Clinical Study Report	
Drug Substance	Savolitinib + Osimertinib
Study Code	D5084C00009
Edition Number	1
Date	31 July 2023
EudraCT Number	2020-000813-33
NCT Number	NCT04606771

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

Study dates: First subject enrolled: 04 November 2020
Last subject enrolled: 21 March 2022
The analyses presented in this report are based on a data cut-off date of 21 December 2022 and a clinical data lock date of 06 February 2023.

Phase of development: Therapeutic exploratory (II)

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This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

2. SYNOPSIS

Study Centre(s)

A total of 116 patients were enrolled (signed informed consent) in 21 study centres across 6 countries (Argentina, India, Taiwan, Thailand, Vietnam, and the United States).

Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary (efficacy)	
• To assess the ORR of savolitinib in combination with osimertinib versus savolitinib in combination with placebo in patients with EGFRm, MET amplified locally advanced or metastatic NSCLC who had progressed on previous osimertinib therapy	• ORR was defined as the proportion of patients with measurable disease who had a CR or PR as determined by the investigator at the local site per RECIST version 1.1.
Secondary	
• To determine the efficacy of savolitinib in combination with osimertinib versus savolitinib in combination with placebo in patients with EGFRm, MET amplified locally advanced or metastatic NSCLC who had progressed on previous osimertinib therapy	• PFS was defined as time from randomisation until progression per RECIST version 1.1 as assessed by the investigator or death due to any cause. • DoR was defined as the time from the date of first documented response until date of documented progression per RECIST version 1.1 as assessed by the investigator or death in the absence of disease progression. • Tumour size assessment was defined as the percentage change from baseline in TLs at 12 weeks per RECIST version 1.1 as assessed by the investigator. • OS was defined as time from randomisation until the date of death due to any cause.
• To evaluate the efficacy of savolitinib plus osimertinib in patients who crossed over after progression on savolitinib plus placebo [a]	• ORR • PFS • DoR • Tumour size assessment
• To evaluate the PK of savolitinib and osimertinib.	• Plasma concentrations of savolitinib, osimertinib, and their metabolites.

Objectives	Endpoints
• To determine the prevalence of ctDNA clearance after savolitinib plus osimertinib or savolitinib plus placebo treatment in this patient population.	• Total clearance in EGFR mutations at 6-weeks after therapy initiation (percentage and absolute change from baseline in EGFR mutation allele frequencies).
Safety	
• To evaluate the safety and tolerability of savolitinib plus osimertinib or savolitinib plus placebo.	• AEs • SAEs • Discontinuations due to AEs • Clinical chemistry/haematology including LFTs • ECHO • ECG • Vital signs including blood pressure and heart rate

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

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

Study Design

This was a multi-centre, Phase II, double-blind, randomised study designed to determine the efficacy of savolitinib in combination with osimertinib versus savolitinib in combination with placebo in patients with epidermal growth factor receptor mutation (EGFRm), hepatocyte growth factor receptor (MET) amplified (confirmed centrally by fluorescence in situ hybridization [FISH]; MET gene copy ≥ 5 or MET/centromere of chromosome 7 (CEP7) ratio ≥ 2), locally advanced or metastatic non-small cell lung cancer (NSCLC) who had progressed on previous osimertinib treatment.

All patients were to be centrally and randomly assigned to one of the 2 study interventions using an Interactive Voice Response System/Interactive Web Response System. Eligible patients were randomised in a ratio of 1:1 to receive treatment with CCI savolitinib CCI CCI plus CCI osimertinib CCI, or CCI savolitinib CCI plus placebo. Randomisation was stratified according to the number of prior lines of therapy (ie, osimertinib monotherapy as first line or ≥ second line [which included patients who received osimertinib monotherapy before or after chemotherapy]).

Based on emerging data from the ongoing Phase II SAVANNAH study (NCT03778229) which shows the potential for increased anti-tumour activity in patients with higher MET biomarker cut-offs, on 22 February 2022, AstraZeneca made the decision to terminate enrolment into this Contribution of Components study, in order to focus on development in the higher biomarker-selected population. Patients who were already in Pre-screening/screening (who have signed the Pre-screening/main informed consent form) at the time of study recruitment termination still had the option to be randomised, if eligible.

