	Survival Follow up	
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	**NA**		**1**	**8**	**15**	**22**	**1**	**1**					
Visit window			**±1 day**				**±3 days**	**±3 days**	**Within 7 days of the final dose of the last IP**	**±7 days**	**±7 days**	**± 7 days**	
Routine safety measurements													
Adverse events		X	At every visit and may be conducted by phone if not tied to a clinic visit						X	X			8.3
Pregnancy test (serum or urine, WOCBP only)		X	Day 1 of every cycle						X				8.2.6
Safety laboratory assessments (clinical chemistry, haematology and urinalysis)		X	X	X	X	X	Every visit		X				8.2.1
Coagulation		X											5.1 and 8.2.1
Liver function tests[i]		X	Weekly for the first 10 weeks, then Day 1 of every subsequent cycle						X				8.2.1
Biomarker analyses													
Blood sample for ctDNA for EGFR mutation alleles and exploratory analysis[j]			Pre-dose on Day 1 and at every subsequent visit in Cycle 1				Day 1 of Cycle 2 and then on occurrence of every RECIST 1.1 scan[j]				X (taken at progression)		8.6

Visit	Pre-screening	Screening	Treatment Period						Follow-up[a]				Details in CSP section
			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]	Progression Follow-up[c]	Survival Follow up	
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	**NA**		**1**	**8**	**15**	**22**	**1**	**1**					
Visit window			**±1 day**				**±3 days**	**±3 days**	**Within 7 days of the final dose of the last IP**	**±7 days**	**±7 days**	**± 7 days**	
Serum sample for circulating proteins for exploratory analysis		X	X						X				8.6
Genetic sample[k] (optional DNA element for long-term storage/future use)		X											8.7, Appendix D
HLA subtype blood sample			X										8.6
CCI [redacted]													8.6
Pharmacokinetic measurements													
PK sampling[n,o]			X[o]				Day 1 of Cycles 2, 3 and 6[o]	Day 1 of Cycle 11[o]					8.5.1

Visit	Pre-screening	Screening	Treatment Period						Follow-up[a]				Details in CSP section
			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]	Progression Follow-up[c]	Survival Follow up	
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	**NA**		**1**	**8**	**15**	**22**	**1**	**1**					
Visit window			**±1 day**				**±3 days**	**±3 days**	**Within 7 days of the final dose of the last IP**	**±7 days**	**±7 days**	**± 7 days**	
Efficacy measurements													
Tumour imaging (RECIST Version 1.1)[p]		X[q]	Q6W (±7 days) up to 24 weeks, then every Q8W (±7 days) until objective disease progression relative to randomisation (patients recruited under CSP v7.0) or the first dose of treatment (patients recruited prior to CSP v7.0)										8.1
EORTC QLQ-C30		X	Q4W (±2 days) relative to randomisation (patients recruited under CSP v7.0) or the first dose of treatment (patients recruited prior to CSP v7.0)[r]						X[s]				8.1.2.1
QLQ-LC13		X	Weekly (±2 days) in Cycles 1 and 2 and then Q4W (±2 days) relative to randomisation (patients recruited under CSP v7.0) or the first dose of treatment from Cycle 3 onwards (patients recruited prior to CSP v7.0)[r]						X[s]				8.1.2.1
PGIS		X	Q8W (±2 days) relative to randomisation (patients recruited under CSP v7.0) or the first dose of treatment (patients recruited prior to CSP v7.0)[r]						X[s]				8.1.2.2
PRO-CTCAE		X	Weekly (±2 days) in Cycles 1 and 2 and then Q4W (±2 days) relative to randomisation (patients recruited under CSP v7.0) or the first dose of treatment (patients recruited prior to CSP v7.0) from Cycle 3 onwards[r]						X[s]				8.1.2.3

Visit	Pre-screening	Screening	Treatment Period						Follow-up[a]				Details in CSP section
			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]	Progression Follow-up[c]	Survival Follow up	
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	**NA**		**1**	**8**	**15**	**22**	**1**	**1**					
Visit window			**±1 day**				**±3 days**	**±3 days**	**Within 7 days of the final dose of the last IP**	**±7 days**	**±7 days**	**± 7 days**	
EQ-5D-5L		X	Q4W (±2 days) relative to randomisation (patients recruited under CSP v7.0) or the first dose of treatment (patients recruited prior to CSP v7.0)[r]						X[s]				8.1.2.4
Study treatment administration													
Dose with osimertinib or placebo to osimertinib			X (daily dosing)										6
Dose with savolitinib			X (daily dosing)										6
Survival follow up													
Survival status[u]												Q12W	8.1.3
Subsequent anti-cancer treatment												Q12W	8.1.3

[a] The follow up period is only applicable for those who discontinue allocated/ 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 both IPs to collect new AEs and follow up on any ongoing AEs and concomitant medications (including any subsequent cancer therapy, if appropriate).

[c] At the investigator's discretion, study treatment may continue after progression if a patient continues to derive clinical benefit per guidelines. Patients who continue on treatment following progression should maintain the schedule of assessments at each cycle (28 days): Routine safety measurements (AEs, safety laboratory assessments [clinical chemistry, haematology and urinalysis], and creatinine clearance calculation) and Routine clinical procedures (physical exam, WHO PS, vital signs, Echo/multi-gated acquisition (MUGA), and concomitant medications). In addition, patients will continue to be followed up for survival status every 12 weeks until death, or withdrawal of consent.

[d] Refer to Laboratory Manual for details of sample processing for blood sample for ctDNA analysis for diagnostic development; at Pre-screening collect 30 mL blood; at Screening collect 20 mL blood. If a patient is repeating Pre-screening following an interval during which the patient was treated with another EGFR TKI, a repeat blood sample for ctDNA analysis for diagnostic development should be collected.

[e] Under CSP version 7.0, only patients with central MET IHC+ and/or FISH+ status will be eligible to Screening; patients with MET status confirmed by local NGS are not eligible. Testing for MET-amplification and overexpression in tumour by FISH (centrally) and by IHC (centrally) will be performed on a tumour sample collected after progression of previous osimertinib treatment. Testing must be performed as initial prescreening with consent obtained using the Pre-screening ICF in advance of obtaining consent for the main study. Approximately CCI freshly cut (within CCI days) unstained sections (CCI micron) from FFPE tissue blocks or FFPE blocks containing equivalent material will be required for all patients. SamplesCCI years old will not be accepted. New samples should only be taken specifically for Pre-screening for this study where the expected risk of an adverse event related to the procedure is <2%.

[f] EGFRm status is an inclusion criterion and part of disease diagnosis; prospective central testing is not required.

[g] For those patients treated on weight-based dosing regimen for savolitinib (prior to introduction of 300 mg od savolitinib dose for all new patients in CSP version 3.0), the weight captured at Screening will be used to determine the assigned dose.

[h] 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.

[i] Liver function tests will be performed weekly for the first 10 weeks (ie, Day 1, Day 8, Day 15 and Day 22 in Cycle 1 and Cycle 2; then Day 1 and Day 8 of Cycle 3). 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 3.3 for enhanced monitoring and management procedures.

[j] At all visits, CCI blood for plasma is required for ctDNA to measure clearance of EGFR mutation alleles and for exploratory analysis. Blood samples for ctDNA analyses requested on occurrence of every RECIST 1.1 scan should be collected on the day of the scan. If this is not possible the blood sample should be collected as close as possible to the scan within a window of ±7 days.

[k] If not taken at screening the sample may be taken at any visit until the final study visit.

[l] Pre-screening tumour sample is to be collected after progression on previous osimertinib treatment and is required during Pre-screening as described in the Laboratory Manual.

[m] CCI for savolitinib and is optional.

[n] 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 dose and last savolitinib dose prior to each PK sample will be collected.

[o] Plasma concentrations of osimertinib, savolitinib and their metabolites. Collected on: Cycle 1, Day 1: predose, 1 and 3 hours postdose; Cycle 2, Day 1; predose, 1 and 3 hours post-dose; Cycle 3 Day 1: pre-dose, 1, 3, 4 and 6 hours post-dose; Cycles 6 and 11, Day 1: predose only. PK sample collection windows are: Pre-dose, up to 2 hours pre-dose; 1 hour post-dose, ±5 minutes; 3, 4, and 6 hours post-dose, ±10 minutes. For patients receiving twice daily dosing (savolitinib 300 mg bid), PK samples will be collected following the first dose of the day.

[p] Patients who discontinue study drug for reasons other than investigator-confirmed disease progression will continue RECIST 1.1 tumour assessments every 6 weeks (±7 days) until Cycle 7 (ie, 24 weeks) and then every 8 weeks (±7 days) (relative to randomisation [patients recruited under CSP v7.0] or the first dose of treatment [patients recruited prior to CSP v7.0]) until objective disease progression per RECIST 1.1 as assessed by the 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. SAEs considered related to study treatment and/or study procedures will be collected throughout progression follow-up.

[q] At screening the MRI/CT scans will include brain imaging (MRI preferred) for all patients randomised under CSP version 7.0. Those determined to have brain metastases at baseline or those who had a history of brain metastases will have their brain rescanned (using the same modality as at baseline) at all subsequent tumour assessments until RECIST 1.1-defined PD (including PD). In patients without brain metastases at baseline and without a history of brain metastases, brain scans will be performed only when there is a suspected CNS progression and at the RECIST 1.1-defined extracranial progression. The brain scan is required for all patients at PD by investigator assessment per RECIST 1.1 and should be performed within 4 weeks, but preferably as soon as possible, to allow the assessment of new lesions in the brain.

[r] ePRO (Electronic devices; LogPads) must be assigned to patients confirmed as eligible for the study, following registration in IWRS after which the device may be taken home by the patient: baseline ePROs must be completed by patients prior to dosing on Cycle 1 Day 1. Screening ePRO assessments offer the opportunity for site staff to set up the device, add the patient, and for the patient to practice reporting ePROs for the first time and make themselves familiar with the device before the baseline assessment at Cycle 1 Day 1. PRO-CTCAE will be administered only in the languages where a linguistically validated version exists. LogPads used for ePRO collection should be returned to site at the nearest visit as soon as the last assessment is completed by patient.

[s] For patients on the savolitinib 300 mg bid + placebo arm who are eligible for cross over to the savolitinib 300 mg + osimertinib combination arm, the ePRO must be completed after progressive disease is assessed and confirmed by the Investigator, and before crossing over to the combination arm (within 7 days of the final dose of savolitinib + placebo).

[t] Triplicate ECGs will be required on Cycle 3 Day 1 collected to coincide with collection of blood samples for assessment of PK of osimertinib and savolitinib at this visit.

[u] Patients will be contacted for survival follow-up every 12 weeks until death, withdrawal of consent or the end of the study ie, at the time of final analysis. Patients should be contacted in the week following the data cut-offs to provide complete survival data. SAEs considered related to study treatment will be collected throughout survival follow-up.

AE Adverse event; bid twice daily; CSP Clinical Study Protocol; ctDNA Circulating tumour deoxyribonucleic acid; CNS Central nervous system; CT Computed tomography; CTSQ-16 Cancer Therapy Satisfaction Questionnaire-16; DNA Deoxyribonucleic acid; ECG Electrocardiogram; ECHO Echocardiogram; ECOG Eastern Cooperative Oncology Group; EGFR Epidermal growth factor receptor; EORTC-QLQ-C30 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; ePRO electronic patient reported outcomes; EQ-5D-5L EuroQol 5 dimensions, 5 levels; FACT-L Functional Assessment of Cancer Therapy – Lung Cancer; HLA human leukocyte antigen; IHC Immunohistochemistry; IP Investigational product; IWRS Interactive Web Response System; MET Mesenchymal epithelial transition factor; MRI Magnetic resonance imaging; MUGA Multi-gated acquisition; NA Not applicable; NGS Next generation sequencing; PD Progressive disease; PK Pharmacokinetics; PRO-CTCAE Patient reported outcomes version of the Common Terminology Criteria for Adverse Events; Q4W Every 4 weeks; Q6W Every 6 weeks; Q8W Every 8 weeks; Q12W Every 12 weeks; QLQ-LC13 Quality of Life Questionnaire-Lung Cancer 13; RECIST 1.1 Response Evaluation Criteria in Solid Tumours version 1.1; TKI Tyrosine kinase inhibitor; WHO World Health Organization; WOCBP Women of child-bearing potential.

Schedule of activities (SoA) for patients who cross over

Table 2 Schedule of activities for patients who cross over to savolitinib plus osimertinib from savolitinib plus placebo

Crossover Visit	**Prior to crossover**	**Crossover Period**						**Follow-up**				**Details in CSP Section**
		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]**	**Progre-ssion Follow-up[b]**	**Survival Follow-up**	
Week (Day 1 of)		**1 to 4**				**5 to 24**	**25 onwards**					
Study day of crossover		**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 the last IP**	**± 7 days**	**± 7 days**	**± 7 days**	
Informed consent for crossover	X											5.1
Routine clinical procedures												
Physical examination		X				Every visit		X				8.2.2
Weight		X				Day 1 of every cycle	Q8W	X				8.2.3
ECOG/WHO performance score		X				Day 1 of every cycle		X	X			5.1
Vital signs		X				Day 1 of every cycle		X	X			8.2.3
Triplicate ECG		X				Day 1 of every cycle		X	X[c]			8.2.4
MUGA/ECHO		Q12W (±2 weeks) relative to crossover C1D1						X	X[c]			8.2.5
Concomitant medication and procedures		At every visit, and may be conducted by phone if not tied to a clinical visit						X	X			6.5

Crossover Visit	Prior to crossover	Crossover Period						Follow-up				Details in CSP Section
		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]	Progre-ssion Follow-up[b]	Survival Follow-up	
Week (Day 1 of)		**1 to 4**				**5 to 24**	**25 onwards**					
Study day of crossover		**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 the last IP**	**± 7 days**	**± 7 days**	**± 7 days**	
Routine safety measurements												
Adverse events		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)		Day 1 of every cycle						X				8.2.6
Safety laboratory assessments (clinical chemistry, haematology and urinalysis)[d]		X[d]				Every visit		X				8.2.1
Liver function tests[e]		Weekly for the first 10 weeks of the study as per Table 1[e], then Day 1 of every subsequent cycle						X				8.2.1

Crossover Visit	Prior to crossover	Crossover Period						Follow-up				Details in CSP Section
		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]	Progre-ssion Follow-up[b]	Survival Follow-up	
Week (Day 1 of)		**1 to 4**				**5 to 24**	**25 onwards**					
Study day of crossover		**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 the last IP**	**± 7 days**	**± 7 days**	**± 7 days**	
Biomarker analyses												
Blood sample for ctDNA for EGFR mutation alleles and exploratory analysis[f]		Pre-dose on Day 1 and Day 22 in Cycle 1				Day 15 of Cycle 2						8.6
Serum sample for circulating proteins for exploratory analysis								X				8.6
CCI [redacted]												8.6
Efficacy measurements												
Tumour imaging (RECIST 1.1)[h]		Scheduled imaging is required for patients who cross over based on a declaration of futility of the savolitinib monotherapy arm and who have not progressed during the initial randomised treatment period: Q6W (±7 days) up to 24 weeks relative to initial randomisation, then every Q8W (±7 days) until objective disease progression										8.1

Crossover Visit	Prior to crossover	Crossover Period						Follow-up				Details in CSP Section
		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]	Progre-ssion Follow-up[b]	Survival Follow-up	
Week (Day 1 of)		1 to 4				5 to 24	25 onwards					
Study day of crossover		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 the last IP**	**± 7 days**	**± 7 days**	**± 7 days**	
Study treatment administration												
Dose with osimertinib		X (daily dosing)										6
Dose with savolitinib[i]		X (daily dosing)										6
Survival follow-up												
Survival status[j]											Q12W	8.1.3
Subsequent anti-cancer treatment											Q12W	8.1.3

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

[b] At the investigator's discretion, study treatment may continue after progression if a patient continues to derive clinical benefit per guidelines. Patients who continue on treatment following progression should maintain the schedule of assessments at each cycle (28 days): Routine safety measurements (AEs, safety laboratory assessments [clinical chemistry, haematology and urinalysis], and creatinine clearance calculation) and Routine clinical procedures (physical exam, WHO PS, vital signs, Echo/multi-gated acquisition (MUGA), and concomitant medications). In addition, patients will continue to be followed up for survival status every 12 weeks until death, or withdrawal of consent.

[c] 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.

[d] The frequency of safety laboratory assessments will depend on the timepoint at which the patient crosses over. Safety laboratory assessments should be performed weekly on Days 1, 8, 15, and 22 during the first 4 weeks of the study (ie, for patients who cross over prior to completing the first 4 weeks of the study) then every subsequent cycle visit in the crossover period.

[e] The frequency of liver function tests will depend on the timepoint at which the patient crosses over. Liver function tests should be performed weekly for the first 10 weeks of the study (ie, for patients who cross over prior to completing 10 weeks of the study) then on Day 1 of every subsequent cycle in the crossover period. 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 3.3 for enhanced monitoring and management procedures.

[f] At all visits, CCI mL blood for plasma is required for ctDNA to measure clearance of EGFR mutation alleles and for exploratory analysis.

[g] CCI for savolitinib and is optional.

[h] For patients who cross over based on confirmed objective disease progression during the initial randomised treatment period, scheduled RECIST 1.1 tumour assessments are not required, and the subsequent assessment of disease progression will be based on standard-of-care scan or investigator determined clinical progression. Scheduled RECIST 1.1 tumour assessments are required (the scan frequency is against initial randomisation) for patients who cross over based on a declaration of futility of the savolitinib monotherapy arm and who have not objectively progressed during the initial randomised treatment period. Patients who cross over based on a declaration of futility, who have no objective progression during initial randomisation period, and who discontinue study drug after cross-over for reasons other than investigator-confirmed disease progression will continue scheduled RECIST 1.1 tumour assessments until objective disease progression per RECIST 1.1 as assessed by investigator, unless they withdraw consent to the entire study. At the same time points, vital signs, and ECGs will be collected. SAEs considered related to study treatment 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 every 12 weeks until death, withdrawal of consent or the end of the study ie, at the time of final analysis. Patients should be contacted in the week following the data cut-offs to provide complete survival data. SAEs considered related to study treatment will be collected throughout survival follow-up.

AE Adverse event; bid twice daily; C Cycle; C1D1 Cycle 1 Day 1; CSP clinical study protocol; ctDNA Circulating tumour deoxyribonucleic acid; D Day; DNA Deoxyribonucleic acid; ECG Electrocardiogram; ECHO Echocardiogram; ECOG Eastern Cooperative Oncology Group; EGFR Epidermal growth factor receptor; IP Investigational product; MUGA Multi-gated acquisition; NA Not applicable; PD progressive disease; PK Pharmacokinetics; Q6W Every 6 weeks; Q8W Every 8 weeks; Q12W Every 12 weeks; RECIST Response Evaluation Criteria in Solid Tumours; SAE Serious adverse event; WHO World Health Organization; WOCBP women of child-bearing potential.

1.2 Synopsis

International Co-ordinating Investigators:

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Protocol Title: A Phase II Study Assessing the Efficacy of Osimertinib in Combination with Savolitinib in Patients with EGFRm+ and MET+, Locally Advanced or Metastatic Non-Small Cell Lung Cancer who have Progressed Following Treatment with Osimertinib (The SAVANNAH Study).

Short Title: Osimertinib plus savolitinib in EGFRm+/ MET+ NSCLC following prior osimertinib

Rationale:

Osimertinib (Tagrisso™) is a potent irreversible inhibitor of sensitising epidermal growth factor receptor (EGFR) mutations and T790M mutation-positive forms of EGFR. Osimertinib acts on tumours by blocking abnormal EGFR-mediated signalling, leading to profound tumour growth inhibition in EGFR mutation bearing non-small cell lung cancer (NSCLC). However, resistance to osimertinib is an emerging and important unmet clinical problem. One of the major mechanisms for resistance is amplification and/or overexpression of the hepatocyte growth factor (HGF) receptor, mesenchymal epithelial transition factor (MET) tyrosine kinase, which activates downstream intracellular signalling independent of EGFR. Presently, there is no approved therapy specifically indicated for the treatment of patients with tumours positive for MET-amplification and/or overexpression, and there is no established standard of care specifically for patients who have developed MET-driven resistance after prior EGFR-tyrosine kinase inhibitor (TKI) therapy (including osimertinib).

Savolitinib is a potent and selective MET-TKI which has been shown to inhibit cell growth against tumours with MET-amplification in the absence of HGF stimulation and in tumours with MET overexpression in the presence of HGF-stimulated cell proliferation. Nonclinical studies have demonstrated the combination effect of savolitinib plus osimertinib, and this alongside clinical evidence has shown that the EGFR should still be inhibited in combination with MET inhibition to overcome resistance to EGFR-TKI and maintain remission.

In a subset of MET-driven EGFR TKI-refractory cancers, low EGFR:MET expression appears to predict MET dependence (ie, EGFR independence) in patient-derived xenograft models, suggesting a subset of patients with EGFR-mutant, MET-driven lung cancers may develop dependence on MET activation alone and may be treated with a single-agent MET-TKI.

This Phase II study (SAVANNAH) will investigate the efficacy and safety of osimertinib (80 mg od) in combination with savolitinib (300 mg od, 300 mg bid or 600 mg od) in patients with EGFRm+ and MET-amplified/overexpressed (patients with FISH10+ and/or IHC90+ status across all clinical study protocol (CSP) versions and patients with FISH5+ and/or IHC50+ status prior to CSP version 7.0), locally advanced or metastatic NSCLC who have progressed following treatment with osimertinib. The study will also investigate the difference in efficacy of savolitinib in combination with osimertinib and savolitinib monotherapy in the population enrolled under CSP version 7.0 with MET-amplified/overexpressed (FISH10+ and/or IHC90+) status who have progressed following treatment with 1L osimertinib therapy.

Objectives and Endpoints

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

To determine the efficacy of savolitinib (300 mg od and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET-amplified/overexpressed (FISH10+ and/or IHC90+)[a], locally advanced or metastatic NSCLC who have progressed following treatment with 1L osimertinib.	• ORR, DoR, and PFS, by investigator assessment in accordance with RECIST 1.1. • OS
To determine the efficacy of savolitinib (300 mg od, 300 mg bid, and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET-amplified/overexpressed (FISH10+ and/or IHC90+)[a], locally advanced or metastatic NSCLC who have progressed following treatment of ≥ 2L osimertinib.	• ORR, DoR, and PFS, by investigator assessment in accordance with RECIST 1.1. • OS
To determine the efficacy of savolitinib (300 mg od, 300 mg bid, and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET-amplified/overexpressed (FISH5+ and/or IHC50+)[b], locally advanced or metastatic NSCLC who have progressed following osimertinib.	• ORR (except 300 mg od), DoR, and PFS by investigator assessment in accordance with RECIST 1.1. • OS
To determine the efficacy of (1) 300 mg od, 300 mg bid and 600 mg od of savolitinib in combination with osimertinib in patients with EGFRm+ MET amplified/ overexpressed (FISH 10+ and/or IHC90+)[a,b]; (2) 300 mg od, 300 mg bid and 600 mg od of savolitinib in combination with osimertinib in patients with EGFRm+ MET amplified/overexpressed (FISH5+ and/or IHC50+)[b] (3) savolitinib 300 mg bid in combination with osimertinib and savolitinib 300 mg bid in combination with placebo, respectively, in patients with EGFRm+ MET amplified/ overexpressed (FISH10+ and/or IHC90+)[a] following treatment with 1L osimertinib.	• ORR, DoR, and PFS assessed by BICR in accordance with RECIST 1.1
To assess the impact of savolitinib and osimertinib on disease-related symptoms and HRQoL in this patient population.	• Mean change from baseline in EORTC QLQ-C30 and QLQ-LC13.
To evaluate the pharmacokinetics of osimertinib and savolitinib in this patient population.	• Plasma concentrations of osimertinib, savolitinib and their metabolites.
To determine the prevalence of ctDNA clearance after osimertinib and savolitinib treatment in this patient population.	• Total clearance in EGFR mutations at 6-weeks after therapy initiation (percentage and absolute change from baseline in EGFR mutation allele frequencies).

Safety Objectives:	**Endpoints:**
To evaluate the safety and tolerability of savolitinib in combination with osimertinib and savolitinib in combination with placebo.	• AEs, SAEs and discontinuation rate due to AEs. • Clinical chemistry/haematology including LFTs. • ECHOs, ECGs and vital signs including blood pressure and heart rate.

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

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

Osimertinib 80 mg od is administered in the combination dosing regimens.

1L First line; 2L Second line; AE Adverse event; bid twice daily; BICR Blinded independent central review; CTCAE Common Terminology Criteria for Adverse Events; DoR Duration of response; ECG Electrocardiogram; ECHO Echocardiogram; EGFR Epidermal growth factor receptor; EGFRm+ Epidermal growth factor receptor mutation positive; EQ-5D-5L EuroQol 5 dimensions, 5 levels; FACT-L Functional Assessment of Cancer Therapy - Lung Cancer; FISH Fluorescence in situ hybridisation; HRQoL Health-related quality of life; IHC Immunohistochemistry; LFT liver function test; MET Mesenchymal epithelial transition factor; MET/CEP7 Mean MET per cell and chromosome 7 centromere ratio; NGS Next generation sequencing; NSCLC Non-Small Cell Lung Cancer; od once daily; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; PRO Patient reported outcomes; QLQ-LC13 Quality of Life Questionnaire-Lung Cancer 13; RNA Ribonucleic acid; SAE Serious adverse events.

Overall design:

This is a Phase II study to investigate the efficacy of osimertinib administered orally with savolitinib in patients with EGFRm+ and MET-amplified/overexpressed, locally advanced or metastatic NSCLC who have progressed following treatment with osimertinib.

Under CSP version 7.0, the SAVANNAH study will be expanded to further investigate the efficacy of savolitinib 300 mg bid + osimertinib in MET-amplified/overexpressed (FISH10+ and/or IHC90+) patients who have progressed following 1L osimertinib treatment. Per CSP version 7.0, the study will also describe the difference in the efficacy of osimertinib in combination with savolitinib 300 mg bid and savolitinib monotherapy in the treatment of EGFRm+ NSCLC patients with MET FISH10+ and/or IHC90+ status whose tumour has progressed following 1L osimertinib treatment.

The study design for patients who were enrolled under CSP versions 1.0 to 6.0, and for patients who will be enrolled under CSP version 7.0 is summarised in Figure 1.

Study Period:

- Estimated date of first patient enrolled: Q4 2018
- Estimated date of last patient completed (final data cut-off): Q1 2025

Patient Population:

Prior to CSP version 7.0, eligible patients were those with histologically or cytologically confirmed diagnosis of EGFRm+, MET-amplified/overexpressed (FISH5+ and/or IHC50+) NSCLC that is locally advanced or metastatic and is not amenable to further surgery or radiotherapy with curative intent. The disease must have progressed following treatment with osimertinib.

Under CSP version 7.0, eligible patients will be those with histologically or cytologically confirmed diagnosis of EGFRm+, MET-amplified/overexpressed (FISH10+ and/or IHC90+) NSCLC that is locally advanced or metastatic and is not amenable to further surgery or radiotherapy with curative intent. The disease must have progressed following treatment with first-line osimertinib.

Number of Patients and intervention groups:

The study has a total of 4 dosing combinations:

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

Overall, approximately CCI patients are planned to be treated in the study, including approximately CCI patients who will receive osimertinib (80 mg od) in combination with either savolitinib 300 mg od (n=CCI patients, approximately), savolitinib 300 mg bid (n=CCI patients, approximately), or savolitinib 600 mg od (n=CCI patients, approximately), and approximately CCI patients who will receive placebo to osimertinib + savolitinib 300 mg bid (with the opportunity to cross over to combination treatment on disease progression).

Under CSP version 7.0, approximately CCI patients with MET-amplified/overexpressed (FISH10+ and/or IHC90+) status who have progressed following treatment with 1L osimertinib will be randomised in a 2:1 ratio to receive savolitinib 300 mg bid + osimertinib 80 mg od (approximately CCI patients) or savolitinib 300 mg bid + placebo (approximately CCI patients) in a double-blind manner. Randomisation will be stratified according to the presence of brain metastases at baseline (yes versus no). At the time of investigator assessment of progressive disease (PD) per RECIST 1.1, the treatment group will be unblinded and patients who were initially randomised to the savolitinib 300 mg bid + placebo arm will be given the opportunity to cross over to the savolitinib 300 mg bid + osimertinib

80 mg od arm. Under CSP version 7.0, patients must have confirmation of MET-amplified/overexpressed (FISH10+ and/or IHC90+) tumour status by FISH (central) and IHC (central) testing. Pre-existing next generation sequencing testing results are not accepted to enter Screening.

Intervention duration

All patients confirmed as eligible will begin treatment on Day 1 with osimertinib + savolitinib combination therapy or placebo to osimertinib + savolitinib. Treatment will continue in 28-day cycles until either objective disease progression by investigator per RECIST 1.1 is assessed, unacceptable toxicity occurs, consent is withdrawn or another discontinuation criterion is met.

Patients randomised to the placebo + savolitinib 300 mg bid arm may cross over to osimertinib 80 mg od + savolitinib 300 mg bid following investigator-assessed PD per RECIST 1.1.

Independent data monitoring committees

An independent data monitoring committee will meet to assess the futility of the savolitinib 300 mg bid + placebo arm after CCI patients have been randomised under CSP version 7.0 and have had an opportunity to have 2 post-baseline scans. The IDMC will also review at this time the safety data of the randomised patients recruited under CSP version 7.0 for both arms (Appendix A 5). More details are provided in the IDMC charter.

In addition, CCI [redacted].

Statistical considerations:

The study will have 5 planned analyses. Interim Analysis 1 was planned and performed after approximately CCI patients treated with osimertinib and 300 mg od savolitinib had the opportunity to be treated for 2 post-baseline Response Evaluation Criteria in Solid Tumour (RECIST) scans (12 weeks) or the CCI patient treated with osimertinib (80 mg od) and savolitinib (300 mg od) had the opportunity to be treated for 6 weeks, whichever was later. Continuous monitoring of the discontinuation due to adverse event (AE) rate and the discontinuation due to a hypersensitivity/anaphylaxis AE rate was to be performed after the CCI patient treated with osimertinib and 300 mg od savolitinib had the opportunity to be treated for 6 weeks up to the first interim analysis.

Interim Analysis 2 was planned and performed after approximately [redacted] patients treated with osimertinib (80 mg od) and savolitinib (300 mg od) in the second line setting had the opportunity to be treated for 2 post-baseline scans (12 weeks).

The third planned analysis is a futility analysis for the placebo + savolitinib arm that is planned after [redacted] patients have been randomised under CSP version 7.0 and have had an opportunity to have 2 post-baseline scans.

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

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

Analyses will be performed by AstraZeneca or its representatives. A comprehensive Statistical Analysis Plan will be developed and will describe the patient populations to be included in the analyses, and procedures for accounting for missing, unused and spurious data. Any deviations from this plan will be reported in the clinical study report.

The analysis of objective response rate will be based on investigator assessment of RECIST 1.1 assessments. Objective response rate will be defined as a visit response of complete response (CR) or partial response (PR) which must be confirmed by a later scan conducted at least 4 weeks after the initial response is observed.

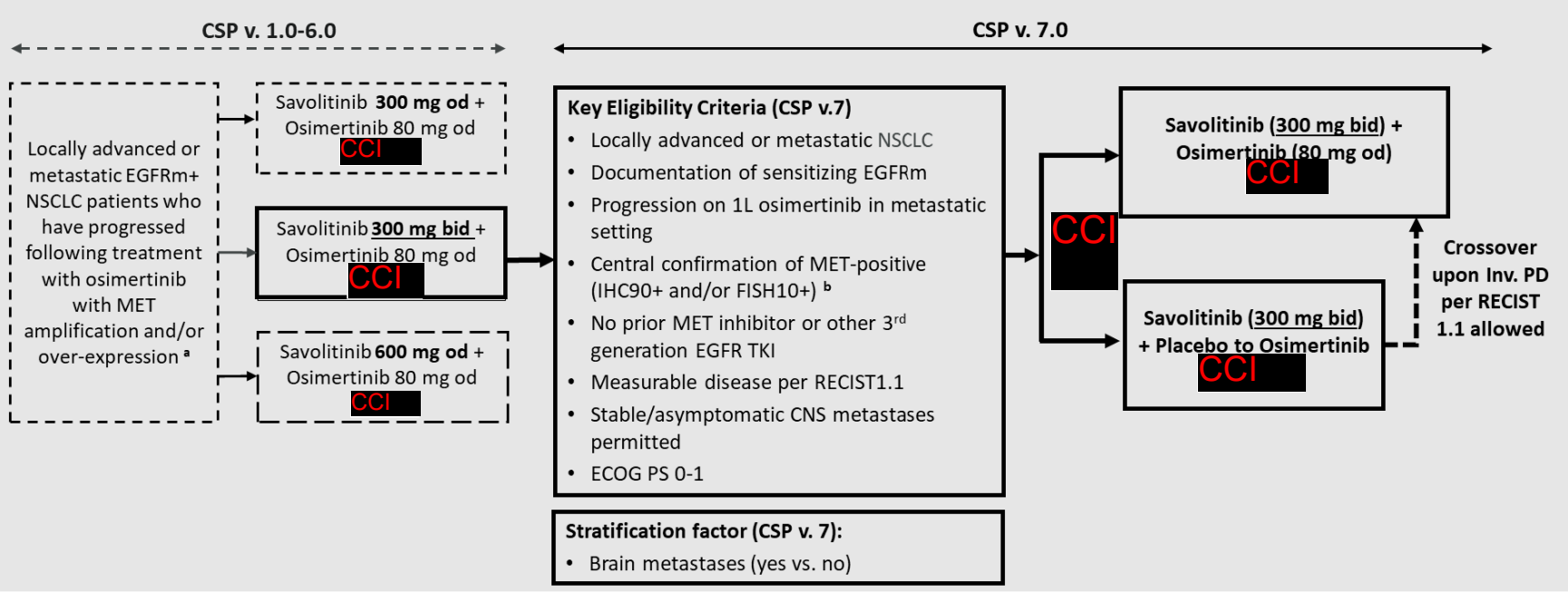
The efficacy endpoints will be summarised on the following datasets:

- Target Population Analysis Set (TPAS), defined as all patients assigned to savolitinib 300 mg bid + osimertinib who have FISH10+ and/or IHC90+ status, have progressed following 1L osimertinib and have taken ≥1 dose of either drug (primary endpoint population).
- Contribution of Components Analysis Set (CAS), defined as all patients randomised under CSP version 7.0 with treatment groups assigned in accordance with the randomisation, regardless of the treatment actually received.
- Safety Analysis Set (SAF), defined as all enrolled patients who take ≥1 dose of either study drug. The SAF will be used for reporting the efficacy of savolitinib 300 mg od + osimertinib in FISH5+ and/or IHC50+ patients (primary endpoint population). The SAF will also be used as the population for reporting the efficacy for patients dosed prior to CSP version 7.0.

Safety data will be summarised on the SAF. See the statistical analysis plan for further details. The general study design is summarised in Figure 1.

1.3 Schema

Figure 1 Study design



[a] IHC50+: ≥50% of tumour cells staining at strong 3+ intensity; FISH5: ≥5 MET gene copies or MET:CEP7 ratio ≥2 as determined by central testing. Under CSP versions 1-5, MET amplification as determined by pre-existing local NGS were also allowed. Under CSP version 6, only MET FISH5+ status as determined by central testing was allowed for eligibility.

[b] IHC90+: >=90% of tumour cells staining at strong 3+ intensity; FISH10: ≥10 MET gene copies; as determined by central testing.

[c] A futility analysis for the savolitinib + placebo arm is planned after CCI patients have been randomised under CSP version 7.0 and have had an opportunity to have 2 post-baseline scans. If the decision is made that treatment with savolitinib + placebo is futile, further enrolment into the savolitinib + placebo arm will be stopped.

1L First-line; bid; Twice daily; CSP Clinical Study Protocol; ECOG Eastern Cooperative Oncology Group; EGFRm+ Epidermal growth factor receptor mutation positive; EGFR-TKI EGFR-tyrosine kinase inhibitor; FISH Fluorescence in situ hybridisation; IHC Immunohistochemistry; MET Mesenchymal epithelial transition factor; MET/CEP7 Mean MET per cell and chromosome 7 centromere ratio; NSCLC Non-small cell lung cancer; od once daily; PD Progressive disease; RECIST Response Evaluation Criteria in Solid Tumours.

2 INTRODUCTION

Lung cancer has been the most common cancer in the world for several decades, and by 2012, there were an estimated 1.8 million new cases, representing 12.9% of all new cancers. It was also the most common cause of death from cancer, with 1.59 million deaths (19.4% of the total) (GLOBOCAN 2012). Non-small cell lung cancer (NSCLC) represents approximately 80% to 85% of all lung cancers. Unfortunately, at the time of diagnosis approximately 70% of NSCLC patients already have advanced or metastatic disease not amenable to surgical resection. Furthermore, a significant percentage of early-stage NSCLC patients who have undergone surgery subsequently develop distant recurrence and die as a result of their lung cancer (Pisters and Le Chevalier 2005). Patients presenting with unselected advanced NSCLC have a median overall survival (OS) of 10 to 12 months (Bonomi 2010).

In current clinical practice, therapeutic decisions for patients with advanced NSCLC are informed by the molecular subtypes of the tumour (Keedy et al 2011; Leigh et al 2014; National Comprehensive Cancer Network [NCCN 2018]; Reck et al 2014; Soria et al 2015; Travis et al 2011). Epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase rearrangement are the most well-known genetic alterations in NSCLC. EGFR-tyrosine kinase inhibitors (EGFR-TKIs) are the established first-line therapy in patients with NSCLC possessing activating mutations in EGFR (EGFRm+) (Masters et al 2015; National Comprehensive Cancer Network [NCCN 2018]; Reck et al 2014). 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 hepatocyte growth factor [HGF] receptor, mesenchymal epithelial transition factor [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 (Camidge et al 2014; Chong and Jänne 2013; Ohashi et al 2012).

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 2018). 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 trials (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 progression free survival (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 (Ballard et al 2016; Cross et al 2014). EGFR tyrosine kinase inhibitors (TKIs) are now the established 1L therapy in patients with NSCLC known to have activating mutations in *EGFR* (EGFRm+) (Masters et al 2015, NCCN 2018, Reck et al 2014). Based on recent data (Becker et al 2011; Mok et al 2016; Langer et al 2013) and Food and Drug Administration approval, the NCCN recommend osimertinib as a 1L 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 2018). Evidence from the AURA Phase I/II study (NCT01802632) of osimertinib in advanced NSCLC patients with disease progression following prior EGFR-TKI therapy, suggest 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 objective response rate (ORR) of 25% (95% CI: 15, 37) and disease control rate of 64% (95% confidence interval [CI]: 51, 75). Subsequently, the Phase III trial FLAURA, 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 versus 10.2 months; hazard ratio [HR] 0.46; 95% CI 0.37 to 0.57; P<0.001; Soria et al 2015).

Up to 22% of patients with NSCLC who progress on first-line 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 1 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. HGF 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 disease progression 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).

There is a considerable unmet clinical need in patients with epidermal growth factor receptor mutation positive (EGFRm+) advanced non small cell lung cancer (NSCLC) following progression on epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) therapy. Resistance to first/second line use of third generation EGFR-TKIs such as osimertinib is an emerging clinical problem. One of the mechanisms for resistance is amplification of the HGF receptor MET tyrosine kinase, which activates downstream intracellular signalling independent of EGFR. The combination of osimertinib with savolitinib is exploring how to overcome resistance driven by MET amplification.

Savolitinib (international non-proprietary name) (AZD6094, HMPL-504, volitinib) 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 2017a). A Phase III trial has been initiated in this indication (Choueiri et al 2017b).

The combination of osimertinib plus savolitinib in the Phase I TATTON study (NCT02143466) explored 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 Part A dose escalation cohort, savolitinib plus osimertinib had an acceptable safety profile and demonstrated evidence of anti-tumour activity in patients with EGFRm+ NSCLC (Oxnard et al 2015). A summary of preclinical combination data is provided in the savolitinib Investigator's Brochure.

Data from the TATTON Part B dose expansion were presented at the World Conference on Lung Cancer 2017 (Ahn et al 2017) and published by Sequist et al 2020 (28 February 2018 data cut-off date). Patients were treated with osimertinib 80 mg in combination with savolitinib 600 mg (both given orally once daily [od]). Encouraging anti-tumour activity was seen in patients with centrally confirmed MET-amplified status in the prior 3rd generation

EGFR-TKI therapy cohort (ORR 28%). Consistent results were seen in all MET-amplified/overexpressed patients (including local MET testing, as well as a small number of MET-overexpressed tumours by immunohistochemistry [IHC] without centrally confirmed MET-amplification). The overall safety profile of the combination was consistent with the known safety profiles of either compound alone. However, the discontinuation rate of savolitinib due to adverse events (AEs) was higher than expected (31.8% of patients) and 11.2% of patients had hypersensitivity events (presenting with an association of symptoms such as but not limited to allergic rash, cytopenias, increased liver enzymes, myalgia/arthralgia with or without pyrexia, and one case of Stevens-Johnson Syndrome), while no such cases were identified in other combination studies with savolitinib. All reported cases of hypersensitivity have been observed within the first 3 weeks of taking savolitinib. Whether there is an association between the development of hypersensitivity (or other AEs) and human leukocyte antigen (HLA) alleles in this population is currently unknown (Karlin and Phillips 2014). Preliminary data from exposure-AE modelling conducted with emerging data from 600 mg cohorts suggested a potential relationship between these events and low body weight, probably due to the higher exposure of savolitinib.

Following this, in March 2018 investigators were requested to apply a weight-based algorithm in patients enrolled in TATTON Part B (savolitinib 600 mg od if body weight is >55 kg at screening and 300 mg od if body weight is ≤55 kg at screening) maintaining the osimertinib dose at 80 mg od. Moreover, TATTON also included an ongoing Part D which tested savolitinib 300 mg in combination with osimertinib 80 mg to assess the impact of lower savolitinib exposure on overall tolerability and hepatotoxicity risk and to explore the efficacy using a dose meaningfully lower than 600 mg od.

Review of emerging preliminary data from TATTON Part D (300 mg od savolitinib dose) indicated that a flat dose of 300 mg in patients who progressed on 1st/2nd generation EGFR-TKI maintains the ORR of the combination but may improve the overall safety profile. As such the risk-benefit of a 300 mg flat dose regimen, in combination with further enhanced hypersensitivity management guidelines introduced to this study in clinical study protocol (CSP) version 2.0, was considered preferable to the previous weight-based dosing regimen. Following this review, all new patients entering the SAVANNAH study after CSP version 3.0 were to be treated with a dose of 300 mg od savolitinib. Patients who commenced on the study with a 600 od mg dose of savolitinib could either continue with treatment at this dose or could choose to change to 300 mg od (no re-escalation was permitted after changing dose to 300 mg even if disease progression occurred).

Subsequently, preliminary results from the first interim analysis (IA1) of the SAVANNAH study showed that the response rate with the 600 mg od dose (ORR CCI 95% CI: CCI CCI compared to the 300 mg od dose (ORR CCI 95% CI: CCI TATTON Part CCI

CCI [redacted]

Preclinical pharmacokinetic-pharmacodynamic (PK-PD) modelling suggests that greater target engagement with near complete inhibition of the MET for the duration of the dosing interval may optimise efficacy of savolitinib. If the near complete inhibition is maintained for a higher proportion of patients, it is hypothesised that it could increase the response in this combination.

Based on the IA1 and preclinical PK-PD analyses, it was considered that evaluation of savolitinib 300 mg bid CCI [redacted]) and further evaluation of 600 mg od doses (to further assess benefit-risk profile at this dose) in combination with osimertinib (80 mg od) was warranted under CSP version 5.0. Evaluation of these doses may help to better understand the impact of dose/dosing regimen and exposure on efficacy and safety of savolitinib in this combination treatment. Administering savolitinib at 300 mg bid and 600 mg od is CCI [redacted] Whilst savolitinib 300 mg bid has not been previously tested in combination with osimertinib, savolitinib bid has been tested as monotherapy in approximately 80 patients, with 6 patients receiving 600 mg bid, and 62 patients receiving 500 mg bid, with no observed dose limiting toxicities.

The preliminary results from IA1 also indicated that the safety profile of the 600 mg od dose (n=CCI CCI had the opportunity of at least 6 weeks of treatment) was consistent with that previously observed across the program at this dose, which has been shown to be tolerable and manageable, after enhanced hypersensitivity management guideline has been implemented. Adverse events considered possibly related to study treatment led to discontinuation of savolitinib in CCI %) of CCI patients with at least 6 weeks of treatment, including CCI anaphylactic shock (CCI %) and CCI hypersensitivity CCI %). Serious adverse events occurred in CCI %) of CCI patients. Grade 3 or above AEs occurred in CCI %) of CCI patients, with CCI (CCI %) deemed to be possibly related to the study treatment. CCI [redacted] %) died due to reasons not related to study treatment. The safety profile of the 300 mg od dose in IA1 was CCI [redacted] compared to that observed previously at the same dose level in the TATTON study. Adverse events considered possibly related to study treatment led to discontinuation of savolitinib in CCI %) of CCI patients with at least 6 weeks of treatment, including CCI anaphylactic reaction CCI %) and CCI hypersensitivity (CCI %).

A second interim analysis (IA2) showed that the response rate at 300 mg od was CCI% (95% CI: CCI in post 1L patients and was CCI% (95% CI: CCI) in post 2/3L patients. An observed trend towards CCI CCI although based on small numbers, is consistent with a-priori study assumption. In addition, the IA2 results suggested an overall encouraging efficacy signal in CCI CCI patients although the number of patients was small. For example, in post 1L patients, the response rate was CCI% (95% CI: CCI CCI) for MET FISH+ tumours and CCI% (95% CI: CCI) for MET IHC+ tumours. As data in post first line (1L) and MET FISH+ patients were very limited for the 600 mg total daily dose, enrolment to the 300 mg bid and 600 mg od dose regimens was restricted to post 1L and MET FISH+ patients only under CSP version 6.0, to assist further evaluation of the efficacy signal in the 2 dosing regimens. Collection of tissue for testing by both central MET FISH and IHC continued to be mandatory to enable exploratory analyses.

Ad hoc exploratory analysis during IA2 was performed to better understand the relationship between levels of MET amplification and/or overexpression and efficacy. Analysis showed a trend toward an improved response rate with increasing level of MET overexpression and amplification. Emerging data from the most recent data review of SAVANNAH study (as of 27 August 2021) showed that among patients who had at least 2 post-baseline tumour scans (N=193) who received savolitinib 300 mg od in combination with osimertinib 80 mg od with MET amplified tumour status by FISH (≥5 MET gene copies or MET:CEP7 signal ratio ≥2 [FISH5+]) and/or MET overexpression by IHC (≥50% of tumour cells staining at strong 3+ intensity [IHC50+]) (regardless of line of therapies), the ORR wasCCI% (95% CI: CCI , CCI In patients (N=86) who received savolitinib 300 mg od in combination with osimertinib 80 mg od with MET amplified tumour status by FISH (≥5 MET gene copies or MET:CEP7 signal ratio ≥2 [FISH5+]) and/or MET overexpression by IHC (≥50% of tumour cells staining at strong 3+ intensity [IHC50+]) and whose tumour progressed following post 1L osimertinib treatment, the ORR was CCI% (95% CI: CCI), the median duration of response (DoR) was CCI (95% CI: CCI), and the median PFS was CCI (95% CI: CCI There were CCI patients who were considered responders among CCI evaluable patients at the savolitinib 300 mg bid combination regimen, and CCI patients considered responders among CCI evaluable patients at the savolitinib 600 mg od combination regimen.

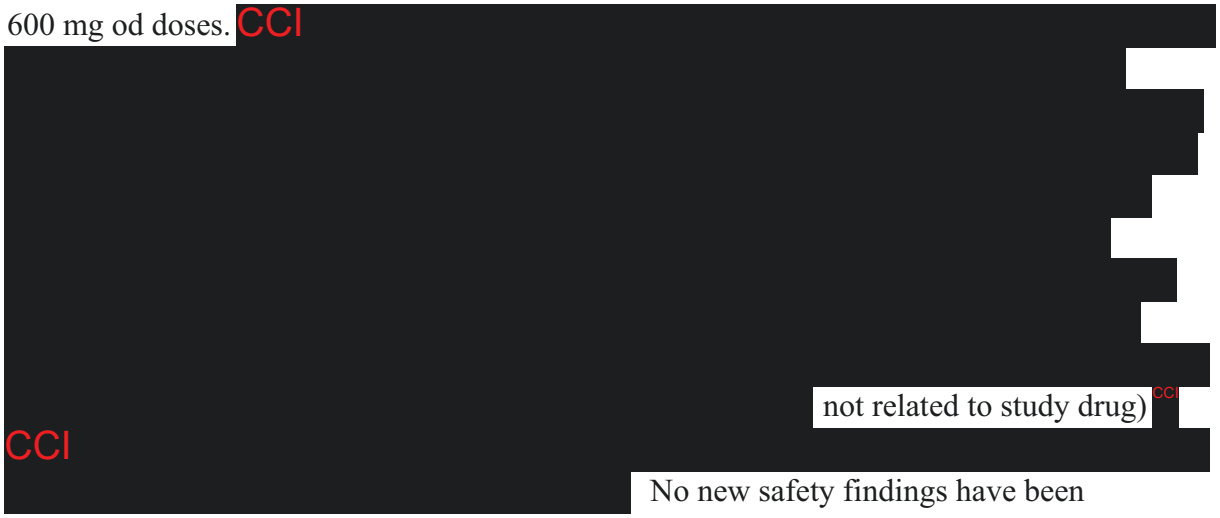
In patients (N=108) identified by higher MET biomarker cut offs (FISH gene copy number ≥10 copies [FISH10+] and/or IHC ≥90% of tumour cells staining at 3+ intensity [IHC90+]) who received savolitinib 300 mg od in combination with osimertinib 80 mg od (regardless of line of therapies), the ORR CCI (95% CI: CCI In patients (N=50) identified by higher MET biomarker cut offs (FISH gene copy number ≥10 copies [FISH10+] and/or IHC ≥90% of tumour cells staining at 3+ intensity [IHC90+]) who received savolitinib 300 mg od in combination with osimertinib 80 mg od and whose tumour progressed following

1L osimertinib treatment, the ORR was CCI (95%CI: CCI), the median DoR was CCI (95% CI: CCI), and the median PFS was CCI (95% CI: CCI). There were CCI patients who were considered responders among CCI evaluable patients at the savolitinib 300 mg bid combination regimen with IHC90+ and/or FISH10+ status. Responses at the savolitinib 600 mg od combination regimen with IHC90+ and/or FISH10+ status were not assessed.

This clinical observation is consistent with and supported by the evidence shown in other clinical studies in NSCLC and in nonclinical models, suggesting that MET amplification is sufficient to confer resistance to EGFR TKI therapy (Bean et al 2007, Engelman et al 2007, Turke et al 2010), and resistance can be associated with high level of MET protein expression (Bean et al 2007, Turke et al 2010, Wu et al 2018, Wu et al 2020, Scagliotti et al 2020, Wolf et al 2020, Hartmaier et al 2021). Since MET-mediated resistance is expected to provide EGFR-bypass growth signalling in a cell intrinsic manner, during the development of resistance, tumour cell growth that is dependent on MET signalling is expected to undergo clonal selection and dominate the cellular population in the fully resistant tumour. Thus, elevated cut-offs are likely to more accurately identify tumours with more homogeneous dependence on MET signalling.

Based on this biological rationale and ad hoc exploratory analysis results, higher MET cut-offs (ie, FISH10+ and/or IHC90+) are considered more appropriate to identify the target patient population that will potentially benefit from the novel combination treatment. Therefore, under CSP version 7.0, only MET amplified/overexpressed (FISH10+ and/or IHC 90+) patients will be enrolled.

The safety data from the most recent data review (as of 27 August 2021) for all patients who received at least one dose has shown that overall, the safety profile of savolitinib in combination with osimertinib is tolerable and manageable at 300 mg od, 300 mg bid and 600 mg od doses. CCI



No new safety findings have been identified, including at the 300 mg bid dose (n=37) with a median duration of exposure of

approximately 2.6 months. CCI [redacted]

Pre-clinical studies conducted by AstraZeneca suggested that MET inhibitors have single-agent activities in the treatment of tumours with MET amplification in vitro (see the savolitinib- Investigator's Brochure Version 8.0 for more information). A recent study (Eser et al 2021) reported that in a subset of MET-driven EGFR TKI-refractory lung cancers, low EGFR:MET expression ratio appears to predict MET dependence (ie-, EGFR independence) in patient-derived xenograft models, and a higher ratio was associated with single-agent EGFR TKI sensitivity or EGFR/MET co-dependency. This finding suggests that a subset of patients with EGFR-mutant, MET-driven lung cancers which developed dependence on MET activation alone could be treated with a single-agent MET-TKI (Eser et al 2021). Preliminary proteomics data from TATTON and SAVANNAH (AZ data on file) suggests that EGFRm, MET amplified tumours appear to be enriched for low EGFR:MET expression ratio. These emerging pre-clinical data suggest that further evaluation of the efficacy of savolitinib monotherapy and its contribution to savolitinib plus osimertinib combination in EGFRm+, MET amplification/overexpression (FISH10+ and/or IHC90+) NSCLC is warranted in CSP version 7.0.

In addition, emerging data from the most recent data review of SAVANNAH study (as of 27 August 2021) CCI [redacted]. The overall safety profile for 300 mg bid savolitinib in combination with osimertinib is overall consistent with the known safety profile of the combination at 300 mg od and 600 mg od and no new safety signal was identified at 300 mg bid dose. Therefore, from the point of view of efficacy, safety, PK and PK-PD, savolitinib 300 mg bid dose in combination with 80 mg od osimertinib is considered appropriate as the dosing regimen for further evaluation in CSP version 7.0 (see details in Section 4.3).

2.1 Study rationale

Resistance to EGFR-TKIs is an unmet clinical need. One of the most frequent known mechanisms for resistance is amplification and/or overexpression of the MET receptor tyrosine kinase, which activates downstream intracellular signalling independent of EGFR. The combination of osimertinib with savolitinib in this study (the SAVANNAH study) will explore if the combination will overcome MET-mediated osimertinib resistance.

The SAVANNAH study will investigate the overall efficacy of osimertinib in combination with savolitinib in patients with EGFRm+ and MET-amplified/overexpressed, locally advanced or metastatic NSCLC who have progressed following treatment with osimertinib.

Based on emerging pre-clinical and clinical data (see Section 2), the SAVANNAH Study (CSP version 7.0) will be expanded to further investigate the efficacy of savolitinib 300 mg bid + osimertinib in MET-amplified/overexpressed (FISH10+ and/or IHC90+) patients who have progressed following 1L osimertinib treatment. Per CSP version 7.0, the study will also describe the difference in the efficacy of osimertinib in combination with savolitinib 300 mg bid and savolitinib monotherapy in the treatment of EGFRm+ NSCLC patients with MET FISH10+ and/or IHC90+ status whose tumour has progressed following 1L osimertinib therapy under CSP version 7.0.

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 osimertinib and savolitinib is provided in their respective Investigator's Brochures.

2.3 Benefit/risk assessment

Detailed information about the known and expected benefits and risks and reasonably expected AEs of osimertinib and savolitinib may be found in their respective Investigator's Brochures.

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 progressive disease (PD) per RECIST 1.1, treatment allocation will be unblinded and those patients randomised to the savolitinib plus placebo arm will have the opportunity to cross over to the savolitinib plus osimertinib regimen. 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 summary of the safety profile of osimertinib based on the program of AstraZeneca-sponsored Phase I to III studies of patients with EGFR TKI-naïve first-line EGFRm disease and in patients with ≥ second line T790M-mutated NSCLC is provided in Section 5 of the osimertinib Investigator's brochure. Overall, osimertinib has been generally well-tolerated in these trials. Based on safety data from the osimertinib clinical development program conducted to date, the risks associated with osimertinib, as applicable to the current study, are presented in Table 3.

Table 3 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
ILD	ILD is an important identified risk and AESI for osimertinib. Adverse events of ILD have been reported in 3.7% (55/1479) of patients in the osimertinib pivotal clinical studies dataset, with 0.8% (12/1479) of these being severe (CTCAE Grade 3 or 4) and 0.3% (5/1479) resulting in a fatal outcome	Patients with a past medical history or concurrent clinically active ILD are excluded from the current study (see Section 5.2). Furthermore, dose modification guidelines for ILD/pneumonitis (which include dose interruption, rechallenge, and permanent discontinuation criteria) are in place to protect study participants (see Appendix I for further details).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Cardiac failure	Cardiac failure is an important potential risk and AESI for osimertinib. A numerical imbalance in the number of patients with an AE from the Cardiac Failure SMQ or Cardiomyopathy SMQ and in LVEF decreases between the 2 treatment arms was noted in the Phase III D5160C00003 study (AURA3; NCT02151981). A similar numerical imbalance was also noted between treatment arms (osimertinib versus SoC therapy [erlotinib or gefitinib]) in Phase III Study D5160C00007 (FLAURA; NCT02296125). However, results from the more recent placebo-controlled ADAURA study demonstrated there is no clinical difference from placebo in decrease LVEF. Based on the complete body of evidence available, the overall interpretation does not support a causal relationship between osimertinib and changes in cardiac contractility manifesting as either LVEF decreases or heart failure.	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 study intervention, should be considered. Consequently, routine cardiac assessment (by ECHO / MUGA) is mandated at baseline and should be considered throughout the study intervention period if clinically indicated. Furthermore, dose modification management guidelines for changes in cardiac contractility (which include dose interruption, rechallenge, and permanent discontinuation criteria) are in place to protect study participants (see Appendix I for further details).

AESI Adverse event of special interest; CTCAE Common Terminology Criteria for Adverse Events; ECHO echocardiogram; ILD Interstitial lung disease; LVEF Left ventricular ejection fraction; MUGA multigated acquisition; SMQ Standardised MedDRA query; SOC standard of care.

The important identified risks for savolitinib are hepatotoxicity and hypersensitivity reactions (including anaphylaxis and Stevens-Johnson syndrome [SJS]). Specific monitoring and guidelines for toxicity management are in place to mitigate/manage these risks (see Appendix I).

Hepatotoxicity has been identified as a risk for patients receiving savolitinib and requires specific monitoring. Frequent monitoring of liver function tests will take place as outlined in the study plan. The hepatotoxicity management algorithm included in the protocol clearly defines and limits the patients who can be re-challenged to those with lower grade abnormalities with rapid resolution (see Appendix I). As stated in the eligibility criteria and risk mitigation sections, patients with abnormal baseline liver function tests will be excluded from the study and patients will be required to discontinue treatment with statins or reduce it to the lowest dose, prior to study entry.

CCI [redacted]. Pyrexia was followed in some cases by hepatotoxicity or an association of symptoms suggestive of hypersensitivity such as but not limited to allergic rash, cytopenias, myalgia/arthralgia and one case of SJS. Patients who experience hypersensitivity or pyrexia with or without an association of the above symptoms after initiation of savolitinib treatment must follow the toxicity management guidelines.

The QTc interval prolongation potential of savolitinib 600 mg was assessed in a thorough QT study in healthy volunteers. Analysis of the data concluded that it was a positive study, as the upper 2-sided 90% CI for the maximum mean ΔQTcF was 13.4 and 14 msec observed at 4 hours and 5 hours, respectively. Regular ECG assessments will be done throughout the study according to the study plan. Patients who present ECG abnormalities with or without symptoms during treatment with savolitinib must follow the QTc prolongation toxicity management guidelines (see Appendix I).

Enrolment criteria, safety monitoring and AE management guidelines including specific guidance for hepatotoxicity, hypersensitivity, pneumonitis and QTc prolongation, have been included in this protocol to ensure patient safety, prevent and manage severe toxicity, and to enable further characterisation of the savolitinib safety profile in combination with osimertinib.

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-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.

The investigation of savolitinib in combination with osimertinib and savolitinib monotherapy in patients with advanced NSCLC is acceptable based upon the emerging pre-clinical and clinical efficacy and safety profile, the risk minimisation and enhanced AE management guidelines, and high unmet need in EGFRm, NSCLC patients whose tumour is resistant to EGFR TKIs due to MET amplification/overexpression.

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 and savolitinib monotherapy in patients with advanced NSCLC with high MET amplification/overexpression based upon: the emerging non-clinical and clinical safety profile, the risk minimisation and enhanced AE management guidelines, 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 emerging clinical efficacy data to date.

3 OBJECTIVES AND ENDPOINTS

Table 4 Study objectives

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

osimertinib in patients with EGFRm+, MET-amplified/overexpressed (FISH10+ and/or IHC90+)[a], locally advanced or metastatic NSCLC who have progressed following treatment with 1L osimertinib.	• OS
To determine the efficacy of savolitinib (300 mg od, 300 mg bid, and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET-amplified/overexpressed (FISH10+ and/or IHC90+)[a], locally advanced or metastatic NSCLC who have progressed following treatment of ≥ 2L osimertinib.	• ORR, DoR, and PFS, by investigator assessment in accordance with RECIST 1.1. • OS
To determine the efficacy of savolitinib (300 mg od, 300 mg bid, and 600 mg od, respectively) in combination with osimertinib in patients with EGFRm+, MET-amplified/overexpressed (FISH5+ and/or IHC50+)[b], locally advanced or metastatic NSCLC who have progressed following osimertinib.	• ORR (except 300 mg od), DoR, and PFS by investigator assessment in accordance with RECIST 1.1. • OS
To determine the efficacy of (1) 300 mg od, 300 mg bid and 600 mg od of savolitinib in combination with osimertinib in patients with EGFRm+ MET amplified/ overexpressed (FISH 10+ and/or IHC90+)[a,b]; (2) 300 mg od, 300 mg bid and 600 mg od of savolitinib in combination with osimertinib in patients with EGFRm+ MET amplified/overexpressed (FISH5+ and/or IHC50+)[b] (3) savolitinib 300 mg bid in combination with osimertinib and savolitinib 300 mg bid in combination with placebo, respectively, in patients with EGFRm+ MET amplified/ overexpressed (FISH10+ and/or IHC90+)[a] following treatment with 1L osimertinib.	• ORR, DoR, and PFS assessed by BICR in accordance with RECIST 1.1
To assess the impact of savolitinib and osimertinib on disease-related symptoms and HRQoL in this patient population.	• Mean change from baseline in EORTC QLQ-C30 and QLQ-LC13.
To evaluate the pharmacokinetics of osimertinib and savolitinib in this patient population.	• Plasma concentrations of osimertinib, savolitinib and their metabolites.
To determine the prevalence of ctDNA clearance after osimertinib and savolitinib treatment in this patient population.	• Total clearance in EGFR mutations at 6-weeks after therapy initiation (percentage and absolute change from baseline in EGFR mutation allele frequencies).

Safety Objectives:	**Endpoints:**
To evaluate the safety and tolerability of savolitinib in combination with osimertinib and savolitinib in combination with placebo.	• AEs, SAEs and discontinuation rate due to AEs. • Clinical chemistry/haematology including LFTs. • ECHOs, ECGs and vital signs including blood pressure and heart rate.
Exploratory Objectives:	
To assess the efficacy of savolitinib plus osimertinib and savolitinib plus placebo, respectively, on CNS metastases in patients with CNS metastases at baseline	• CNS PFS by BICR assessments in accordance with RECIST 1.1
To assess the efficacy of savolitinib plus osimertinib and savolitinib plus placebo, respectively, on the prevention of CNS metastases in patients without CNS metastases at baseline.	• The presence/absence of CNS lesions at progression by BICR assessments in accordance with RECIST 1.1
To assess the impact of savolitinib in combination with osimertinib on patient reported treatment-related symptoms.	• PRO CTCAE symptoms.
To assess patients' overall impression of severity of cancer symptoms.	• Patient's Global Impression of Severity (PGIS).
To explore the impact of treatment and disease on health state utility	• EQ-5D-5L
To explore the factors of resistance and sensitivity to treatment.	• Protein, RNA and DNA research on blood and tumour prior to treatment, during the course of treatment, at disease progression and at treatment discontinuation.
To assess the predictive value of changes in circulating biomarkers on clinical efficacy endpoints.	• Longitudinal changes in circulating DNA and/or RNA compared with PFS, OS and ORR.
To collect and store DNA (according to each country's local and ethical procedures) for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to study treatments and or susceptibility to disease (optional).	• Pharmacogenetic analyses on blood samples.
To collect and store tissue, plasma, and serum samples for diagnostic development and exploratory analyses.	• Disease-relevant or response markers in tumour tissue and circulating tumour DNA/RNA/protein including but not limited to EGFR mutations and MET amplifications.
To collect and store germline DNA for exploration of the role of HLA alleles in developmental toxicity.	• HLA alleles associated with susceptibility to drug related AEs (such as but not limited to hypersensitivity).

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

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

Osimertinib 80 mg od is administered in the combination dosing regimens.

1L First line; 2L Second line; AE Adverse event; bid twice daily; BICR Blinded independent central review; CNS Central nervous system; CTCAE Common Terminology Criteria for Adverse Events; DNA Deoxyribonucleic acid; DoR Duration of response; ECG Electrocardiogram; ECHO Echocardiogram; EGFR Epidermal growth factor receptor; EGFRm+ Epidermal growth factor receptor mutation positive; EQ-5D-5L EuroQol 5 dimensions, 5 levels; FACT-L Functional Assessment of Cancer Therapy - Lung Cancer; FISH Fluorescence in situ hybridisation; HLA Human leukocyte antigen; HRQoL Health-related quality of life; IHC Immunohistochemistry; LFT liver function test; MET Mesenchymal epithelial transition factor; MET/CEP7 Mean MET per cell and chromosome 7 centromere ratio; NGS Next generation sequencing; NSCLC Non-Small Cell Lung Cancer; od once daily; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; PRO Patient reported outcomes; QLQ-LC13 Quality of Life Questionnaire-Lung Cancer 13; RNA Ribonucleic acid; SAE Serious adverse events.

4 STUDY DESIGN

4.1 Overall design

4.1.1 Treatment allocation /randomisation study design

This is a Phase II study investigating the efficacy of osimertinib administered orally with savolitinib in patients with EGFRm+ and MET-amplified/overexpressed, locally advanced or metastatic NSCLC who have progressed following treatment with osimertinib.

It was originally planned to treat approximately CCI patients in this study (osimertinib 80 mg od plus savolitinib 300 mg od) to achieve the required CCI centrally confirmed MET-amplified/overexpressed by FISH and/or IHC patients (FISH5+ and/or IHC50+) at this dose. Prior to CSP version 3.0, patients weighing >55 kg were dosed with 600 mg savolitinib.

Following review of IA1 data, to better characterise benefit-risk at different doses of savolitinib in combination with osimertinib 80 mg od, a dosing regimen of savolitinib 300 mg bid plus osimertinib 80 mg od was introduced, and additional patients were enrolled to receive savolitinib 600 mg od plus osimertinib 80 mg od (under CSP version 5.0). Enrolment of patients to the 300 mg od dosing regimen was stopped. Patients who were receiving the combination with savolitinib 600 mg od or 300 mg od continued to be treated at that dose and followed as per protocol.

Following review of IA2 data, under CSP version 6.0, enrolment of patients to the 300 mg bid and 600 mg od dosing regimens was restricted to post 1L osimertinib. Enrolment was also restricted to patients with confirmation of MET-amplified tumour by central FISH (FISH5+).

Emerging data from SAVANNAH has indicated that FISH10+ and/or IHC90+ was considered more appropriate to identify the target patient population that will potentially benefit from the novel combination (see Section 2). Therefore, under CSP version 7.0, approximately CCI patients with MET amplification/overexpression (FISH10+ and/or IHC90+) who have progressed following treatment with 1L osimertinib will be randomised in a CCI ratio to receive savolitinib 300 mg bid + osimertinib 80 mg od (approximately CCI patients) or savolitinib 300 mg bid + placebo (approximately CCI patients) in a double-blind manner. Randomisation will be stratified according to the presence of brain metastases at baseline (yes versus no). At investigator assessed PD per RECIST 1.1, treatment allocation will be unblinded and those patients randomised to the savolitinib 300 mg bid + placebo arm will have the opportunity to cross over to the savolitinib 300 mg bid + osimertinib 80 mg od arm (see Sections 4.1.2 and 6.3).

Patients must not have received prior or current treatment with savolitinib or another MET inhibitor. Under CSP version 7.0, patients must not have received prior chemotherapy or immunotherapy in the metastatic setting.

Patient enrolment into SAVANNAH to date is summarised in Table 5.

Table 5 Patient Enrolment onto SAVANNAH Dosing Regimens

Dosing Regimen	Osimertinib 80 mg od + savolitinib 300 mg od		Osimertinib 80 mg + savolitinib 300 mg bid		Osimertinib 80 mg + savolitinib 600 mg od		Placebo to osimertinib + savolitinib 300 mg bid	Total sample size	
	Post 1L	Post 2/3L	Post 1L	Post 2/3L	Post 1L	Post 2/3L	Post 1L	Post 1L	Post 2/3L
Initial no. of planned patients[a]	CCI								
No. of patients enrolled to date under CSP v1.0 to v6.0									
Revised no. of planned patients under CSP v1.0 to v7.0									

[a] The original sample size for savolitinib 300 mg od was CCI As per CSP version 4.0, CCI patients were planned to receive savolitinib 300 mg od and approximately CCI patients to receive savolitinib 600 mg od.

[b] A total of CCI patients CC post 1L and CCI post 2/3L) received savolitinib 600 mg od prior to CSP version 5.0, under the previous weight-based dosing schedule.

[c] Planned to include approximately CCI post 1L MET FISH+ patients enrolled under CSP versions 5.0 and 6.0. One post 1L patient additionally received savolitinib 600 mg od dosing (under the previous weight-based dosing schedule).

[d] CCI post 2/3L patients who received 600 mg od dosing (under the previous weight-based dosing schedule).

[e] Planned to include approximately CCI post 1L patients with MET amplification/overexpression (FISH10+ and/or IHC90+) under CSP version 7.0 to receive savolitinib 300 mg bid + osimertinib 80 mg.

1L First line; 2/3L Second/third line; CSP Clinical study protocol; NA Not applicable.

Under CSP version 7.0, patients must have central confirmation of MET amplification and/or overexpression (FISH10+ and/or IHC90+) by FISH and IHC (central) testing. Pre-existing next generation sequencing (NGS) testing results are not accepted to enter Screening. Provision of a formalin fixed and paraffin embedded (FFPE) tumour sample is mandatory. Approximately CCI freshly cut (within CCI days) unstained sections (CCI micron) from FFPE tissue blocks or FFPE blocks containing equivalent material will be required per patient (refer to Central Laboratory Manual for detailed tissue requirements). Samples CCI years old will not be accepted.

Patients determined to be MET-amplified and/or overexpressed by FISH and IHC in Pre-screening will undergo screening during the 28 days prior to first administration of study medication to confirm eligibility (Sections 5.1 and 5.2).

Patients will continue to receive study medication in 28-day cycles until objective disease progression, unacceptable toxicity occurs, consent is withdrawn or another discontinuation criterion is met (Section 7). Patients may continue to receive treatment with osimertinib + savolitinib or osimertinib monotherapy (if savolitinib was stopped earlier) beyond RECIST 1.1-defined progression as long as they continue to receive clinical benefit, in the opinion of the investigator, and do not meet any of the discontinuation criteria (this may be beyond disease progression in the absence of clinical symptoms or signs indicating clinically significant disease progression; no decline in performance status; absence of rapid disease progression or threat to vital organs or critical anatomical sites [eg, CNS 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 treatment) (Section 7.1). Patients can continue on savolitinib monotherapy (if osimertinib was stopped earlier or if randomised to the savolitinib + placebo arm) until objective disease progression. Savolitinib monotherapy post progression is not permitted.

The study will have 5 planned analyses. Interim analysis 1 was planned and performed after approximately CCI patients treated with osimertinib and 300 mg od savolitinib had the opportunity to be treated for 2 post-baseline scans (12 weeks) or the CCI patient treated with

osimertinib (80 mg od) and savolitinib (300 mg od) had the opportunity to be treated for 6 weeks, whichever was later.

Interim analysis 2 was planned and performed to assess ORR after approximately [redacted] post 1L patients treated with osimertinib (80 mg od) and savolitinib (300 mg od) had the opportunity to be treated for 2 post-baseline scans (12 weeks).

The third planned analysis is a futility analysis for the savolitinib + placebo arm that is planned after [redacted] patients have been randomised under CSP version 7.0 and have had an opportunity to have 2 post-baseline scans.

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

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

For patients who continue to receive treatment beyond the time of the final data cut-off 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 8.4.1 (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 8.3.3 (Follow-up of AEs and SAEs), any SAE or non-serious AE that is ongoing at the time of the final data cut-off, must be followed up by the investigator for as long as medically indicated.

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

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

4.1.2 Crossover

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 crossover to savolitinib plus osimertinib during the initial informed consent process and at the

time of progression on randomised treatment. A separate informed consent form (ICF) for crossover patients must be signed prior to starting crossover treatment.

Patients who cross over must not receive any other anti-cancer therapies between the initial 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 once daily in 28-day cycles until objective PD by RECIST 1.1 is assessed by investigator, unacceptable toxicity occurs, consent is withdrawn or another discontinuation criterion is met. As in the treatment allocation/ randomisation 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.

If, after the planned futility analysis the savolitinib + placebo arm is declared futile, all patients remaining on savolitinib + placebo will be contacted and asked to return for a discussion of the futility findings and their options for remaining in the savolitinib + placebo arm (as long as, in the opinion of the investigator, they are still receiving clinical benefit and have not reported PD) or crossing over to the savolitinib + osimertinib arm. Patients who cross over must not receive any other intervening anti-cancer therapies before the addition of osimertinib.

All patients who cross over to receive savolitinib + osimertinib (whether based on objective PD by RECIST 1.1 or a declaration of futility of the savolitinib + placebo arm) will follow the scheduled procedures described in Table 2.

4.2 Scientific rationale for study design

Refer to Sections 2 and 2.1.

4.2.1 Rationale for study design

The expansion cohort Part B of the TATTON study has demonstrated anti-tumour activity of osimertinib in combination with savolitinib (ORR 28%) in MET-amplified 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 (Ahn et al 2017).

This Phase II study has been designed to further assess the efficacy of osimertinib in combination with savolitinib by assessment of ORR in patients with EGFRm+ and

MET-amplified/overexpressed, locally advanced or metastatic NSCLC who have progressed following treatment with osimertinib. Overall, 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. For savolitinib 300 mg bid or 600 mg od in combination with osimertinib 80 mg od under CSP version 5.0, patients must have documented radiologic disease progression following treatment with 1L or 2L osimertinib as the most recent anti-cancer therapy (ie, up to 2 lines of prior therapy); chemotherapy and/or immunotherapy in metastatic setting will not be allowed. This is to reduce heterogeneity of the patient population and more closely match the proposed target population in the planned phase 3 study. Furthermore, patients enrolled to savolitinib 300 mg bid or 600 mg od in combination with osimertinib 80 mg od under CSP version 6.0, must have documented radiologic disease progression on 1L osimertinib and must have confirmed MET amplification by central FISH (FISH5+).

Emerging pre-clinical data (see Section 2) has suggested that savolitinib monotherapy may have anti-tumour activities in EGFRm NSCLC patients with higher MET amplification/overexpression. In order to describe the difference in efficacy of savolitinib in combination with osimertinib and savolitinib monotherapy in the treatment of patients with MET amplification/overexpression (FISH10+ and/or IHC90+) in EGFRm NSCLC with resistance to osimertinib, a savolitinib 300 mg bid + placebo arm has been included in the study design. Patients will be randomised in a double-blind manner to receive either savolitinib 300 mg bid + osimertinib or savolitinib 300 mg bid + placebo in order to minimise the assessment bias.

The objective response to platinum-pemetrexed chemotherapy has been consistent in NSCLC population (approximately ORR[redacted]%) and will be used as external reference (and thus is not included in the SAVANNAH study) when determining the efficacy of savolitinib + osimertinib in EGFRm MET amplified/overexpressed NSCLC.

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. This study also includes the option for patients randomised to the savolitinib plus placebo arm to cross over to receive savolitinib in combination with osimertinib upon investigator-assessed objective PD per RECIST 1.1.

Brain metastases are detected in 20% to 30% of patients with advanced NSCLC upon initial diagnosis and are associated with a poor prognosis (Porta et al 2011). The central nervous system is a common site of first progression for patients receiving treatment with TKIs, despite concomitant systemic disease control. The randomisation under CSP version 7.0 will

be stratified by brain metastasis at baseline to account for potential impact due to imbalance of patients with brain metastasis across arms.

4.2.2 Rationale for endpoints

ORR, PFS, duration of response (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 Phase 1 TATTON study data indicated encouraging anti-tumour activity in patients with centrally-confirmed MET-amplified status. Responses were also observed in a small number of MET overexpressed tumours by IHC without centrally-confirmed MET-amplification by FISH. In SAVANNAH, the primary endpoint to assess the ORR in patients treated at the 300 mg od savolitinib dose level, in combination with 80 mg od osimertinib, and whose tumours are FISH5+ and/or IHC50+ and had disease progression following prior osimertinib therapy was based on the TATTON study data.

Under CSP version 7.0, an additional primary endpoint has been added to evaluate the efficacy at an alternative savolitinib dose and using a higher biomarker cut-off for MET amplification and/or overexpression. Emerging clinical data (including from the TATTON study and SAVANNAH study) and published literature support a biological rationale for the apparent association of increasing MET overexpression or amplification levels with improvement in responses to MET inhibitors in EGFRm+ NSCLC patients with MET amplification and/or overexpression. Therefore, an additional primary endpoint will determine the ORR in patients treated at the 300 mg bid savolitinib dose level in combination with 80 mg od osimertinib, and whose tumours are FISH10+ and/or IHC90+ and have progressed following treatment with 1L osimertinib.

Secondary endpoints include, but are not limited to, assessment of efficacy parameters by varying savolitinib dose levels in combination with 80 mg od osimertinib and varying MET FISH and IHC cut-offs in order to allow a thorough assessment of dose-response relationships. A description of the difference in response rate between the 300 mg bid savolitinib + 80 mg od osimertinib group and the 300 mg bid savolitinib + placebo group as well as an exploration of the prevalence of plasma ctDNA clearance after 6 weeks of study therapy are also secondary objectives of this study.

The secondary symptoms and overall HRQoL endpoints, assessed using the European Organisation for Research and Treatment of Cancer (EORTC) 30-item core quality-of-life questionnaire (QLQ-C30), version 3 (QLQ-C30 v3) and the complementary 13-item lung cancer symptoms questionnaire (QLQ-LC13), will show the overall influence of the benefits and toxicity of the treatment from the patient’s perspective and will aid in understanding the

benefit/risk evaluation. These PRO questionnaires are well-established instruments that have been previously included in cancer clinical studies.

Standard safety parameters (discontinuation rate due to AEs/SAEs, vital signs, clinical chemistry/haematology parameters and electrocardiograms [ECGs]) will be used to assess the safety and tolerability of osimertinib in combination with savolitinib. 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 administered in combination in this population.

Exploratory endpoints, including, but not limited to, circulating tumour deoxyribonucleic acid (ctDNA), circulating proteins and germline deoxyribonucleic acid (DNA), will be used to understand mechanisms of response (where response is defined broadly to include biomarker change, tolerability or safety) and resistance to treatment.

4.3 Justification for dose

The evaluation of the recommended daily dose of osimertinib (80 mg od), which is the approved dose for EGFRm+ NSCLC, was based on non-clinical data in addition to PK, efficacy and safety data from across the clinical programme and is the approved dose for first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations (see Section 5.2.2 of the Investigator's Brochure for more information).

Final review of data from TATTON Part D (savolitinib 300 mg od dose) indicated that in the no prior third generation EGFR-TKI cohort (TATTON Part D), there was an improvement in overall safety profile, such as Common Terminology Criteria for Adverse Event (CTCAE) Grade 3 toxicity, with no apparent reduction in ORR relative to the 600 mg od dose. To date there were limited data available in patients who progressed on the 3rd generation EGFR-TKIs (such as osimertinib) when used as the 1L treatment. As such the risk-benefit of a savolitinib 300 mg flat dose regimen, in combination with further enhanced hypersensitivity management guidelines introduced to this study in CSP version 2.0, was considered preferable to the previous weight-based dosing regimen. Following this review (per CSP version 3.0), all new patients entering the SAVANNAH study were to be treated with a 300 mg od dose of savolitinib. Patients who commenced on the study with a 600 mg od dose of savolitinib could either continue with treatment at this dose or could choose to change dose to 300 mg od (no re-escalation was permitted after changing dose to 300 mg even if disease progression occurred).

As summarised in Section 2, based on the IA1 and preclinical PK-PD data, it was considered that evaluation of savolitinib 300 mg bid and 600 mg od doses in combination with osimertinib (80 mg od) was warranted, to better understand the impact of dose/dosing regimen and exposure on efficacy and safety of savolitinib in this combination treatment.

To date, in the SAVANNAH study, approximately CCI patients with EGFR mutation-positive, MET-amplified/overexpressed NSCLC have been treated with either the 600 mg od, 300 mg od, or 300 mg bid savolitinib dose in combination with 80 mg osimertinib in the TATTON (n=CCI or SAVANNAH (n=CCI study. A review of data from the SAVANNAH study (300 mg od, 600 mg od and 300 mg bid) has indicated that there is an improvement in the safety profile at both the 300 mg od and 300 mg bid dose, such as CTCAE Grade 3 toxicity and SAE profile, relative to the 600 mg od dose. Initial review of the safety and pharmacology data from the SAVANNAH study indicates that the 300 mg bid dose provides a safety profile similar to that observed with the 300 mg od dose from a small number of patients in the bid dose, n=CCI with a short follow-up).

The preliminary PK exposure from CCI dose compared to CCI or CCI shows CCI doses. Based on population PK analysis, the PK of savolitinib is CCI CCI by CCI . Although there are limited data from a small number of patients with follow-up for CCI . The safety for CCI CCI with median exposure duration of CCI shows no new safety events and is tolerable. Exposure-response for liver function changes shows that there is CCI between Japanese and non-Japanese in ALT, AST, alkaline phosphatase, and bilirubin elevation with increasing exposure. There is a CCI is an important covariate in regression model of maximum liver function test (LFT) elevation versus exposure, suggesting that patients with CCI CCI . At the 300 mg bid dose, there have been no additional safety concerns compared to 300 mg od dose and there is potential for greater benefit.

In summary, the currently available analysis shows that: (1) based on preclinical data, consistent with other drugs in this class, sustained target inhibition appears to be necessary for efficacy; (2) sufficient target engagement is likely to be achieved with a savolitinib bid dose due to a CCI ; (3) CCI

CCI (4) the overall safety profile for 300 mg bid savolitinib in combination with osimertinib is consistent with the known safety profile of the combination; and (5) CCI Therefore, from the point of view of efficacy, safety, PK, and PK-PD, savolitinib 300 mg bid dose in combination with 80 mg od osimertinib is considered appropriate as the dosing regimen for further evaluation.

4.4 End of study definition

For the purpose of Clinical Trial Transparency the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol related activity.

Food and Drug Administration requirements define two completion dates:

Primary Completion Date – the date that the final patient is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical trials with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final patient is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last patient's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A patient is considered to have completed the study if they have completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities (SoA; Table 1 and Table 2).

The study may be stopped if, in the judgement of AstraZeneca, study participants are placed at undue risk because of clinically significant findings.

See Section 6.7 for details on patient management following the final DCO as well as following study completion.

See Appendix A 6 for guidelines for the dissemination of study results.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol 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.

In this protocol, "Enrolled" patients are defined as those who sign informed consent for the main study and are confirmed as eligible for the study.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3.

5.1 Inclusion criteria

Patients are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

Informed consent

1 Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

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

The ICF process is described in Appendix A 3.

Age

3 Patients must be ≥18 years of age at the time of signing the ICF (≥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 which 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 disease progression on 1L osimertinib.

6 MET amplification and/or overexpression (FISH10+ and/or IHC90+) as determined by FISH (central) and IHC (central) testing on tumour sample collected following progression on 1L osimertinib treatment.

7 Available tumour sample for central MET FISH and IHC analysis or willingness to collect additional sample 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 sample to meet the minimum sample requirement defined in the current Central Laboratory Manual.

8 At least 1 lesion, not previously irradiated, not biopsied during the screening period, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) which is suitable for accurate repeated measurements. If only 1 measurable lesion exists, it is acceptable to be used as long as baseline tumour assessment scans are done at least 14 days after the screening tumour sample collection is performed.

9 Prior lines of therapy in locally advanced/metastatic setting: Only prior 1L osimertinib treatment in metastatic setting is permitted.

10 Adequate haematological function defined as:
   – Absolute neutrophil count ≥1500/μL
   – Haemoglobin ≥9 g/dL (no transfusion in the past 2 weeks)
   – Platelets ≥100,000/μL (no transfusion in the past 10 days)

11 Adequate liver function defined as:
   – Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x the upper limit of normal (ULN) with total bilirubin (TBL) ≤ ULN

     OR

   – TBL >ULN to ≤1.5x ULN with ALT and AST ≤ ULN

12 Adequate renal function defined as a serum 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:
   – International Normalisation Ratio (INR) <1.5 and activated partial thromboplastin time <1.5 x ULN unless patients are receiving therapeutic anti-coagulation which affects these parameters.

14 Patients with known tumour thrombus or deep vein thrombosis are eligible if clinically stable on low molecular weight heparin (LMWH) for ≥2 weeks. The use of direct oral anticoagulants such as apixaban/rivaroxaban will be accepted as treatment for

cancer-related thromboembolism treatment. The use of warfarin for oral anticoagulation is not recommended.

15 Eastern Cooperative Oncology Group (ECOG)/World Health Organization (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 must be using highly effective contraceptive measures (see Section 5.3.2), should not be breast feeding, 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 50 years or more 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.
- 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 Women of Childbearing Potential 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 drug. Patients should refrain from donating sperm from the start of dosing until 6 months after discontinuing study treatment.

5.2 Exclusion criteria

Patients must not enter the study if any of the following exclusion criteria are fulfilled:

Medical conditions

1 Unresolved toxicities from any prior therapy greater than CTCAE Grade 1 at the time of starting study treatment with the exception of alopecia and Grade 2, prior platinum-therapy related neuropathy.

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 (New York Heart Association [NYHA] ≥Grade 2)
- Acute myocardial infarction
- Stroke or transient ischemic attack
- Uncontrolled hypertension (blood pressure [BP] ≥150/95 mmHg despite medical therapy).
- Mean resting correct QT interval (QTcF) >470 msec for women and >450 msec for men at Screening, obtained from 3 ECGs using the screening clinic ECG machine derived QTcF value.
- Any factors that may increase the risk of QTcF prolongation or risk of arrhythmic events such as heart failure, chronic hypokalaemia not correctable with supplements, congenital or familial long QT syndrome, family history of unexplained sudden death under 40 years of age in first-degree relatives or any concomitant medication known to prolong the QT interval and cause Torsade de Pointes
- Any clinically important abnormalities in rhythm, conduction or morphology of resting ECGs, eg, complete left bundle branch block, third degree heart block, second degree heart block, P-R interval >250 msec.
- Acute coronary syndrome

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 drug or has not recovered from side effects of such therapy.

5 Major surgical procedures ≤28 days of beginning study drug 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, active bleeding diatheses or uncontrolled hypertension, which in the investigator's opinion makes it undesirable for the patient to participate in the study or which would jeopardise compliance with the protocol.

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

- Negative for HBsAg and positive for hepatitis B core antibody [anti-HBc-IgG]. In addition, patients must be receiving anti-viral prophylaxis for 2 to 4 weeks prior to

study treatment and 6 to 12 months (to be determined by hepatologist) post treatment or

- Positive for HBsAg, but for >6 months have had normal transaminases and HBV DNA levels < 100 IU/mL (ie, are in an inactive carrier state). In addition, patients must be receiving anti-viral prophylaxis for 2 to 4 weeks prior to study treatment and 6 to 12 months (to be determined by hepatologist) post treatment. See Appendix I 2.
- Patients with a past or resolved HBV infection must have monthly monitoring of ALT and HBV DNA (see Appendix I 2).
- HBV DNA levels >2000 IU/mL but on prophylactic antiviral treatment for the past 3 months and will maintain the antiviral treatment during the study.
- Patients with positive HCV antibody are eligible only if the polymerase chain reaction is negative for HCV ribonucleic acid.

8 Known serious active infection including, but not limited to, tuberculosis, or human immunodeficiency virus (positive human immunodeficiency virus 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 treatment.

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

12 History of liver cirrhosis of any origin and clinical stage; or history of other serious liver disease or chronic disease with relevant liver involvement, with or without normal LFTs, such as:

- Haemochromatosis
- Alpha-1 antitrypsin deficiency
- Autoimmune hepatitis
- Primary sclerosing cholangitis
- Primary biliary cirrhosis
- Biopsy-confirmed non-alcoholic steatohepatitis with advanced fibrosis
- Biopsy-confirmed alcoholic steatohepatitis with advanced fibrosis
- Wilson's disease
- Hepatocellular carcinoma.

Prior/concomitant therapy

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

14 Prior or current treatment with savolitinib or another MET inhibitor (eg, foretinib, crizotinib, cabozantinib, onartuzumab, capmatinib).

15 Criterion removed (duplication of information).

16 Any cytotoxic chemotherapy, investigational agents or other anticancer 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 treatment with the exception of monotherapy osimertinib which may continue uninterrupted during screening.

17 Patients currently receiving (or unable to stop use prior to receiving the first dose of study treatment) medications or herbal supplements known to be strong inducers of CYP3A4, strong inhibitors of CYP1A2, within 3 weeks of the first dose of study treatment (including 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 strong inducer effects on CYP3A4 during the study and for 3 months later the last dose intake.

18 Criterion removed (no longer relevant).

Prior/concurrent clinical study experience

19 Participation in another clinical study with a cytotoxic, investigational product (IP), or other anticancer drug for the treatment of advanced NSCLC if received IP from that study within 14 days of the first dose of study treatment.

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

Other exclusions

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

22 Judgement 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.

23 Previous enrolment in the present study.

24 Criterion removed (duplication of information).

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

Exclusions from exploratory genetic research

26 Previous allogeneic bone marrow transplant.

27 Non-leukocyte depleted whole blood transfusion within 120 days of the date of the genetic sample collection.

5.3 Lifestyle restrictions

5.3.1 Meals and dietary restrictions

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

For patients receiving savolitinib 300 mg bid, a pre-dose meal will be provided if the second dose of the day is given in the clinic. Patients who will take the second dose at home should be reminded that savolitinib should be taken within 15 minutes after the start of the meal.

5.3.2 Pregnancy and contraception

Women of childbearing potential

Females of childbearing potential should use highly effective methods of contraception from the time of screening until 6 weeks after discontinuing study treatment. 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 (see Appendix G). 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 treatment. If the partner is not of childbearing potential, male patients should use a condom during the study and for 5 elimination half-lives afterwards (48 hours after last dose of savolitinib) with all sexual partners.

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

5.3.3 Other lifestyle restrictions

For savolitinib, during the study therapy and for 4 weeks after the last dose of study treatment 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, SP30+ 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 signed the main study ICF to participate in the clinical study but are not subsequently assigned to study treatment(s). 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 (CONSORT) publishing requirements, to respond to queries from regulatory authorities and to support clinical diagnostic development. Minimal information includes demography, screen failure details, MET status information, eligibility criteria and any SAE.

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 electronic case report form (eCRF).

Pre-screen failures are defined as patients who signed the pre-screening ICF but are not confirmed as MET-amplified/overexpressed 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 treatment is defined as any IP(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to osimertinib and/or savolitinib.

6.1 Study Intervention(s) administered

6.1.1 Investigational products

Refer to Table 6 for information regarding the study treatments.

Table 6 Study treatments

	Osimertinib/Placebo to Osimertinib	Savolitinib
Dosage formulation:	80 mg osimertinib/placebo to osimertinib (1 × 80 mg tablet once daily) 40 mg osimertinib/placebo tablets are available if a dose reduction is required	300 mg savolitinib once daily CCI [redacted] OR 600 mg savolitinib once daily CCI [redacted] OR 300 mg savolitinib twice daily CCI [redacted]
Route of administration:	Oral	Oral
Dosing instructions:	Osimertinib/placebo to osimertinib will be administered once daily 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. Doses should be taken approximately 24 hours apart at the same time point each day. 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 drug, they should not make up for this dose, but should take the dose at the next scheduled time.	Savolitinib will be taken once daily or twice daily within 15 minutes after the start of a meal except for the day on which PK samples are taken when savolitinib will be taken after a meal prepared by the clinic. Doses should not be missed. If a patient vomits after taking their study drug, they should not make up for this dose, but should take the next dose at the next scheduled time. Once daily dosing: Doses should be taken approximately 24 hours apart at the same time point each day. 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. Twice daily dosing: Doses should be taken approximately 12 hours apart at the same time point each day. If a patient misses taking a scheduled dose, within a window of 6 hours, it is acceptable to take the dose. If it is more than 6 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.
Packaging and labelling:	Study treatment will be provided in HDPE bottles with child resistant closures. Each package will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.	Study treatment will be provided in HDPE bottles with child resistant closures. Each bottle will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.

Table 6 Study treatments

	Osimertinib/Placebo to Osimertinib	Savolitinib
IMP or NIMP/AxMP	IMP	IMP
Provider:	AstraZeneca	AstraZeneca

AxMP Auxilliary medicinal product; eCRF Electronic Case Report Form; HDPE High-density polyethylene; IMP investigational medicinal product; NIMP Non-investigational medicinal product; 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 treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only patients enrolled in the study may receive study treatment and only authorised site staff may dispense study treatment. All study treatments 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 treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation and final disposition records).

Further guidance and information for the final disposition of unused study treatment are provided in the Central Laboratory Manual.

6.3 Measures to minimise bias: randomisation and blinding

Patients who sign the ICF for pre-screening MET status testing will be registered in an interactive web response system (IWRS) to receive an E code. Patients who have tumour MET-status subsequently assessed as eligible for the study will be registered as eligible in the IWRS prior to starting study treatment. Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site.

Patients will complete treatments as specified above or until objective disease progression, unacceptable toxicity occurs, consent is withdrawn, or another discontinuation criterion is met.

If a patient withdraws from the study, then his/her enrolment code cannot be reused. Withdrawn patients will not be replaced.

Patients enrolled under CSP versions 1.0 to 6.0

Patients enrolled under CSP versions 1.0 to 5.0 who had tumour MET-status subsequently assessed as eligible for the study were registered as eligible in the IWRS prior to starting study treatment.

Under CSP versions 5.0 and 6.0, patients were centrally assigned to randomised study intervention (300 mg bid and 600 mg od regimens), using IWRS. Before recruitment for the 300 mg bid and 600 mg od regimens was initiated, the telephone number and call-in directions and/or the log in information and directions for the IWRS were provided to each site. The site was to contact the IWRS prior to the start of study intervention administration for each patient and record the intervention assignment on the applicable eCRF for patients receiving open-label treatment, if required.

Patients enrolled under CSP version 7.0

Under CSP version 7.0, all patients will be centrally assigned to randomised study intervention (savolitinib 300 mg bid + osimertinib or savolitinib 300 mg bid + placebo) using IWRS. Before recruitment is initiated, the telephone number and call-in directions and/or the log in information and directions for the IWRS will be provided to each site.

Patients randomised to the savolitinib 300 mg bid + placebo arm may cross over to savolitinib 300 mg bid plus osimertinib 80 mg od following investigator assessment of PD per RECIST 1.1. 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 treatment code should not be unblinded except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment allocation. The investigator documents and reports the action to the AstraZeneca study physician, without involvement of other personnel to maintain study integrity.

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.

Treatment codes will not be unblinded 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 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' treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If a patient's treatment assignment is unblinded, the sponsor must be notified within 24 hours after

breaking the blind. The investigator documents and reports the action to the AstraZeneca physician, without involvement of other personnel to maintain study integrity. Additionally, patients with investigator-assessed objective PD may be unblinded.

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

The AstraZeneca study team will be unblinded at the time of the primary analysis. Site staff and patients will remain blinded until database lock for the final analysis.

6.4 Study intervention compliance

The study medication should only be used as directed in this protocol. Details of treatment with study medication for each patient will be recorded in the appropriate sections in the eCRF. Treatment compliance will be assessed by the tablet or capsule count and the information should be recorded in the appropriate section of the eCRF.

Patients should return all unused medication and empty containers to the investigator.

The study personnel at the investigational site will account for all drugs dispensed and for appropriate destruction. Certificates of delivery and destruction should be signed.

It is the investigator/institution's responsibility to establish a system for handling study treatments, including IPs, so as to ensure that:

- Deliveries of such products from AstraZeneca or its representative are correctly received by a responsible person.
- Such deliveries are recorded.
- Study treatments are handled and stored safely and properly as stated on the label.
- Study treatments are only dispensed to study patients in accordance with the protocol.

The study personnel will account for all study drugs dispensed to and returned from the patient.

At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed/returned stock. Records of usage should include the identification of the person to whom the study treatment was dispensed, the quantity and date of dispensing and unused study treatment returned to the investigator. This record is in addition to any drug accountability information recorded on the eCRF. Any discrepancies must be accounted for on the appropriate forms. Certificates of delivery and return must be signed, preferably by the investigator or a pharmacist, and copies retained in the investigator site file.

Dispensing and accountability records will continue to be collected for as long as patients continue to receive study treatment, although they will not be entered on the eCRF after the database has closed.

Any change from the dosing schedule, dose interruptions, dose reductions, dose discontinuations should be recorded in eCRF.

Study site personnel, if applicable, or the AstraZeneca monitor will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, and destruction should be signed.

6.5 Concomitant therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives within 4 weeks prior to the first dose, during the study, and until the 28 day follow-up visit must be recorded along with:

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

In addition, 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.

The use of medications listed in Table 7 is restricted, these medications are permitted with caution and careful monitoring of patients.

Table 7 Restricted medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed)
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, CYP2C9, and CYP2D6 substrates	In vitro savolitinib is an inhibitor of CYP2C8, CYP2C9, and CYP2D6. Those drugs defined as sensitive CYP2C8, CYP2C9, and CYP2D6 substrates (almost exclusively metabolised by these enzymes should be used with caution when co-dosed with savolitinib.

Table 7 Restricted medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed)
Sensitive CCI substrates.	Those drugs defined as sensitive CCI substrates should be used with caution when co-dosed with savolitinib.
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.
Warfarin	The use of warfarin for oral anticoagulation is not recommended. Patients who are taking warfarin should be monitored closely for INR changes.
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 Breast Cancer Resistance Protein	Patients taking concomitant medications whose disposition is dependent upon the Breast Cancer Resistance Protein 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 Breast Cancer Resistance Protein-mediated increase in exposure). If the patient experiences any potentially relevant adverse events 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. See Appendix J).

Table 7 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. See Appendix J.

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.

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.

6.5.1 Rescue Medicine

Recommendations on rescue medicine, regarding hypersensitivity management or pre-treatment for such reactions and other AE management or prophylaxis are provided in Appendix I.

The study site will supply required rescue medication that will be obtained locally.

Although the use of rescue medications is allowable at any time during the study, the period of delay in rescue medication following study intervention will be decided based on study investigator's discretion. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

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 treatments will be administered as follows:

Table 8 Dose reduction for osimertinib (or placebo to osimertinib) to manage adverse events

Starting osimertinib (or placebo) dose	**80 mg od** (1 × 80 mg tablet once daily)
Reduced dose -1	40 mg od (1 × 40 mg tablet once daily)

od Once daily.

Table 9 Dose reduction for savolitinib to manage adverse events

Starting savolitinib dose	**300 mg bid**	**300 mg od**	**600 mg od**
Reduced dose -1	CCI		
Reduced dose -2			

Note: Only 2 dose reductions of savolitinib are permitted.

Bid Twice daily; od Once daily.

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

6.6.1 Meals and dietary restrictions

Refer to Section 5.3.1 for details of meals and dietary restrictions.

6.7 Intervention after the end of the study

After the final DCO, the clinical study database will be closed to new data. Patients receiving study treatment at the time of the final data cut will be able to continue to receive study treatment (either combination or monotherapy) as long as, in the opinion of the investigator, they are still receiving clinical benefit.

Patients who remain on study treatment after the final analysis will be monitored according to routine clinical practice as defined by the investigator. Study treatment will be supplied to sites manually outside of the IWRS. 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 last patient treated. Last patient last visit will be defined as the last patient's treatment discontinuation.

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.

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 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 Informed Consent.

7 DISCONTINUATION OF STUDY INTERVENTION AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of study intervention

Patients may be discontinued from IP in the following situations. Note that discontinuation from study treatment is NOT the same thing as a complete 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 Clinical Study Protocol.
- Objective disease progression as per RECIST 1.1. Patients may continue to receive treatment with osimertinib + savolitinib beyond RECIST 1.1-defined progression as long as they continue to receive clinical benefit, in the opinion of the investigator, and do not meet any of the discontinuation criteria.
- 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 SoA (Table 1 and Table 2) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

Continuing on monotherapy

A patient can continue on savolitinib monotherapy (if osimertinib was stopped earlier or if randomised to the savolitinib plus placebo arm) until objective disease progression. Savolitinib monotherapy beyond RECIST 1.1 progression is not permitted.

A patient who is originally randomised to savolitinib + osimertinib arm may continue to receive treatment with osimertinib monotherapy (if savolitinib was stopped earlier) beyond RECIST 1.1-defined progression as long as they continue to receive clinical benefit, in the opinion of the principal investigator and do not meet any of the discontinuation criteria (this may be beyond disease progression in the absence of clinical symptoms or signs indicating clinically significant disease progression; no decline in performance status; absence of rapid disease progression 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 treatment), according to the SoA (Table 1).

7.1.1 Rechallenge

See guidance in Appendix I for circumstances under which a patient whose study treatment was temporarily interrupted due to an AE can restart treatment.

7.1.2 Procedures for discontinuation of study treatment

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

Discontinuation of study treatment(s), for any reason, does not impact on the patient´s participation in the study. The patient should continue attending subsequent study visits and data collection should continue according to the study protocol. 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.

7.1.3 Follow-up of patients post discontinuation of study intervention

As a minimum, telephone contact should be made with the patient 28 days following the discontinuation of both IPs to collect new AEs and follow up on any ongoing AEs and concomitant medications (including any subsequent cancer therapy, if appropriate). Refer to Section 8.3.3 for full details on AE recordings during follow-up.

Patients who have discontinued study intervention prior to RECIST 1.1 defined radiological progression will be followed up with tumour assessments as indicated in the SoA until RECIST 1.1-defined PD or death regardless of whether or not the patient started a subsequent anti-cancer therapy, unless they have withdrawn all consent to study related assessments.

All patients will be followed for survival until the end of the study.

Patients who decline to return to the site for evaluations should be contacted by telephone as indicated in the SoA as an alternative.

7.1.4 Follow-up for survival

Patients will be followed up for survival status as indicated in the SoA until death, withdrawal of consent, or the end of the study. Survival information may be obtained via telephone contact with the patient or the patient's family, by contact with the patient's current physician, or publicly available death registries (if available). Additional assessments to be performed at the time of survival follow-up are detailed in the SoA.

7.2 Lost to follow-up

A patient will be considered potentially lost to follow-up if he or she 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.
- Before a patient is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the patient or next of kin by eg, repeat telephone calls, 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.
- Efforts to reach the patient should continue until the end of the study. Should the patient be unreachable at the end of the study the patient should be considered to be lost to follow-up with unknown vital status at end of study and censored at latest follow-up contact.

7.3 Withdrawal from the study

A patient may withdraw from the study (eg, withdraw consent), at any time (IP **and** assessments) at his/her own request, without prejudice to further treatment.

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).

If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before consent is withdrawn.

If a patient withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records. The AstraZeneca study team should be informed of withdrawn patient sample destruction by the site or at the central laboratory in a prompt manner.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AEs. The investigator will follow up patients as medically indicated. The patient will return electronic PRO (ePRO) devices.

AstraZeneca or its delegate will request investigators to collect information on patients' vital status (dead or alive; date of death when applicable) during survival follow-up until the end of the study from publicly available sources, in accordance with local regulations. Knowledge of the vital status at study end in all patient is crucial for the integrity of the study.

See SoA (Table 1 and Table 2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. All study treatment should be returned by the patient.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Table 1 and Table 2).

The investigator will ensure that data are recorded on the eCRF. The Electronic Data Capture system will be used for data collection and query handling.

The investigator ensures the accuracy, completeness, legibility and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRF. A copy of the completed eCRFs will be archived at the study site.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA (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 protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 Efficacy assessments

8.1.1 CT and MRI scans tumour assessments (RECIST 1.1)

RECIST 1.1 guidelines for measurable, non-measurable, target lesions (TLs) and non-target lesions (NTLs) and the objective tumour response criteria are presented in Appendix H of this Clinical Study Protocol.

Baseline tumour assessments should include CT/MRI of chest and abdomen (including liver and adrenal glands) and should be performed within 28 days of treatment start, and ideally as close as possible to the start of study treatment.

At screening the MRI/CT scans will include brain imaging (MRI preferred) for all patients randomised under CSP version 7.0. Those determined to have brain metastases at baseline or those who had a history of brain metastases will have their brain rescanned at all subsequent tumour assessments (using the same modality as at baseline) until RECIST 1.1-defined PD, and lesions should be captured as non-target lesions in the RECIST 1.1 assessment. In patients without brain metastases at baseline and without a history of brain metastases, brain scans will be performed only when there is a suspected CNS progression and at the RECIST 1.1-defined extracranial progression. The brain scan is required for all patients at PD by investigator assessment per RECIST 1.1 and should be performed within 4 weeks, but preferably as soon as possible, to allow the assessment of new lesions in the brain. 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 every 6 weeks (±7 days) after the start of treatment until Cycle 7, and then every 8 weeks until objective disease progression as defined

by RECIST 1.1 even if a patient discontinues treatment prior to progression (unless they withdraw consent).

Patients randomised to the 300 mg bid savolitinib + placebo arm may cross over to 300 mg bid savolitinib + 80 mg od osimertinib following investigator assessed PD per RECIST 1.1. For patients who cross over after PD per RECIST 1.1, scheduled imaging is not required as specified in the crossover SoA (Table 2).

Patients may also cross over to 300 mg bid savolitinib + 80 mg od osimertinib based on a declaration of futility of savolitinib + placebo without PD per RECIST 1.1. For patients who cross over based on a declaration of futility of the savolitinib monotherapy arm who have not objectively progressed during the initial randomised treatment period, scheduled imaging will be performed per the crossover SoA (Table 2).

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 disease progression by RECIST as per the SoA (Table 1).

Categorisation of objective tumour response at each visit will be based on the RECIST 1.1 guidelines for response: complete response (CR), partial response (PR), stable disease (SD) and progression of disease (PD). For ORR, a visit response of CR or PR must be confirmed by a later scan conducted at least 4 weeks after the initial response is observed.

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) 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 discontinuation of therapy. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal disease progression 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 contract research organisation (CRO) to enable blinded independent central review (BICR). Guidelines for image acquisition, de-identification, storage at the investigative site as source data, and transfer to the imaging CRO will be provided by the CRO (signed by AstraZeneca) in a separate document. Further details of the BICR will be documented in the Independent Review Charter (also referred to as "Imaging Charter") provided by the CRO (signed by AstraZeneca). 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.

Guidelines for the evaluation of tumour response per RECIST 1.1 are provided in Appendix H.

8.1.2 Clinical outcome assessments

A Clinical Outcome Assessment (COA) is any assessment that may be influenced by human choices, judgement, or motivation and may support either direct or indirect evidence of treatment benefit. Patient Reported Outcomes (PROs) is one of the types of COAs.

PROs, an umbrella term referring to all outcomes and symptoms, are directly reported by the patient. PROs have become a significant endpoint when evaluating effectiveness of treatments in clinical trials.

The following PRO instruments will be administered in this study and will be completed by patients if available in their language for the country in which they live: EORTC QLQ-C30 v3 (core questionnaire), EORTC QLQ-LC13 (lung cancer module), PRO-CTCAE, Patient's Global Impression of Severity (PGIS), and 5-level health state utility index (EQ-5D-5L) (see Appendix K). Each is described below.

8.1.2.1 EORTC-QLQ-C30 and QLQ LC13

The EORTC-QLQ-C30 was developed by the EORTC Quality of Life Group 1993; it consists of CCI items and measures cancer patients' CCI CCI (Aaronson et al 1993) for all cancer types. Questions can be grouped into CCI CCI scales CCI CCI scales CCI a CCI scale; CCI single items assessing CCI CCI and CCI The EORTC QLQ-C30 is a valid and reliable PRO instrument in this patient population.

QLQ-LC13 is a supplementary lung cancer module questionnaire module to be employed in conjunction with the QLQ-C30. The QLQ-LC13 incorporates CCI multi-item scale to assess CCI

8.1.2.2 PGIS

The PGIS item is included to assess how a patient perceives his/her overall current severity of cancer symptoms. Patients will choose from response options from "no symptoms" to "very severe."

8.1.2.3 PRO-CTCAE

The PRO-CTCAE will only be administered in countries where a linguistically validated version exists.

PRO-CTCAE was developed by the NCI in recognition that CCI CCI data directly from patients can CCI . This was based on findings from multiple studies demonstrating that physicians and nurses underestimate CCI in comparison with CCI (Basch et al 2009, Litwin et al 1988, Sprangers and Aaronson 1992). To date, CCI symptoms of the CTCAE (version 4) have been identified to be amenable to patient reporting, but not all items are administered in any clinical study. Response options vary in CCI CCI . For this study, CCI are considered relevant for this cancer treatment (See Appendix K).

8.1.2.4 EQ-5D-5L

The EQ-5D-5L will be used to explore the impact of treatment and disease state on health state utility.

The EQ-5D-5L, developed by the EuroQol Group, is a generic questionnaire that provides a simple descriptive CCI and a CCI for CCI CCI (EuroQol 2015). The EQ-5D-5L questionnaire comprises CCI questions that cover CCI dimensions of health CCI CCI . Respondents also assess CCI using the CCI CCI scale), which ranges from CCI CCI

8.1.2.5 Administration of ePRO questionnaires

All PRO questionnaires are to be completed using the ePRO device. If the device is not yet at the site or there is a technical problem, the study team may grant use of a paper backup using electronic screenshots for baseline only. For technical problems the device help desk should be called.

Patients will complete ePRO assessments at home, and sometimes at site, using the same handheld electronic device (ePRO). Patients will be issued with the ePRO device and given training on how to use it, once the patient is confirmed as eligible for the study, is registered in IWRS and prior to starting treatment. This may be at the Screening visit or prior to dosing on Cycle 1 Day 1.

All assessments should be completed according to the following parameters:

Each centre must allocate the responsibility for the administration of the ePROs to a specific individual (eg, a research nurse or study coordinator) and, if possible, assign a backup person to cover if that individual is absent.

The investigator will arrange for relevant training in the set-up of the electronic device and training patients in how to self-administer the ePROs using the device. Patients should complete the PROs in accordance with the study schedule as shown in Table 1. The significance and relevance of the data should be explained carefully to patients so that they are motivated to comply with the data collection. Reminders should be sent to patients at home as needed to ensure compliance with the assessment schedule.

The following guidelines should be followed:

The research nurse or appointed site staff must explain to patients the value and relevance of study participation and inform them that these questions are being asked to find out, directly from them, how they feel. The research nurse or appointed site staff should also stress that the information is confidential. Therefore, if the patients have any medical problems, they should discuss them with the doctor or research nurse separately from the ePRO assessment.

The research nurse or appointed site staff must train the patient on how to use the ePRO device, using the materials and training provided by the ePRO vendor, and provide guidance on whom to call if there are problems with the device when the patient is completing the ePROs at home.

The research nurse or appointed site staff should remind patients that there are no right or wrong answers.

If the patient is unable to read (eg, blind or illiterate), that patient is exempted from completing the ePROs but may still participate in the study. Patients exempted in this regard should be flagged appropriately by the site staff and recorded in the eCRF.

The research nurse or appointed site staff must monitor compliance to ensure all data is captured. Compliance must be checked at each study visit to identify problems early.

8.1.3 Survival Follow-up

Patients who have discontinued study treatment will be followed up for survival status every 12 weeks 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 data cut-offs 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

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

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

8.2.1 Clinical safety laboratory assessments

See Table 10 for the list of clinical safety laboratory tests to be performed and the SoA (Table 1 and Table 2) for the timing and frequency.

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

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.7.

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 and serum pregnancy tests will be performed at a local laboratory or near to the investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

Table 10 Laboratory safety variables

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

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

[b] Designates tests that are considered liver function tests and are to be done weekly for the first 10 weeks on study treatment (ie, Day 1, Day 8, Day 15 and Day 22 in Cycle 1 and Cycle 2; then Day 1 and Day 8 of Cycle 3), then Day 1 of every cycle and at progression.

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

NB: In case a patient shows an AST **or** ALT ≥3×ULN together with total bilirubin ≥2×ULN please refer to Appendix E ‘Actions required in cases of increases in liver biochemistry and evaluation of Hy’s Law’, for further instructions.

8.2.2 Physical examinations

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

Physical examination will be performed at timelines as specified in the SoA (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 8.3.7 for details.

8.2.3 Vital signs

Vital signs (BP, pulse, temperature and respiration rate) will be evaluated according to the SoA (Table 1 and Table 2). Weight will be assessed on Day 1 of each cycle for the first 6 cycles then every 8 weeks after; height will be assessed at screening only.

- Temperature, pulse rate and BP will be assessed.
- BP and pulse measurements will be assessed in the semi-supine position with a completely automated device. Manual techniques will be used only 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.

8.2.4 Electrocardiograms

ECGs will be collected centrally.

- Triplicate 12-lead ECG will be obtained as outlined in the SoA (Table 1 and Table 2) using an ECG machine that automatically calculates the heart rate and measures RR, P-R, QRS, QT, and QTcF intervals.
- Triplicate ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes. The 3 individual ECG tracings should be obtained in succession, no more than 2 minutes apart. The full set of triplicates should be completed within 5 minutes. ECGs 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. If there is a clinically significant abnormal finding during the treatment period, the investigator will record it as an AE on the eCRF, according to standard AE collection and reporting processes. A 28-day follow-up assessment will be required if an on-treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality. The original ECG traces must be stored in the patient medical record as source data.

8.2.5 Multi-gated acquisition (MUGA)/echocardiogram (ECHO)

An ECHO or MUGA scan to assess left ventricle ejection fraction will be conducted during the main study screening period, every 12 weeks (±2 weeks) relative to randomisation (patients recruited under CSP version 7.0) or the first dose of study drug (patients recruited prior to CSP version 7.0), and at the end of treatment as indicated in the SoA (Table 1 and Table 2). 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. 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.

The patients should also be examined using the same machine and operator whenever possible.

8.2.6 Pregnancy assessments

A pregnancy test on urine or blood sample will be performed for pre-menopausal women of childbearing potential, at the study screening visit, and prior to the first dose of study drug 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 treatment immediately.

8.2.7 ECOG Performance Status

ECOG performance status will be assessed as specified in the SoA and at the time of PD based on the following:

0 Fully active; able to carry out all usual activities without restrictions.

1 Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (eg, light housework or office work).

2 Ambulatory and capable of self-care, but unable to carry out any work activities; up and about more than 50% of waking hours.

3 Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.

4 Completely disabled; unable to carry out any self-care and totally confined to bed or chair.

5 Dead.

Any significant change from baseline or screening must be reported as an AE as described in Section 8.3.7.

8.3 Collection of 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.

AE 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 or SAE. For information on how to follow/up AEs see Section 8.3.3.

8.3.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.2 Time period and frequency for collecting AE and SAE information

AEs and SAEs will be collected from time of signing 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 treatment is discontinued.

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

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Section 8.4.1. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available. SAEs will be reported according to local regulations.

Investigators are not obligated to actively seek AE or SAE in former study patients. However, if the investigator learns of any SAE, including a death, at any time after a patient’s last visit and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator may notify the sponsor.

The method of defining, evaluating, and assessing causality of AE and SAE are provided in Appendix B.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All AEs and SAEs, will be followed until resolution, stabilisation, the event is otherwise explained, or the patient is lost to follow-up

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.

8.3.4 Adverse event data collection

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 IP(s) (yes or no)
- Action taken with regard to IP(s)
- 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

8.3.5 Causality collection

The investigator will assess causal relationship between each IP 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 investigational products?'.

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

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

8.3.6 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.

8.3.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests, ECGs and vital signs will be summarised in the Clinical Study Report. Deterioration as compared with baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

If deterioration in a laboratory value/ECG/vital sign/other safety assessment 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 disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study, see Sections 8.3.9 and 8.3.10.

8.3.8 Hy's law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3×ULN together with total bilirubin ≥2×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 Hy's Law.

8.3.9 Disease-under study

Symptoms of disease-under study are those which might be expected to occur as a direct result of advanced 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 IP.

8.3.10 Disease progression

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

Progression of the malignancy under study, including signs and symptoms progression, should not be reported as an SAE. Hospitalisation due to signs and symptoms of disease progression should not be reported as SAE.

8.3.11 New cancers

The development of a new cancer should be regarded as an AE and will generally meet at least 1 of the serious criteria. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer.

8.3.12 Handling of deaths

All deaths that occur during the study, or within the follow-up period after the administration of the last dose of IP, should be reported as follows:

- Death, which is unequivocally due to disease progression, should be communicated to the study monitor at the next monitoring visit and should be documented in the eCRF module, but should not be reported as a SAE during the study.
- Where death is not clearly due to disease progression of the disease under study the AE causing the death should be reported to the study monitor as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes.
- Deaths with an unknown cause should always be reported as a SAE but every effort should be made to establish a cause of death. A post-mortem may be helpful in the

assessment of the cause of death, and if performed a copy of the post-mortem results (with translation of important parts into English) should be reported in an expedited fashion to an AstraZeneca representative within the usual timeframes.

8.3.13 Adverse events of special interest

AESIs are events of scientific and medical interest specific to the further understanding of the study treatment safety profile and require close monitoring and rapid communication by the investigators to AstraZeneca. An AESI can be serious or non-serious. All AESIs will be recorded in the eCRF within 24 hours. Serious AESIs will be recorded and reported as per Section 8.4.1. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterise and understand them in association with the use of a study treatment.

AESIs will be recorded in the eCRF using a recognised medical term or diagnosis that accurately reflects the event. AEs will be assessed by the Investigator for severity, relationship to the study treatment, possible aetiologies, and whether the event meets criteria for an SAE and therefore requires immediate notification to AstraZeneca. If an AESI evolves into a condition that meets the regulatory definition of "serious" it will be reported on the SAE Report Form.

Based on the available preclinical and clinical data, review of the cumulative literature, reported toxicities for the same class of agents and biological plausibility, reports of hepatotoxicity, hypersensitivity (including anaphylaxis and CCI QTc prolongation and pyrexia, for the savolitinib clinical program regardless of seriousness, are to be collected through the clinical study database.

AESIs for osimertinib are ILD or ILD-like adverse reactions (eg, pneumonitis), QTc interval prolongation, keratitis, haematological events, erythema multiforme and SJS, changes in cardiac contractility, and aplastic anaemia. ILD events are to be reported as AEs in the CRF, with additional details captured in the "ILDIS" CRF.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, 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 1 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 1 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 a SAE to the appropriate AstraZeneca representative by telephone.

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

Section 5.4 of the osimertinib and savolitinib investigator brochures provides information related to the emerging safety profile of both study treatments. For further guidance on the definition of a SAE, see Appendix B of the Clinical Study Protocol.

8.4.2 Pregnancy

All pregnancies and outcomes of pregnancy during the course of study and within 6 weeks of the last dose of osimertinib should be reported to AstraZeneca except for:

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

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.

8.4.2.1 Maternal exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP 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, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 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 1 or 5 calendar days for SAEs (see Section 8.3.2) 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.

8.4.2.2 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. Consent from the partner must be obtained before the Pregnancy Report Form is completed.

8.4.3 Reporting of 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 clinical study protocol.

- 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 IMP or AstraZeneca NIMP 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 1 (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) or 5 (other serious initial and follow-up) calendar days for overdoses associated with an SAE (see Sections 8.3.2 and 8.4.1) and within 30 days for all other overdoses.

8.4.4 Medication Error, Drug Abuse, and Drug Misuse

8.4.4.1 Timelines

If an event of medication error, drug abuse, or drug misuse occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 calendar day, ie, immediately but no later than 24 hours of when they become aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within 1 (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, drug abuse, or drug misuse (see Sections 8.3.2 and 8.4.1) and within 30 days for all other events.

8.4.4.2 Medication Error

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

The full definition and examples of medication error can be found in Appendix B 8.

8.4.4.3 Drug Abuse

Drug abuse is the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 8.

8.4.4.4 Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study patient) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 8.

8.4.5 Management of IP-related toxicities

8.4.5.1 Management of osimertinib-related toxicities

Potential osimertinib-related toxicities during the course of the study can be managed by interruption of the dose of osimertinib or dose reductions (see Appendix I Section I 1). Repeat dose interruptions are allowed as required. If a patient experiences a CTCAE Grade 3 (CTCAE version 5.0) and/or unacceptable toxicity, dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines. If the toxicity resolves or reverts to ≤CTCAE Grade 2 after 3 weeks of onset, treatment with osimertinib

may be restarted at the same dose (80 mg) or a lower dose (40 mg) using the rules in Appendix I Section I 1 and with discussion and agreement with the AstraZeneca Study Team Physician as needed. There will be no individual modifications to dosing schedule in response to toxicity, only potential dose reduction or dose modification. If the toxicity does not resolve to ≤CTCAE Grade 2 after 3 weeks, then the patient should be withdrawn from the study and observed until resolution of the toxicity. Osimertinib can be dose reduced to 40 mg od: if the reduced dose of 40 mg od is not tolerable, no further dose reduction is allowed and study treatment should be discontinued. Once a dose is reduced escalation is not permitted.

Dose modifications are permitted in the management of IP-related toxicities as described in Table 11 with further information being provided in Appendix I Section I 1.

Dose modification guidelines for QTc prolongation are shown in Table 12.

Table 11 Osimertinib dose adjustment information for adverse reactions

Target organ	Adverse reaction[a]	Dose modification
Pulmonary	ILD/pneumonitis	Permanently discontinue osimertinib
Other	Grade 3 or higher adverse reaction	Withhold osimertinib for up to 3 weeks
	If Grade 3 or higher adverse reaction improves to Grade 0 to 2 after withholding of osimertinib for up to 3 weeks	Osimertinib may be restarted at the same dose (80 mg) or a lower dose (40 mg)
	Grade 3 or higher adverse reaction that does not improve to Grade 0 to 2 after withholding for up to 3 weeks	Permanently discontinue osimertinib

[a] The intensity of the clinical adverse events graded by the National Cancer Institute CTCAE Version 5.0.
ILD Interstitial lung disease.

8.4.5.2 Management of savolitinib-related toxicities

Potential savolitinib-related toxicities during the course of the study can be managed as medically indicated and with interruption of the dose of savolitinib or dose reductions as appropriate, **unless symptoms are associated with hypersensitivity** (see Appendix I Section I 3). Repeat dose interruptions are allowed as required, taking into consideration the additional precautions for restart of savolitinib as illustrated in Appendix I. For each patient the savolitinib dose can be reduced a maximum of 2 times (Table 9). No dose re-escalations are allowed.

Dose modification guidelines for QTc prolongation are shown in Table 12.

Table 12 Dose modifications for QTc prolongation

NCI CTCAE Toxicity Grade	Action with savolitinib	Action with osimertinib
Grade 0, 1, or 2	None	None
Grade 3 Patients with QTcF prolongation to >500 msec on at least 2 separate ECGs If the toxicity does not resolve to QTcF <481 msec within 21 days	Hold dosing and follow algorithm below: 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 and then restart drug at one reduced dose level.* Permanently discontinue study drug and consult with a cardiologist for further management as clinically indicated.	Hold dosing and follow algorithm below: Withhold until QTc interval is <481 msec or recovery to baseline if baseline QTc is more than 481 msec within 21 days of onset, then restart at a reduced dose (40 mg) or at 80 mg (at the discretion of the investigator). Permanently discontinue osimertinib.
Grade 4 QTcF ≥501 or >60 msecs change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Permanently discontinue study drug and consult with a cardiologist for further management as clinically indicated.	Permanently discontinue osimertinib.

CTCAE Common Terminology Criteria for Adverse Events; ECG Electrocardiogram; NCI National Cancer Institute; QTc corrected QT interval; QTcF corrected QT interval using Fridericia's formulas.

***For French sites only**, as per ANSM advice, the patient must remain hospitalised with continuous cardiac monitoring (ECG) until specialist advice is obtained by a cardiologist.

8.5 Human biological samples

Instructions for the collection and handling, storage and shipping of biological samples will be provided in the study-specific Central 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 Samples, see Appendix C.

Samples will be stored for a maximum of 15 years from the end of the study (as defined in this CSP; see Section 4.4) in line with consent and local requirements, after which they will be destroyed/repatriated.

- 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.
  - Samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the clinical study report (CSR).
- Remaining sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years from the end of the study (as defined in the CSP; see Section 4.4). Additional use includes but is not limited to further characterisation of any anti-drug antibodies, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

For further details on Handling of Human Biological Samples, see Appendix C.

8.5.1 Pharmacokinetics

Plasma samples will be collected for measurement of plasma concentrations of osimertinib, savolitinib and their metabolites as specified in Table 13. The timing of PK samples may be adjusted during the study if warranted and agreed upon between the investigator and the sponsor dependent upon emerging data to ensure appropriate characterisation of the plasma concentration-time profiles. Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and sponsor. Total volume of blood taken from each patient will not exceed that described in Section 8. Instructions for the collection and handling of biological samples will be provided by the sponsor or analytical test site. The actual date and time (24-hour clock time) of each sample will be recorded. The actual date, time and amount of the last savolitinib and osimertinib doses prior to each PK sample will be recorded.

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

Table 13 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 (N.B. Triplicate ECGs to be collected at these timepoints as described in section 8.2.4.)
Cycle 6, Day 1	Pre-dose
Cycle 11, Day 1	Pre-dose

[a] Samples may be collected at additional timepoints.

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 osimertinib and savolitinib dose at the same time. Fasting state will be collected in the eCRF. Pre-dose PK sample may be drawn at any time before dosing occurs (before or after breakfast).

Samples will be used to evaluate the PK of osimertinib and savolitinib. The savolitinib plasma concentration data obtained from the samples collected in this study may be included in the listings of 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 protocol amendment. The Institutional Review Board (IRB)/Independent Ethics Committee (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 analysed by Covance Bioanalytical Laboratories on behalf of AstraZeneca, using appropriate bioanalytical methods. Full details of the analytical methods used will be described in a separate bioanalytical report.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a bioanalytical report. 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.

8.5.2 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

Mandatory collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all patients in this study as specified in Table 1 and Table 2):

- Tumour sample, taken following progression on prior treatment with osimertinib, will be required at Pre-screening. MET status by FISH and IHC will be determined at a central laboratory. Additional analyses of predictive biomarkers may also be performed. Tumour sample requirements for biomarker testing will be defined in the supporting Central Laboratory Manual.
  - Sampling should be undertaken by experienced physicians in appropriate medical facilities in accordance with standard clinical practice for subjects with advanced NSCLC.
  - Patients will only undergo sample collection procedure 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 (ESMO) guidelines, tumour re-sampling at disease progression 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 for diagnostic development (plasma ctDNA) will be collected at Pre-Screening and Screening and analysed for predictive biomarkers including, but not limited to, MET gene copy number and EGFR mutations. These data may be used for development of diagnostics to identify patients most likely to respond to combination therapy.
- Blood samples for circulating DNA/RNA will also be collected from enrolled patients at baseline (prior to their first dose), on treatment and at progression to monitor dynamic changes in CCI [redacted].
- CCI [redacted] samples will be collected from enrolled patients prior to their first dose and at progression to monitor CCI [redacted]
- CCI [redacted] will be also collected to explore changes in CCI [redacted].
- CCI [redacted] samples will be collected and stored for diagnostic development and possible retrospective exploratory biomarker analysis which may include, but will not be limited to, understanding mechanisms of CCI [redacted] This may include the analysis CCI [redacted]
- DNA will be collected and stored for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to osimertinib and savolitinib treatment and/or susceptibility to cancer.

- Germline DNA will be collected from a blood sample and stored for exploration of the role of HLA alleles in development of drug-related toxicity (such as but not limited to hypersensitivity).

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 drugs to generate hypotheses to be tested in future studies.

8.6.2 Storage, re-use and destruction of biomarker samples

Samples will be stored for a maximum of 15 years from the date of the last patient's last visit, after which they will be destroyed. The results of this biomarker research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

8.6.3 Collection of optional biomarker samples

Collection of CCI for CCI is also part of this study as specified in the SoAs (Table 1 and Table 2).

A CCI is requested following CCI on the study intervention, collected at or after CCI visit. The CCI requested at CCI CCI is to look at CCI for savolitinib and is optional.

8.6.4 Other study related biomarker research

Already collected samples may be analysed for CCI

For further details on Handling of Human Biological Samples, including storage, re-use and destruction, refer to Appendix C and the Central Laboratory Manual.

8.7 Optional genomics initiative sample

Approximately CCI will be collected from patients who have consented to participate in the genetic analysis component of the study. Participation in

the genetic research is optional. Patients who do not wish to participate in the genetic research may still participate in the study.

See Appendix D for information regarding the storage and destruction of Genomics Initiative genetic sample. Details on processes for collection and shipment and destruction of these samples can be found either in the appendices or in the Laboratory Manual.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

For the primary endpoint of ORR in patients with 300 mg bid savolitinib + osimertinib dosing and FISH10+ and/or IHC90+ status whose tumours have progressed following treatment with 1L osimertinib, the observed ORR, which is assumed to be associated with a true population ORR of CCI%, will be provided along with its associated CIs, and be compared with the historical reference platinum-pemetrexed chemotherapy ORR of approximately CCI%.

For the primary endpoint of ORR in patients with 300 mg od savolitinib + osimertinib dosing and FISH5+ and/or IHC50+ status whose tumours have progressed following prior osimertinib treatment, the following hypothesis will be analysed at the 5% 2-sided alpha level for the defined primary analysis population.

H_0: ORR=CCI% versus

H_1: ORR=CCI%

9.2 Sample size determination

The study has a total of 4 dosing combinations:

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

The savolitinib 300 mg od regimen was originally sized to ensure there were sufficient patients in each of the diagnostic populations. Approximately CCI centrally confirmed MET FISH+ patients were planned to be treated with osimertinib 80 mg od plus savolitinib 300 mg od. To achieve CCI centrally confirmed MET FISH+ patients at this dose, it was anticipated that CCI patients at this dose would be treated in this study, assuming CCI% of these would be centrally confirmed FISH+ patients and CCI% (CCI patients) would be centrally

confirmed MET IHC+ patients. As the overall prevalence rates and the level of concordance between FISH and IHC methods may vary and a small number of patients recruited by pre-existing NGS may not have a central confirmation, it was anticipated that greater or less than CCI patients would be required to achieve CCI centrally confirmed MET FISH+ patients, however this was not expected to exceed CCI treated patients at this dose. If the proportion of patients who had central confirmation by IHC was lower than expected, additional patients were to be recruited to ensure there were at least CCI centrally confirmed MET IHC+ patients.

Under CSP version 5.0, approximately CCI patients (post 1L or 2L osimertinib) were planned to be randomised in a CCI ratio to receive osimertinib 80 mg od in combination with either savolitinib 300 mg bid (approximately CCI patients) or savolitinib 600 mg od (approximately CCI patients). Since CCI patients had already received the 600 mg od dose (enrolled prior to CSP version 5.0, under the previous weight-based dosing schedule), approximately CCI patients in total were planned to receive osimertinib in combination with savolitinib 600 mg od. Under CSP version 6.0, the enrolment was further restricted to post 1L osimertinib and central MET FISH+ only, therefore approximately CCI patients that were planned to be randomised in a CCI ratio to osimertinib 80mg od in combination with either savolitinib 300 mg bid or savolitinib 600 mg od applied to the new population (ie, post 1L osimertinib and central MET FISH+).

Under CSP version 7.0, approximately CCI patients (post 1L osimertinib with MET amplification/overexpression [FISH10+ and/or IHC90+]) will be randomised in a CCI ratio to receive savolitinib 300 mg bid + osimertinib 80 mg (approximately CCI patients) or savolitinib 300 mg bid + placebo to osimertinib (approximately CCI patients). With assumed ORRs of 55% and CCI%, for the savolitinib 300 mg bid + osimertinib 80 mg and the savolitinib 300 mg bid + placebo arms respectively, there will be at least CCI% power at a 2-sided 0.05 significance level to detect a difference in ORRs of the 2 arms.

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

Primary and final analyses:

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

For the savolitinib 300 mg od dosing regimen, with approximately CCI patients with FISH5+ and/or IHC50+ status who have progressed following osimertinib treatment, there will be at least CCI% power for an exact binomial test with a 2-sided significance level of 0.05 to detect a

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

Interim Analyses:

Interim Analysis 1 was planned to assess ORR and discontinuations due to AEs. This was to occur after approximately CCI patients treated with osimertinib (80 mg od) and savolitinib (300 mg od) had the opportunity to be treated for 2 postbaseline scans (12 weeks) or CCI patients treated with osimertinib (80 mg od) and savolitinib (300 mg od) had the opportunity to be treated for 6 weeks, whichever was later.

For IA1, it was considered that it may be insufficient evidence for efficacy if there was CCI% probability for the ORR to be greater than CCI%. This translated into observing CCI or fewer responders out of CCI patients; an ORR of CCI% which has a 2-sided exact binomial CCI% CI of CCI% to CCI%; wherein the upper confidence limit is CCI %. Additionally, it was considered that a greater than CCI% probability for the ORR to be above CCI% may be considered a good signal, which translated into observing CCI or more responders out of CCI patients: an ORR of CCI%.

For IA1, based on CCI patients overall who had the opportunity to be treated for at least 6 weeks with osimertinib (80 mg od) and savolitinib (300 mg od) with respect to the proportion of patients discontinuing due to any AE and the proportion of patients discontinuing due to a hypersensitivity/anaphylaxis AE: In the context of a response rate of CCI% to enable decisions on the benefit/risk, a lower reference value of CCI% and a target value (a desired signal to be observed) of CCI% for the discontinuation due to any AE rate and a lower reference value of CCI% and a target value of CCI% for the discontinuation due to a hypersensitivity/anaphylaxis AE rate was to be used to create a decision framework for the study (Frewer et al 2016).

At IA1 (CCI patients treated with 300 mg od savolitinib) it was considered that it may be futile to continue the study if there was CCI% probability for the discontinuation due to any AE rate to be below the target value (CCI%). This translated into observing CCI or more out of CCI patients; a discontinuation due to any AE rate of CCI% which has a 2-sided exact binomial CCI% confidence interval (CI) of CCI% to CCI%, wherein the lower confidence limit is above the chosen target value of CCI%. Additionally, as it was considered that a greater than CCI% probability for the discontinuation due to any AE rate to be below the lower reference value (CCI%) may be considered a good signal, this translated into observing CCI or fewer out of CCI patients discontinuing due to any AE. It was also considered that it may be futile to continue the study if there was CCI% probability for the discontinuation due to a hypersensitivity/anaphylaxis AE rate to be below the target value CCI%). This translated into

observing [redacted] or more out of [redacted] patients; a discontinuation due to a hypersensitivity/anaphylaxis AE rate of [redacted]% which has a 2-sided exact binomial [redacted]% confidence interval (CI) of [redacted]% to [redacted]%, wherein the lower confidence limit is above the chosen target value of [redacted]%. Additionally, as it was considered that a greater than [redacted]% probability for the discontinuation due to a hypersensitivity/anaphylaxis AE rate to be below the lower reference value ([redacted]%) may be considered a good signal, this translated into observing [redacted] or fewer out of [redacted] patients discontinuing due to a hypersensitivity/anaphylaxis AE.

Additionally, for IA1, once the first [redacted] patients treated with 300 mg od savolitinib had the opportunity to be treated for at least 6 weeks a predictive power calculation was to be used to assess the chance of observing a discontinuation due to any AE rate of [redacted]% [redacted] and a discontinuation due to a hypersensitivity/anaphylaxis AE rate of [redacted]% [redacted]. The method of calculating predictive power was based on a parameter-free approach to predictive power as it applies to variables that follow a binomial distribution (Jennison and Turnball 2000). Predictive power was to be recalculated after each patient's (in treatment order) outcome post 6 weeks of treatment was available. If, following the observation of any patient's outcome, predictive power fell below [redacted]%, the study could be stopped. Simulation methods were used to estimate the operating characteristics. When the true discontinuation due to any AE rates were [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]%, the expected sample sizes were [redacted] and [redacted] respectively. Thus, with this study design including Interim Analysis 1 and predictive power monitoring, given discontinuation due to any AE rates of [redacted]%, [redacted]%. [redacted]%, [redacted]% and [redacted]%, the probability to stop was [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]%, respectively. When the true discontinuation rates due to a hypersensitivity/anaphylaxis AE rates were [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]%, the expected sample sizes were [redacted], [redacted] and [redacted] respectively. Thus, with this study design including IA1 and predictive power monitoring, given discontinuation due to a hypersensitivity/anaphylaxis AE rates of [redacted]%, [redacted]%. [redacted]%, [redacted]% and [redacted]%, the probability to stop was [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]%, respectively.

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

Futility Analysis:

A futility analysis for the savolitinib + placebo arm is planned after [redacted] patients have been randomised under CSP version 7.0 and have had an opportunity to have 2 postbaseline scans.

9.3 Populations for analyses

For purposes of analysis, the following populations are defined:

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

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

Patients will be assigned to each of these populations and to the diagnostic populations (centrally confirmed by FISH [FISH5+, FISH10+] and centrally confirmed by IHC [IHC50+, IHC90+]), prior to any analyses being performed.

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

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

The SAF will be used for reporting efficacy of savolitinib 300 mg od + osimertinib in FISH5+ and/or IHC50+ patients (primary endpoint population). The SAF will also be used as the population for reporting efficacy and to summarise baseline characteristics for patients dosed prior to CSP version 7.0. The Safety Analysis Set (SAF) will be used as the population for reporting safety for patients dosed under all CSP versions.

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

9.4 Statistical analyses

9.4.1 General considerations

Analyses will be performed by AstraZeneca or its representatives. A comprehensive SAP will be developed and will describe the patient populations to be included in the analyses and procedures for accounting for missing, unused and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the clinical study report.

Descriptive statistics will be used for all variables. 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.

Analyses will be presented by the assigned starting dose (300 mg od savolitinib, 300 mg bid savolitinib and 600 mg od savolitinib in combination with osimertinib, or 300 mg bid savolitinib as monotherapy [savolitinib + placebo]).

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

9.4.2 Stratification factor(s)

There is one stratification factor of baseline brain metastases (Yes/No) in the randomised part of the study under CSP version 7.0. The stratification in the statistical analyses will be based

on the baseline brain scan assessed by the investigator using the values entered in the IWRS at randomisation, even if it is subsequently discovered that these values were incorrect.

9.4.3 Efficacy analyses

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 Version 1.1. It will be used to determine the endpoints PFS, ORR, 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 Not Evaluable (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 + placebo is required prior to cross over to savolitinib plus osimertinib.

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

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.

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

9.4.3.1 Analysis of the primary endpoints

The ORR will be defined as a visit response of CR or PR, with the denominator defined as subset of all dosed patients with measurable disease at baseline. For ORR, a visit response of CR or PR must be confirmed by a later scan conducted at least 4 weeks after the initial response is observed.

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.

For the analyses of the primary endpoint of savolitinib 300 mg bid + osimertinib, ORR and its associated CIs will be provided, and compared with the historical reference platinum-pemetrexed chemotherapy ORR of approximately [redacted]%. Summaries will be produced that present the number and percentage of patients with a tumour response (CR/PR).

For the analyses of the primary endpoint of savolitinib 300 mg od + osimertinib, ORR and its 95% CI (Clopper-Pearson) will be summarised and will be analysed using an exact binomial test against the null H_0: ORR=[redacted]% at the 2-sided significance level of α=0.05. Summaries will be produced that present the number and percentage of patients with a tumour response (CR/PR).

Analyses for the primary endpoint of savolitinib 300 mg bid + osimertinib in FISH10+ and/or IHC90+ patients who have progressed following treatment with 1L osimertinib will be summarised using the TPAS. Analyses for the primary endpoint of savolitinib 300 mg od + osimertinib regimen in FISH5+ and/or IHC50+ patients who have progressed following treatment with osimertinib will be summarised using the SAF. See Section 9.3 for analysis set definitions.

ORR will also be analysed as a secondary endpoint based on the BICR assessment of disease progression by RECIST 1.1 (see Section 9.4.3.2).

9.4.3.2 Analysis of the secondary endpoints

Analyses for the efficacy secondary endpoints will be summarised using the TPAS, CAS, and SAF datasets (see Section 9.3 for analysis set definitions).

Objective response rate

To describe the difference in the efficacy of savolitinib (300 mg bid) in combination with osimertinib and savolitinib (300 mg bid) in combination with placebo in patients with EGFRm+, MET amplified/overexpressed (FISH10+ and/or IHC90+), locally advanced or metastatic NSCLC who have progressed following treatment with 1L osimertinib therapy under CSP version 7.0, ORR with 95% confidence intervals will be constructed in the CAS for:

- Osimertinib + savolitinib (300 mg bid)
- Placebo to osimertinib + savolitinib (300 mg bid)

Additional details for the analysis of ORR on other dosing regimen/lines of therapy/biomarker population will be specified in the SAP.

Duration of response

The DoR will be defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression (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 patients will be produced and appropriate descriptive summary statistics will be presented (n, number of responses that have progressed, median, quartile, minimum and maximum DoR).

Progression-free survival

PFS is defined as the time from randomisation (patients recruited under CSP version 7.0) or start of treatment (patients recruited prior to CSP version 7.0) until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from 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.

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.

Summaries of PFS (n, events, medians, quartiles, proportion progression free at CCI months and corresponding 95% CIs) and Kaplan-Meier plots will be provided by treatment group.

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

Overall survival

OS is defined as the time from randomisation (patients recruited under CSP version 7.0) or the start of treatment (patients recruited prior to CSP version 7.0) until death due to any cause. 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 every 12 weeks. Patients should be contacted in the week after data cut-off for each analysis to establish survival status. The impact of cross over on OS may need to be assessed depending on the number of patients crossing over to savolitinib plus osimertinib. Further details will be provided in the SAP.

Summaries of OS (n, events, medians, quartiles, proportion alive at 12 and 15 months and corresponding 95% CIs) and a Kaplan-Meier plot will be provided.

9.4.3.3 EORTC QLQ-C30 and QLQ-LC13

Symptoms and overall quality of life will be assessed using EORTC QLQ-C30 and QLQ-LC13 (secondary endpoints). Questionnaires will be scored according to published guidelines or the developer's guidelines, if published guidelines are not available. Analyses will be summarised using the TPAS, the CAS and the SAF (see Section 9.3 for analysis set definitions). Further details of the statistical analyses will be given in the SAP.

The QLQ-C30 consists of 30 questions, which can be combined to produce 5 functional scales (Physical, Role, Cognitive, Emotional, Social), 3 symptom scales (Fatigue, Pain, Nausea/vomiting), 5 individual items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea) and a global measure of health status. The QLQ-LC13 is a lung cancer specific module comprising 13 questions to assess lung cancer symptoms (cough, haemoptysis, dyspnoea and site-specific pain), treatment related side-effects (sore mouth, dysphagia, peripheral neuropathy and alopecia) and pain medication. With the exception of a multi-item scale for dyspnoea, all are single items. The dyspnoea scale will only be used if all 3 items have been scored, otherwise the items are treated as single-item measures.

An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales/symptom items, the functional scales and the global health status/QoL scale

in the QLQ-C30 and for each of the symptom scales/items in the QLQ-LC13 according to the EORTC QLQ-C30 Scoring Manual and EORTC QLQ-LC13 instructions.

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

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

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

Definition of clinically meaningful changes

Changes in score compared to baseline will be evaluated. A minimum clinically meaningful change is defined as a change in the score from baseline of ≥10 for scales/items from the QLQ-LC13 and the QLQ-C30 (Osoba et al 1998).

For example, a clinically meaningful deterioration or worsening in chest pain (as assessed by QLQ-LC13) is defined as an increase in the score from baseline of ≥10. A clinically meaningful improvement in fatigue (as assessed by QLQ-C30) is defined as a decrease in the score from baseline of ≥10.

At each post-baseline assessment, change in symptoms/functioning from baseline will be categorised as improved, stable or worsening as shown in Table 14.

Table 14 Visit Response for HRQoL and disease-related symptoms

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

Time to symptom deterioration

Time to deterioration in symptoms, functioning and global health status/QoL will be evaluated, more details will be specified in the SAP.

Symptom improvement rate

Improvement in symptoms, functioning and global health status/QoL will be evaluated, more details will be specified in the SAP.

9.4.4 Safety analyses

The SAF will be used as the population for reporting safety for patients dosed under all CSP versions (see Section 9.3 for analysis set definitions).

Safety and tolerability will be assessed in terms of AEs, deaths, laboratory data, vital signs, ECG data and ECOG performance status.

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code AEs. AEs 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 and preferred term. 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 and preferred term. SAEs will be summarised separately if a sufficient number occur.

Any AE occurring before the first dose of study drug will be included in the data listings but will not be included in the summary tables of AEs. AE summary tables will include only treatment-emergent adverse events. AEs will be defined as treatment emergent if they have an onset, or worsen (by investigator report of a change in intensity), during the study treatment period (defined from date of first dose of any study treatment to date of last dose of any study treatment) or safety follow-up period (28 days [±7 days] after last dose of study treatment).

Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of IP) will be flagged in the data listings.

Discontinuation rate due to AEs will be summarised for the first 6 weeks and at any time.

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

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.

Any AE occurring within the defined 28-day follow-up period after discontinuation of study drug will be included in the AE summaries. AEs occurring after the 28-day follow-up period after discontinuation of study drug or after starting subsequent anti-cancer therapy will be listed separately, but not included in the summaries.

Duration of exposure will be summarised. The number and percentage of patients with at least 1 dose interruption/dose delay and at least 1 dose reduction will also be summarised separately for the first 6 weeks and at any time.

Haematology, clinical chemistry, coagulation, urinalysis, vital signs and ECG data will be listed individually by patient and suitably summarised. For all laboratory variables, which are included in the current version of CTCAE, the CTCAE grade will be calculated.

Details of any deaths will be listed for all patients.

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

9.4.5 Pharmacokinetic analyses

PK analyses of the plasma concentration data for osimertinib, savolitinib and their metabolites (AZ5104 for osimertinib; M2 and M3 for savolitinib) will be performed by QCP, AstraZeneca or a delegate on behalf of QCP. The actual sampling times will be used in the parameter calculations and PK parameters will be derived using standard non-compartmental methods.

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

- After single dosing: plasma concentration at 1 hour (C_{1h}) and 3 hours (C_{3h}) post-dose.
- After multiple dosing at Cycle 3 Day 1: plasma concentration pre-dose ($C_{pre\text{-}dose}$), and at C_{1h}, C_{3h}, C_{4h} and C_{6h} post-dose.
  AUCss, Cssmax, Cssmin, tssmax, CLss/F, Vss/F and t1/2 (if applicable) will be calculated for savolitinib, osimertinib and its metabolites, if applicable.

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

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

Where possible, the appropriate PK parameters will also be determined for the metabolites of osimertinib and savolitinib.

9.4.6 Other analyses

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

ctDNA 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 osimertinib and savolitinib will be determined.

CCI [redacted]

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.

CCI [redacted]

Handling of missing data will be described in the SAP.

CCI

CCI

CCI

Other pharmacogenetics and biomarker analysis may be presented separately from the main CSR.

Patient Reported Outcome version of the CTCAE data will be presented using descriptive statistics and further details will be provided in the SAP.

PGIS data will be presented using descriptive statistics. Further details will be provided in the SAP.

EQ-5D-5L data, including domain responses, VAS and utility score will be presented using descriptive statistics. Further details will be provided in the SAP.

The efficacy of savolitinib plus osimertinib and savolitinib plus placebo, respectively, on CNS metastases in patients with CNS metastases at baseline will be presented using descriptive statistics. Further details will be provided in the SAP.

The efficacy of savolitinib plus osimertinib and savolitinib plus placebo, respectively, on the prevention of CNS metastases in patients without CNS metastases at baseline will be presented using descriptive statistics. Further details will be provided in the SAP.

9.5 Interim, futility, primary, and final analyses

The study has 5 planned analyses.

Interim analysis 1 was planned and performed after approximately CCI patients treated with osimertinib (80 mg od) and savolitinib (300 mg od) had the opportunity of being treated for at least 2 post-baseline scans (12 weeks) or the CCI patient treated with osimertinib (80 mg od) and savolitinib (300 mg od) had the opportunity to be treated for 6 weeks, whichever was the later. To evaluate the safety and tolerability of savolitinib in combination with osimertinib, continuous monitoring and assessment of the discontinuation due to AE rate and the discontinuation due to a hypersensitivity/anaphylaxis AE rate was to be performed after the CCI patient treated with osimertinib (80 mg od) and savolitinib (300 mg od) had the opportunity to be treated for 6 weeks up to IA1.

Interim analysis 2 was planned and performed to provide more efficacy data in post 1L patients that was not available in IA1, after approximately CCI post 1L patients treated with osimertinib (80 mg od) and savolitinib (300 mg od) had the opportunity to be treated for 2 post-baseline scans (12 weeks).

A futility analysis for the savolitinib + placebo arm is planned after CCI patients have been randomised under CSP version 7.0 and have had an opportunity to have 2 post-baseline scans. The futility rule is defined as no responses observed among the first CCI randomised savolitinib + placebo arm patients who have had the opportunity for 2 post-baseline scans.

- CCI
- CCI
- CCI

Recruitment will not be paused during the futility analysis. If the decision is made that treatment with savolitinib + placebo is futile, further enrolment into the savolitinib + placebo arm will be stopped, all randomised patients will be unblinded, and those randomised to savolitinib + placebo will be given the opportunity to cross over to savolitinib + osimertinib (see Section 4.1.2). Recruitment to the savolitinib + osimertinib arm will continue regardless of the results of futility analysis until the planned sample size for the savolitinib + osimertinib arm is reached.

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

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

The SAP will describe the interim and final analyses in greater detail.

9.6 Data Monitoring Committees

An independent data monitoring committee (IDMC) will meet to assess the futility of the savolitinib 300 mg bid + placebo arm after CCI patients have been randomised under CSP version 7.0 and have an opportunity to have 2 post-baseline scans. The IDMC will also review at this time the safety data of the randomised patients recruited under CSP version 7.0 for both arms (Appendix A 5). More details are provided in the IDMC charter.

CCI (Appendix A 5).

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 protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, investigator's brochure, 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 revised protocol 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.

The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a 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 utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure or state other documents and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches of Protocol or GCP

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A "serious breach" means a breach likely to affect to a significant degree the safety and rights of a patient or the reliability and robustness of the data generated in the clinical trial.
- AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators.
  - Where the EU Clinical Trials Regulation 536/2014 applies, AstraZeneca has in place processes to enter details of serious breaches into the European Medicines Agency Clinical Trials Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
- The investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

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 1 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. Patients or their legally authorised will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) 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 and time 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.

If a patient declines to participate in any voluntary exploratory genetic 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 patients' 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 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 the use of remaining mandatory samples for optional exploratory research. The investigator or authorised designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The patient will give a separate agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will indicate this in the ICF. If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, within a reasonable

timeframe, and the action documented. If samples already have been analysed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

A 4 Data protection

- Patients will be assigned a unique identifier by AstraZeneca. Any patient records or datasets that are transferred to AstraZeneca 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 their personal study-related data will be used by AstraZeneca 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 their medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by AstraZeneca, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The patient must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our business activities and will not make personal data available to anyone (including internal staff) who is not authorised or does not have a business need to know the information.
- The patient must be informed that in some cases their data may be pseudonymised. The General Data Protection Regulation (GDPR) defines pseudonymisation as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

Personal Data Breaches

A ‘personal data breach’ means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored or otherwise processed.

- In compliance with applicable laws, the Data Controller[1] for the processing activity where the personal data breach occurred (AstraZeneca or respectively the site), will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.

[1] The Data Controller determines the purposes for which and the means by which personal data is processed, as defined by the European Commission.

- Whilst AstraZeneca has processes in place to deal with personal data breaches it is important that investigators that work with AstraZeneca have controls in place to protect patient data privacy.

The investigator should have a process in place to ensure that:

- Site staff or service providers delegated by the investigator/institution are allowed to identify the occurrence of a (potential) personal data breach.
- Any (potential) personal data breach is promptly reported to AstraZeneca or delegated party, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

AstraZeneca and the site must demonstrate that they:

- have taken all necessary steps to avoid personal data breaches and
- have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (eg, applying encryption, maintaining and keeping systems and IT security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).
- where possible, have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.
- where it has not been possible to develop an internal data breach reporting and investigation process, the site follows AstraZeneca's instructions.

Notification of personal data breach to patients:

- notification to patients is done by the site for the data breaches that occurred within the processing activities for which the site is the Data Controller and for data breaches that occurred within the processing activities of AstraZeneca as the Data Controller, the notification is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of AstraZeneca, so that AstraZeneca has no access to the identifying personal information of the patients. The site and/or Principal Investigator shall conduct the notification by contacting the patients using the information that they gave for communication purposes in clinical research.
- If a personal data breach occurs in a processor's systems, engaged by AstraZeneca, the processor under contractual obligations with AstraZeneca promptly and in due course after discovering the breach notifies AstraZeneca and provides full cooperation with the investigation. In these cases, to the extent AstraZeneca is the Data Controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to patients. If the personal data breach needs to be notified to the patients, the notification to patients is done in collaboration with the

site and is performed by the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the patients.

- If a personal data breach involving an AstraZeneca representative's device (e.g., Study Monitor laptop), the AstraZeneca representative will provide AstraZeneca with all of the information needed for notification of the breach, without disclosing data that allows AstraZeneca directly or indirectly to identify the patients. The notification will be done by AstraZeneca solely with the information provided by the Study Monitor and in no event with access to information that could entail a risk of re-identification of the patients. If the data breach must be notified to the data subjects, the notification will be done directly by the Study Monitor in collaboration with the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the patients. The contract between AstraZeneca and the Study Monitor shall expressly specify these conditions.
- The contract between the site and AstraZeneca for performing the clinical research includes the provisions and rules regarding who is responsible for coordinating and directing the actions in relation to the breaches and performing the mandatory notifications to authorities and patients, where applicable.

A 5 Committees structure

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the Clinical Study Protocol and letters to investigators.

An IDMC will meet to assess the futility of the savolitinib 300 mg bid + placebo arm after CCI patients have been randomised under CSP version 7.0 and have had an opportunity to have 2 post-baseline scans. The IDMC will also review at this time the safety data of the randomised patients recruited under CSP version 7.0 for both arms. More details are provided in the IDMC charter.

In addition, CCI [redacted]

A 6 Dissemination of clinical study data

Any results both technical and lay summaries for this study, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons as otherwise statistical analysis is not relevant.

A description of this clinical trial will be available on http://astrazenecaclinicaltrials.com, http://www.clinicaltrials.gov and https://euclinicaltrials.eu, as will the summary of the main study results when they are available. The clinical trial 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 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, including definition of study-critical data items and processes (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 included in the Monitoring Plan.

AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Monitoring Plan.

AstraZeneca or designee is responsible for the data management of this study including quality checking of the data.

AstraZeneca assumes accountability for actions delegated to other individuals (eg, CROs).

Study monitors will perform ongoing source data verification as per the Monitoring Plan 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 protocol 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 a minimum of 25 years after study archiving or as required

by local regulations, according to the AstraZeneca Global Retention and Disposal (GRAD) Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

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 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.

Definitions of what constitutes source data can be found in the Source Data Verification Plan.

A 9 Study and site closure

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

The first subject pre-screening visit is considered the first act of recruitment 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 protocol, 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(s) 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.

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 multicentre 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 event definitions and additional safety information

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 treatment has been administered.

B 2 Definitions of serious adverse event

A serious adverse event 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.

B 3 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).

B 4 Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, 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.

B 5 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

B 6 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.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 7 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 judgement. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as ‘not related’.

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

B 8 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP 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 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 e.g., 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 e.g., tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g., kept in the refrigerator when it should be at room temperature
- Wrong patient received the medication (excluding interactive response technology [IRT]/randomization and trial supply management [RTSM] errors)
- Wrong drug administered to patient (excluding IRT/RTSM errors)

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

- Errors related to or resulting from IRT/RTSM - including those which led 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.

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the data entry site (DES) using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study patient or if the drug abuse involves a person not enrolled in the study (such as a relative of the study patient).

Examples of drug abuse include but are not limited to:

- The drug used with the intent of getting a perceived reward (by the study patient or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study patient) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study patient or if the drug misuse regards a person not enrolled in the study (such as a relative of the study patient).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study patient feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

Appendix C Handling of human biological samples

C 1 Chain of custody of biological samples

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).

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

AstraZeneca 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 AZ-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire 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, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological sample(s) is an integral part of the study, then the patient is withdrawn from further study participation.

The investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca.
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented.
- Ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

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:

- are to be packed and shipped in accordance with IATA Instruction 602.

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, B, C, D, and E viruses, Human immunodeficiency virus types 1 and 2. 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 - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient
- temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are patient to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk

of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix D Genetics optional genomics initiative sample

D 1 Use/analysis of DNA

Genetic variation may impact a patient's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting patients.

AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect CCI

Genetic research may lead to CCI

Genetic research may consist of the analysis of the structure of the patient´s DNA, ie, the entire genome.

The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on study treatments of this class or indication continues but no longer than 15 years or other period as per local requirements.

D 2 Genetic research plan and procedures

Selection of genetic research population

Study selection record

All patients will be asked to participate in this genetic research. Participation is voluntary and if a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

Inclusion criteria

For inclusion in this genetic research, patients must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol and: Provide informed consent for the genetic sampling and analyses.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Withdrawal of consent for genetic research

Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7 of the main Clinical Study Protocol.

Collection of samples for genetic research

The blood sample for genetic research will be obtained from the patients at screening. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an AE, such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at screening, it may be taken at any visit until the last study visit. Only 1 sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Central Laboratory Manual.

Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years, from the date of last patient last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the blood either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).

The link between the patient enrolment code (E-code) and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant DNA samples for

analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in A 1.

Informed consent

The genetic component of this study is optional and the patient may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the patient must indicate their consent to donate an optional extra sample in the main study consent form. A copy of the signed and dated consent form must be given to the patient and the original filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely withdraw from the genetic aspect of the study at any time.

Patient data protection

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician unless required to do so by law.

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

Data management

Any genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyse the samples.

AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health related research purposes. Researchers may see summary results but they will not be able to see individual patient data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical methods and determination of sample size

The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan may be prepared where appropriate.

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 Potential Hy's Law and Hy's Law 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 all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT **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 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 ≥3×ULN **together with** TBL ≥2×ULN at any point during the study following the start of study intervention irrespective of an increase in alkaline phosphatase.

Hy's Law

AST or ALT ≥3×ULN **together with** TBL ≥2×ULN, where no other reason, other than the study intervention, can be found to explain the combination of increases, eg, elevated alkaline phosphatase 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 ≥3×ULN
- AST ≥3×ULN
- TBL ≥2×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 1 day of PHL criteria being met, the investigator will report the case as an SAE of PHL; serious criterion "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 3 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 a 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 PHL 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 PHL, (report term now "Hy's Law case") ensuring causality assessment is related to study intervention and seriousness criterion 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 patient's 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 of this Appendix.

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 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.

E 8 Laboratory Tests

Hy's Law lab tests suggested for local laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc
	HBsAg HCV DNA[a] IgM and IgG anti-HCV HCV RNA[a] IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate-deficient transferrin[b]

Autoimmune hepatitis	Antinuclear antibody Anti-liver/kidney microsomal antibody Anti-smooth muscle antibody
Metabolic diseases	Alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin[b] Transferrin saturation

CMV=cytomegalovirus; DNA=deoxyribonucleic acid; EBV=Epstein-Barr virus; GGT=gamma glutamyl transferase; HAV=hepatitis A virus; HBc=hepatitis B core antigen; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HEV=hepatitis E virus; HSV=herpes simplex virus; IgG=immuno-globulin G; IgM=immuno-globulin M; INR=international normalised ratio; LDH=lactate dehydrogenase; RNA=ribonucleic acid.

[a] HCV RNA; HCV DNA are only tested when IgG anti-HCV is positive or inconclusive.

[b] Carbohydrate-deficient transferrin and transferrin are not available in China. Study teams should amend this list accordingly.

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; 1994:253-256.

Appendix G Definition of women of childbearing potential and acceptable contraceptive methods

Definition of Women of Childbearing Potential

Women of Childbearing Potential (WoCBP):

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

Women NOT of Childbearing Potential:

Women who are permanently or surgically sterilised or 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 trials as if they are of WoCBP (eg, undergo pregnancy testing etc, as required by the study protocol).
- Women will be considered post-menopausal if they are amenorrheic 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 amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range.
- Women aged 50 years or more will be considered post-menopausal if they have been amenorrheic 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 (IUD) - provided coils are copper-banded, plus male condom
- Intra-uterine system (IUS) 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 trials:

- Triphasic combined oral contraceptives (COCs)
- All progesterone only pills except, Cerazette
- All barrier methods, if intended to be used alone
- Non-copper containing Intra-Uterine Devices (IUDs)
- Fertility awareness methods
- Coitus interruptus

Appendix H Guidelines for evaluation of objective tumour response using RECIST 1.1

H 1 Introduction

This appendix details the implementation of RECIST 1.1 guidelines (Eisenhauer et al 2009) for the study with regards to investigator assessment of tumour burden including protocol-specific requirements for this study.

H 2 Definition of measurable, non-measurable, target and non-target lesions

At least 1 lesion, not previously irradiated, not biopsied during the screening period, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short access ≥15 mm) with CT or MRI which is suitable for accurate repeated measurements.

H 2.1 Measurable lesions

A lesion, not previously irradiated and not chosen for biopsy during the screening period that can be measured accurately at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have a short axis ≥15 mm) with CT or MRI and which is suitable for accurate repeated measurements.

H 2.2 Non-measureable lesions

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis at baseline. Nodes with <10 mm short axis are considered non-pathological and should not be recorded as non-target lesions (NTLs).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that are not measurable by CT or MRI.
- Previously irradiated lesions as localised post-radiation changes, which affect lesion sizes, may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and should be selected as NTLs at baseline and followed up as part of the NTL assessment
- Skin lesions assessed by clinical examination
- Lesions biopsied within the screening period
- Brain metastasis

H 2.3 Special cases

- 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 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 non-cystic lesions should be selected as the target lesions (TLs).

H 2.4 Target lesions

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as TLs at baseline.

H 2.5 Non-target lesions

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline.

H 3 Methods of assessment

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up.

The methods to be used for RECIST assessment are summarised in Table 15 and those excluded for tumour assessments in this study are discussed below, with the rationale provided.

Table 15 Summary of methods of assessment (RECIST)

Target lesions	Non-target lesions	New lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Plain X-ray (includes chest X-ray)	Plain X-ray (includes chest X-ray)
		Bone scan (scintigraphy)
		FDG-PET

CT Computed tomorgraphy; FDG-PET Fluorodeoxyglucose-positron emission tomography; MRI Magentic resonance imaging; RECIST Response Evaluation Criteria in Solid Tumours.

H 3.1 CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TLs selected for response assessment and to assess NTLs and identification of new lesions.

In this study it is recommended that CT examinations will be used to assess tumour burden at baseline and then every 6 weeks (±7 days) relative to the start of treatment until Cycle 7 then every 8 weeks until objective radiological progression or withdrawal from the study. CT examination with intravenous contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For assessment of brain lesions MRI is the preferred method.

H 3.2 Clinical examination

Clinical examination will not be used for assessment of TLs. Clinically detected lesions can be selected as TLs if they are then assessed by CT or MRI scans. Clinical examination can be used to assess NTLs in patients that also have other lesions assessable by CT, MRI or plain X-ray and to identify the presence of new lesions.

H 3.3 X-rays

H 3.3.1 Plain X-ray

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

H 3.3.2 Chest X-rays

Chest X-rays will not be used for assessment of TLs as they will be assessed by CT or MRI examination. Chest X-rays can, however, be used to assess NTLs and to identify the presence of new lesions.

H 3.4 Ultrasound

Ultrasound examination will not be used for assessment of TLs and NTLs as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is patient and operator dependent. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

H 3.5 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 3.6 Tumour markers

Tumour markers will not be used for tumour response assessments per RECIST 1.1.

H 3.7 Cytology and histology

Histology will not be used as part of the tumour response assessments per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumour has met criteria for response or stable disease. In such circumstances, the cytology is necessary to differentiate between response/stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or the appearance of a clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTLs or disease progression due to new lesions.

H 3.8 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 will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and X-ray is recommended where bone scan findings are equivocal.

H 3.9 FDG-PET

FDG-PET (fluorodeoxyglucose positron emission tomography) scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake (defined as when an uptake greater than twice that of the surrounding tissue is observed) not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

H 4 Tumour response evaluation

H 4.1 Schedule of evaluation

Baseline tumour assessments should include CT/MRI of lung and abdomen (including liver and adrenal glands) and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed no more than 28 days before the start of study treatment. CT/MRI scan of the brain should be performed in patients with known or suspected brain metastases. Follow-up assessments should be performed every 6 weeks (±7 days) after the start of treatment for the first 6 cycles then every 8 weeks (±7 days) until objective disease progression as defined by RECIST 1.1 or withdrawal of consent. Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

H 4.2 Target lesions

H 4.2.1 Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), 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, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimetres. 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 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.
- 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 TL splits into 2 or more parts, then record the sum of the diameters of those parts.
- If 2 or more TLs merge, then the sum of the diameters of the combined lesion should be recorded for 1 of the lesions and 0 mm recorded for the other lesion(s).

- 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.
- When a TL has had any intervention eg, radiotherapy, embolisation, surgery etc, during the study, the size of the TL should still be provided where possible.

H 4.2.2 Evaluation of target lesions

Table 16 provides the definitions of the criteria used to determine objective tumour visit response for TLs.

Table 16 Overall visit response for 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 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 shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Progressive disease (PD)	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
Not evaluable (NE)	Only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response.

CR Complete response; PD Progression of disease; PR Partial response; NTL Non-target lesion; TL Target lesion.

H 4.3 Non-target lesions

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. Table 17 provides the definitions of the criteria used to determine and record overall response for NTLs at the investigational site at each visit.

Table 17 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.

CR Complete response; PD Progression of disease; NTL Non-target lesion; TL Target lesion.

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 stable disease or PR in TLs, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest ‘increase’ in the size of 1 or more NTLs is usually not sufficient to qualify for unequivocal progression status.

H 4.4 New lesions

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

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

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

If a new lesion is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

H 4.5 Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective evidence of disease progression at that time will continue to be followed until objective disease progression by RECIST 1.1 or withdrawal of consent.

H 4.6 Evaluation of overall visit response and best overall response

The overall visit response will be derived using the algorithm shown in Table 18.

Table 18 Overall visit response

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

CR Complete response, SD Stable disease, PD Progression of disease, PR Partial response, NE Not evaluable, NA Not applicable (only relevant if there were no target lesions/non-target lesions at baseline, however at least one target lesion is an entry criterion for the study).

H 5 Specifications for radiological imaging

These notes are recommendations for use in clinical studies. The use of standardised protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

H 5.1 CT scan

CT scans of the chest and abdomen (including liver and adrenal glands) should be contiguous throughout all the anatomical regions of interest.

The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST 1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

Anatomic coverage

Optimal anatomic coverage for most lung tumours is the chest and abdomen (including liver and adrenal glands). 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. The brain should be imaged by MRI or CT in patients with known or suspected brain lesions. 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.

Intravenous contrast administration

Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of intravenous contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient.

It is very important that the same technique be used at baseline and on follow-up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of TLs on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study, then the recommended methods are: CT thoracic examination without

contrast and abdominal and pelvic MRI with contrast. If MRI cannot be performed then CT without intravenous contrast is an option for the thorax, abdomen and pelvic examinations. For assessment of brain lesions MRI is the preferred method however CT is acceptable in this study.

Slice thickness and reconstruction material

It is recommended that CT scans be performed at 5 mm contiguous slice thickness and this guideline presumes a minimum 5 mm thickness in recommendations for the measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline 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 TLs should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not "selected" images of the apparent lesion.

H 5.2 MRI scan

MRI has excellent contrast, spatial and temporal resolution; 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. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium-enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the specific body part being imaged as well as the scanner utilised. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

For these reasons, CT is the imaging modality of choice.

H 5.3 FDG-PET scans

FDG-PET has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. If FDG-PET scans are included in a protocol, an FDG uptake period of 60 min prior to imaging has been decided as the most appropriate for imaging of patients with malignancy. Whole-body acquisition is important since this allows for sampling of all areas of interest and can assess if new lesions have appeared thus determining the possibility of

interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 min post injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and serial scans in the clinical trial.

H 5.3.1 PET/CT scans

At present, low dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted 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 is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET–CT can be used for RECIST measurements. However, this is not recommended because the PET portion of the CT introduces additional data that may bias an investigator if it is not routinely or serially performed.

Appendix I Dose modifications for the management of adverse events

I 1 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 dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines.

If a toxicity resolves or reverts to ≤ CTCAE Grade 2 within 3 weeks of onset, treatment with osimertinib may be restarted at the same dose (80 mg) or a lower dose (40 mg) using the rules below for dose modifications (Table 19) 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 does not resolve to ≤CTCAE Grade 2 after 3 weeks, then the patient should be withdrawn from the study and observed until resolution of the toxicity (Table 20).

Table 19 Dose reduction for osimertinib to manage adverse events

	Starting osimertinib dose 80 mg
Reduced dose -1	40 mg

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.

Table 20 Osimertinib Dose Adjustment Information for Adverse Reactions

Target organ	Adverse reaction[a]	Dose modification
Pulmonary	ILD/pneumonitis	Permanently discontinue osimertinib
Cardiac	QTc interval > 500 msec on at least 2 separate ECGs	Withhold osimertinib until QTc interval is < 481 msec or recovery to baseline if baseline QTc is ≥ 481 msec within 3 weeks of interruption, then restart at a reduced dose (40 mg) or at 80 mg (at the discretion of the investigator), to allow for situations where causality in relation to osimertinib may be difficult to determine).
	QTc interval prolongation with signs/symptoms of serious arrhythmia, symptomatic congestive heart failure	Permanently discontinue osimertinib
Other	Grade ≥ 3 adverse reaction	Withhold osimertinib for up to 3 weeks
	If Grade ≥ 3 adverse reaction improves to Grade 0 – 2 after withholding osimertinib for up to 3 weeks	Osimertinib may be restarted at the same dose (80 mg) or at a lower dose (40 mg)
	Grade ≥ 3 adverse reaction that does not improve to Grade 0 – 2 after withholding osimertinib for up to 3 weeks	Permanently discontinue osimertinib

[a] The intensity of the clinical adverse events graded by the NCI CTCAE version 5.0.
CTCAE Common Terminology Criteria for Adverse Events; ECG Electrocardiogram; ILD Interstitial lung disease; NCI National Cancer Institute.

I 1.1 ILD/Pneumonitis-like toxicity

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormality suggestive of ILD is observed, an interruption in study treatment 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 computed tomography (HRCT), blood and sputum culture, haematological parameters) will be captured by eCRF. All image data should be provided to AstraZeneca. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of interstitial lung disease should be considered and study treatment permanently discontinued.

I 1.2 QTcF prolongation

In light of the potential for QT changes associated with osimertinib, and in accordance with good clinical practice, it is recommended that correction of clinically significant electrolyte

abnormalities (hypokalaemia, hypomagnesaemia, hypocalcaemia) to within normal ranges takes place prior to first dose and during study treatment with osimertinib.

Table 21 Dose Modifications for Osimertinib-Related QTc Prolongation

NCI CTCAE version 5 toxicity grade	Action
Grade 0, 1, or 2	None
Grade 3 • Patients with QTcF prolongation to > 500 msec on at least 2 separate ECGs	Hold dosing and follow algorithm below • 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. Restart drug at a reduced dose of 40 mg or at the same dose 80 mg at the discretion of the investigator
• If the toxicity does not resolve to QTcF < 481 msec within 21 days	• Discontinue osimertinib and consult with a cardiologist for further management as clinically indicated
Grade 4 • QTcF ≥ 501 or > 60 msec change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	• Discontinue osimertinib and consult with a cardiologist for further management as clinically indicated

CTCAE = Common Terminology Criteria for Adverse Events; ECG = Electrocardiogram; NCI = National Cancer Institute; QTcF = QT corrected according to Fridericia's formula.

I 1.3 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 1.4 Erythema Multiforme and Stevens-Johnson syndrome

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

I 1.5 Changes in cardiac contractility

Based on the available clinical trial data, a causal relationship between effects on changes in cardiac contractility and osimertinib has not been established. In patients with cardiac risk factors and those with conditions that can affect left ventricular ejection fraction (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 1.6 Permanent discontinuation due to toxicity

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

I 1.7 Aplastic anaemia

Rare reports of aplastic anaemia have been reported in association with osimertinib treatment. Some cases had a fatal outcome. Before initiating treatment, patients should be advised of signs and symptoms of aplastic anaemia including but not limited to persistent fever, bruising, bleeding, and/or pallor. If signs and symptoms suggestive of aplastic anaemia develop, close patient monitoring and drug interruption or discontinuation of osimertinib should be considered. Osimertinib should be discontinued in patients with confirmed aplastic anaemia.

I 2 Hepatitis B viral reactivation management guideline

In patients with resolved or chronic hepatitis B infection (inactive carrier state) or active controlled HBV infection on treatment with osimertinib:

- Recommend monthly monitoring of ALT/AST, HBV DNA levels and HBsAg (if negative at baseline)
- Where liver signs and symptoms of viral reactivation appear (HBV DNA levels exceeding 10-fold from baseline or ≥100 IU/ml (if baseline HBV DNA levels are undetectable) or conversion of HBsAg negative to positive):
    - Expert hepatologist/specialist oversight of the patient is required
    - Consider interruption or discontinuation of study treatment, based on risk-benefit assessment

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 2.4).

Dose reductions or holds are allowed as clinically indicated by the treating physician and in line with Table 22 and Table 23. 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 22.

Table 22 Dose reduction for savolitinib to manage adverse events

Starting savolitinib dose	300 mg bid	300 mg od	600 mg od
Reduced dose -1	CCI	CCI	CCI
Reduced dose -2	CCI	CCI	CCI

Note: Only 2 dose reductions of savolitinib are permitted.

I 3.2 Dose modifications due to savolitinib-related toxicity

Dose modification guidelines for general savolitinib-related toxicities are shown in Table 23 below. Appropriate and optimal treatment of the toxicity is assumed prior to considering dose modifications. Prior to discontinuation of savolitinib due to toxicities please consult with the study physician. Please see Section I 3.3 for hepatotoxicity management guidelines and Section I 3.4 for management of savolitinib specific toxicities including dermatologic toxicity, hypersensitivity, and QTc prolongation.

Table 23 Dose modifications for savolitinib-related toxicities

NCI CTCAE version 5.0 toxicity grade	Action
Grade 0, 1 or 2	None
Grade 3[a] • Grade 3 toxicity for ≤7 days. • Grade 3 toxicity for >7 days.	Hold dosing and follow algorithm below • Resume dosing at same dose or 1 reduced dose level (maximum of 2 dose reductions) as clinically appropriate[b] • Discontinue study drug
Grade 4 • Expected to be manageable/reversible with dose reduction • Not expected to be manageable/reversible with dose reduction	• Hold dose and consult with study medical monitor • Discontinue study drug
Recurrence of Grade 3 • Grade 3 toxicity for ≤7 days. • Grade 3 toxicity for >7 days.	• Resume dosing at same dose or 1 reduced dose level (maximum of 2 dose reductions) as clinically appropriate[b] • Discontinue study drug
Recurrence of Grade 4	Discontinue study drug

[a] Despite appropriate supportive care.

[b] Restart of savolitinib must follow the specific restart guidelines if the event includes symptoms of pyrexia, skin reactions, myalgia, arthralgia, or hypersensitivity, as per section I 3.4

No more than 2 dose reductions of savolitinib will be allowed for any patient. Patients requiring additional dose modifications due to toxicity will discontinue savolitinib.

I 3.3 Hepatoxicity management guideline

- Promptly evaluate patients with elevated LFTs during study treatment for alternative aetiologies and potential Hy's law criteria, and discontinue potential contributing concomitant medications or alternative causal agents, as well as anti-coagulants, if appropriate.
- 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 3.3.1 Dose modification due to drug-related hepatotoxicity

- Permanently discontinue drug if:
  - ALT or AST >8 × ULN with total bilirubin elevation above baseline or ULN, or
  - ALT or AST >5 × ULN for up to 1 week (<7 days) with total bilirubin elevation above baseline or ULN, following immediate withholding of savolitinib. 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 (total bilirubin >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 x ULN for > 2 weeks or 8 × ULN without total bilirubin elevation above baseline or ULN, repeat LFT testing twice a week for 1 week:
  - If improved to Grade 1 or baseline in 1 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 total bilirubin >1.5 × ULN, repeat LFT testing twice a week for 1 week:
  - If both ALT/AST and total bilirubin improved to Grade 1 or baseline in 1 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 total bilirubin >1 × ULN to 1.5 × ULN. Repeat LFT testing twice a week for 1 week:
  - If both ALT/AST and total bilirubin improve to normal range (< Grade1) or baseline in 1 week, resume at same dose with LFT testing twice a week for 6 weeks
  - If not, resume at reduced dose, (as per bullet 3 above).
- Continue dosing if ALT or AST >3 × ULN without total bilirubin 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 1 week
  - If improve to Grade 1 or baseline in 1 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 total bilirubin >1.5 × ULN
- Withhold dosing for recurrent ALT or AST >3 × ULN without total bilirubin elevation above baseline or ULN, repeat LFT testing twice a week for 1 week
  - If improve to Grade 1 or baseline in 1 week, resume at reduced dose with LFT testing every week for 6 weeks; if not, discontinue

I 3.4 Guidance for management of savolitinib specific toxicities

Dermatologic: A case of Stevens-Johnson syndrome (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.

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. If patients do need dose interruption, restarting savolitinib must be done under controlled conditions as per below. If the patient experiences an acute hypersensitivity or anaphylactic reaction, immediate intervention must be instituted and treatment with savolitinib should be permanently discontinued.

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 study treatment 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 (blood pressure, temperature, respiratory rate, heart rate, etc.) before administration of study drug, every 15 mins after savolitinib dosing for the 1st hour, every 30 mins for the next hour and hourly for a total of at least 4 hours.
  - 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.

QTC prolongation:

Table 24 Dose modifications for savolitinib-related QTc prolongation

NCI CTCAE version 5.0 Toxicity Grade	Action
Grade 0, 1, or 2	None
Grade 3 • Patients with QTcF prolongation to >500 msec on at least 2 separate ECGs	Hold dosing and follow algorithm below: • 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 and then restart drug at one reduced dose level

Table 24 Dose modifications for savolitinib-related QTc prolongation

NCI CTCAE version 5.0 Toxicity Grade	Action
• If the toxicity does not resolve to QTcF <481 msec within 21 days	• Discontinue study drug and consult with a cardiologist for further management as clinically indicated
Grade 4 • QTcF ≥501 or >60 msecs change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	• Discontinue study drug and consult with a cardiologist for further management as clinically indicated

CTCAE Common Terminology Criteria for Adverse Events; ECG Electrocardiogram; NCI National Cancer Institute; QTcF corrected QT interval using Fridericia's formulas.

I 3.5 Guideline for the Management of Overlapping Toxicities Between Osimertinib and Savolitinib

QTc Prolongation

QT prolongation is a recognised toxicity of osimertinib and savolitinib; management of this toxicity is summarised in Table 25.

Table 25 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 within 21 days of onset, then restart osimertinib at a reduced dose of 40 mg. Dose may be resumed at 80 mg at the discretion of the investigator if the event of QTc interval is considered to be non-related to osimertinib treatment	• 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 a 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

CTCAE Grade	Instructions for osimertinib	Instructions for savolitinib	Further investigation required
	• 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; QTcF QT interval calculated using Fridericia's correction; TdP Torsades de Pointes.

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

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 (Section 1.1).

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.

Appendix J Guidance regarding potential interactions with concomitant medications

The use of any permitted concomitant medications must be recorded in the eCRF. Any investigational anti-cancer therapy, concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study must not be given concomitantly while the patient is on study intervention. Concurrent use of hormones for non-cancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable (eg, by local surgery or radiotherapy).

Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (mahuang), gingkobiloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 3 weeks prior to first dose of study drug (3 weeks for St. John's wort).

Based upon studies of in vitro liver microsomes and S9 fractions, savolitinib is metabolised by several metabolic enzymes, including both CYP450 enzymes (CYP3A4, CYP1A2) and some non-CYP enzymes (aldehyde oxidase, UDP-glucuronosyltransferases). Additionally, osimertinib is mainly metabolised by CYP3A4/5.

J 1 Drugs inducing CYP3A4 metabolism that AstraZeneca strongly recommend are not combined with osimertinib or savolitinib

Drug-drug interaction (DDI) studies of osimertinib or savolitinib evaluated in patients showed that there is potential for osimertinib or savolitinib being a victim when co-administered with strong inducers of CYP3A4 (osimertinib or savolitinib 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. Additionally, the use of moderate CYP3A4 inducers may be permitted with caution.

Table 26 Drugs inducing CYP3A4

Strong CYP3A4/5 inducers (should not be combined)	**Moderate CYP3A4/5 inducers (permitted with caution)**
Avasimibe, carbamazepine, enzalutamide, mitotane, nevirapine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, St John's Wort	semagacestat[a], talviraline[a], bosentan, efavirenz, etravirine, genistein, lersivirine, lopinavir, modafinil, nafcillin, thioridazine, tipranavir, ritonavir[b]

[a] Not available on the US market.

[b] Ritonavir has dual effects of simultaneous CYP3A inhibition and induction; the net pharmacokinetic outcome during

chronic ritonavir therapy is inhibition of CYP3A activity.
CYP = Cytochrome P450.

This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to be strong inducers of CYP3A4. Appropriate medical judgement 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 27 Drugs inhibiting CYP1A2

Contraindicated drugs	Withdrawal period prior to savolitinib start
Ciprofloxacin, enoxacin, clinafloxacin, fluvoxamine	3 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 judgement is required. Please contact AstraZeneca with any queries you have on this issue.

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 breast cancer resistance protein (BCRP) or P-glycoprotein (P-gp) substrate (concentrations of sensitive BCRP substrate, rosuvastatin or P-gp substrate, fexofenadine is increased).

Table 28 Exposure, pharmacological action and toxicity may be increased or decreased by osimertinib

Warning of possible interaction	Advice
Rosuvastatin Sulfasalazine Doxorubicin Daunorubicin Topotecan Aliskerin 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

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 should not be combined with savolitinib. Based on in vitro data, savolitinib may be an CCI of CYP2C8, CYP2C9, CYP2D6, and CYP3A4/5. A clinical study with a sensitive CYP3A4 substrate (midazolam) showed no effect when co-dosed with savolitinib and hence, CYP3A4 substrates can be co-dosed with savolitinib.

Savolitinib is a CCI of CYP2C8 (CCI CYP2C9 CCI and CYP2D6 (CCI Those drugs defined as CCI CYP2C8, CYP2C9, and CYP2D6 CCI CYP2C8, CYP2C9, and CYP2D6 [please see Table 7 for the example of sensitive substrates]) should be avoided as far as possible during the study unless considered essential by the investigator, in which case patients must be monitored closely for the potential for increased toxicity due to the concomitant medication.

Savolitinib is a substrate of P-gp but unlikely to have clinically relevant effect as the clinical study with itraconazole (a P-gp inhibitor) had no effect on the PK of savolitinib. Savolitinib is a CCI in vitro CCI) and hence, drugs that are sensitive substrates of P-gp such as digoxin, quinidine, loperamide, saquinavir and ritonavir should be used with caution. Based on in vitro data, savolitinib is an CCI of OCT2, OATP1B1 and OATP1B3, and clinically significant drug-drug interactions CCI when co-administered with the CCI . Drugs that are known to be significantly affected by CCI activity should be used with caution.

In addition, based on in vitro data savolitinib and CCI may also CCI MATE1, MATE2K, and OAT1/3 leading to an increased chance of a clinically relevant CCI between savolitinib and any co-administered drug that is a substrate for these transporters including metformin. Thus, metformin should be used with caution in case of potential for increased metformin exposure.

In vitro, savolitinib is an CCI of uridine diphospho-glucuronosyltransferase CCI (CCI and hence, sensitive substrates of CCI (such as irinotecan, lamotrigine) should be used with caution.

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 website: https://www.crediblemeds.org. The website categorises drugs based on the risk of inducing Torsades de Pointes (TdP). During

screening, the drugs that patients are currently prescribed should be checked opposite the Arizona Center website above.

J 5.1 Drugs with a known risk of Torsades de Pointes (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 treatment, in accordance with guidance provided in Table 29 and should not be co-administered with savolitinib or osimertinib and for a period of one week after discontinuing study treatment.

The list of drugs may not be exhaustive and is subject to change as new information becomes available. As such, investigators are recommended to search the 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 29.

Table 29 Drugs with a known risk of Torsades de Pointes (TdP)

Contraindicated drug	Withdrawal period prior to osimertinib 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
Bepridil, chlorpromazine, halofantrine, haloperidol, 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 compounds pharmacokinetic half-life and determination of the washout period

This list should be checked against the full and most current list presented in the CredibleMeds® website (https://www.crediblemeds.org/).).

J 5.2 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 30 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 website
Available at URL: https://www.crediblemeds.org.

Appendix K Patient reported outcome assessments

This appendix includes example copies of the following PRO questionnaires:

- EORTC QLQ-C30 v3 (core questionnaire)
- EORTC QLQ-LC13 (lung cancer module)
- PGIS
- PRO-CTCAE
- EQ-5D-5L

K 1 EORTC QLQ-C30

Patient Reported Outcomes questionnaires EORTC QLQ-C30 removed due to copyrights.

Patient Reported Outcomes questionnaires EORTC QLQ-C30 removed due to copyrights.

K 2 EORTC OLO-LC13

Patient Reported Outcomes questionnaires EORTC QLQ-LC13 removed due to copyrights.

K 3 PGIS

Patient Global Impression of Severity for Cancer Symptoms

Overall, how would you rate the severity of your cancer symptoms today?

- ☐ No symptoms
- ☐ Very mild
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

K 4 PRO-CTCAE

Patient Reported Outcomes questionnaire PRO-CTCAE removed due to copyrights.

K 5 EQ-5D-5L

Patient Reported Outcomes questionnaire EQ-5D-5L removed due to copyrights.

Patient Reported Outcomes questionnaire EQ-5D-5L removed due to copyrights.

Appendix L Abbreviations

Abbreviation or special term	Explanation
1L	First line
2L	Second line
3L	Third line
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BICR	Blinded independent central review
bid	Twice daily
BP	Blood pressure
CAS	Contribution of Components Analysis Set
CI	Confidence interval
C_{1h}	Plasma concentration at 1 hour post-dose
C_{3h}	Plasma concentration at 3 hours post-dose
C_{max}	Maximum observed plasma drug concentration
C_{min}	Minimum observed plasma drug concentration
$C_{pre\text{-}dose}$	Pre-dose plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CRF	Case report form (electronic/paper)
CRO	Contract research organisation
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTIS	Clinical Trials Information System
CTSQ-16	Cancer Therapy Satisfaction Questionnaire-16
CYP	Cytochrome P450
DCO	Data cut-off
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
DoR	Duration of response

Abbreviation or special term	Explanation
EC	Ethics committee, synonymous to institutional review board and independent ethics committee
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EGFRm	Epidermal growth factor receptor mutation
EGFRm+	Epidermal growth factor receptor mutation positive
EGFR-TKI	Epidermal growth factor receptor-tyrosine kinase inhibitor
EM	Erythema Multiforme
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC-QLQ-LC13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13
EQ-5D-5L	EuroQol 5 dimensions, 5 levels
FACT-L	Functional Assessment of Cancer Therapy - Lung Cancer
FDG-PET	Fluorodeoxyglucose-positron emission tomography
FFPE	Formalin fixed and paraffin embedded
FISH/ FISH+	Fluorescence in situ hybridisation/ fluorescence in situ hybridisation positive
FISH5+; FISH10+	≥5 MET gene copies or MET:CEP7 signal ratio ≥2 by FISH; ≥10 gene copies by FISH
GCP	Good clinical practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
GRAD	Global Retention and Disposal
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B
HCV	Hepatitis C
HDPE	High density polyethylene
HGF	Hepatocyte growth factor
HL	Hy's Law
HLA	Human leukocyte antigen
HR	Hazard ratio
HRCT	High resolution computed tomography
HRQoL	Health-related quality of life

Abbreviation or special term	Explanation
IA1	Interim Analysis 1
IA2	Interim Analysis 2
IC_{50}	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IHC50+; IHC90+	≥50% of tumour cells staining at strong 3+ intensity by IHC; ≥90% of tumour cells staining at strong 3+ intensity by IHC
ILD	Interstitial lung disease
I(M)P	Investigational (medicinal) product
INR	International normalised ratio
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IRB	Institutional Review Board
IRT	Interactive response technology
IWRS	Interactive web response system
LFT	Liver function test
LMWH	Low molecular weight heparin
LVEF	Left ventricular ejection fraction
MET	Mesenchymal epithelial transition factor
MET/CEP7	Mean MET per cell and chromosome 7 centromere ratio
MRI	Magnetic resonance imaging
MUGA	Multi-gated acquisition
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not evaluable
NGS	Next generation sequencing
NIMP	Non-investigational medicinal product
NSCLC	Non-Small Cell Lung Cancer
NTL	Non-target lesion
NYHA	New York Heart Association
od	Once daily

Abbreviation or special term	Explanation
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PHL	Potential Hy's Law
PI	Principal investigator
PK	Pharmacokinetic(s)
PK-PD	Pharmacokinetic-pharmacodynamic
PR	Partial response
PRO	Patient reported outcomes
PRO-CTCAE	Patient reported outcomes version of the Common Terminology Criteria for Adverse Events
QLQ-LC13	Quality of Life Questionnaire-Lung Cancer 13
QTcF	QT interval corrected for heart rate using Fridericia's formulas
RECIST (1.1)	Response Evaluation Criteria in Solid Tumours (version 1.1)
RNA	Ribonucleic acid
RTSM	Randomization and trial supply management
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SD	Stable disease
SJS	Stevens-Johnson syndrome
SoA	Schedule of Activities
SUSAR	Suspected unexpected adverse reaction
TBL	Total bilirubin
TdP	Torsades de Pointe
TKI	Tyrosine kinase inhibitor
TL	Target lesion
TPAS	Target Population Analysis Set
ULN	Upper limit of normal
WHO	World Health Organization

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