Target Population and Sample Size

In order to be eligible for the study, patients (all genders) must have been aged at least 18 years with histologically or cytologically confirmed locally advanced or metastatic EGFRm NSCLC harbouring an EGFR mutation known to be associated with EGFR tyrosine kinase inhibitor sensitivity and that was permitted in the osimertinib national label (such as exon 19 deletion and/or L858R), which was not amenable to curative therapy. Patients were to have: documented radiologic progressive disease (PD) following treatment with osimertinib (osimertinib did not need to be the most recent therapy); MET amplification as determined by central MET FISH testing on a tumour specimen collected following progression on prior osimertinib treatment (MET gene copy ≥ 5 or MET/CEP7 ratio ≥ 2); and at least one measurable lesion. Patients must have received at least one but no more than 3 prior lines of therapy (including investigational therapy) in the locally advanced/metastatic setting.

Prior to Clinical Study Protocol (CSP) version 3.0, approximately 200 patients were planned to be screened to achieve 56 patients randomly assigned to study intervention, with the primary analysis to occur 6 months after the last patient was randomised. CCI [redacted]

Under CSP version 3.0, the planned number of randomised patients would not be met.

Investigational Product and Comparator(s): Dosage, Mode of Administration and Batch Numbers

Savolitinib tablets were provided by AstraZeneca as CCI [redacted] tablets. Savolitinib tablets were taken orally at a dosage of CCI [redacted]. The batch numbers for the savolitinib tablets used in the study were: CCI [redacted], CCI [redacted], CCI [redacted].

Osimertinib (or placebo to osimertinib) tablets were provided by AstraZeneca as CCI [redacted] tablets (CCI [redacted] osimertinib/placebo tablets were also available if a dose reduction was required). Osimertinib/placebo tablets were taken orally at a dosage of CCI [redacted]. Ten batches of osimertinib/placebo were used in this study.

Individual batch numbers and further information are included in the Clinical Study Report.

Duration of Treatment

All patients confirmed as eligible were to begin treatment on Day 1 with savolitinib (CCI [redacted]) plus osimertinib (CCI [redacted]) or savolitinib (CCI [redacted]) plus placebo (placebo to osimertinib). Treatment continued once daily in 28-day cycles for as long as patients were deriving clinical benefit, or until either objective PD by Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 was assessed, unacceptable toxicity occurred, consent was withdrawn, or another discontinuation criterion was met. Patients randomised to the savolitinib plus placebo arm were able to cross-over to open-label savolitinib plus osimertinib following investigator-assessed objective PD, ensuring that all patients enrolled had the opportunity to receive the combination of savolitinib plus osimertinib.

An initial DCO occurred following the early termination of study recruitment to allow an early review of the data by AstraZeneca. The study was unblinded after completion of data cleaning activities on the initial DCO data, and patients on savolitinib monotherapy (savolitinib plus placebo) were given the opportunity to cross-over to the savolitinib plus osimertinib arm after approval by AstraZeneca. Patients may have otherwise chosen to remain on savolitinib monotherapy (as long as, in the opinion of the investigator, they were still receiving clinical benefit and had not reported PD).

Statistical Methods

Statistical analyses were performed by AstraZeneca using SAS® Version 9.4 in accordance with the Statistical Analysis Plan. All analyses and reporting are presented by treatment group, unless otherwise specified.

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

The primary efficacy endpoint of ORR was defined as the proportion of patients with measurable disease who had a complete response (CR) or partial response (PR) as determined by the investigator at the local site per RECIST version 1.1. The ORR was to be summarised by n (%) in each treatment arm. Summaries by treatment group were to be produced that present the number and percentage of patients with a tumour response (CR/PR) based upon the number of patients with measurable disease at baseline per the site investigator. The response rates by treatment group are presented with a 2-sided 95% confidence interval (CI) using the Clopper-Pearson method.

Secondary efficacy endpoints were progression-free survival (PFS), duration of response (DoR), tumour size assessment, and overall survival (OS).

CCI

Safety and tolerability were to be assessed in terms of adverse events (AEs), serious adverse events (SAEs), discontinuation rate due to AEs, deaths, laboratory data, vital signs, echocardiogram (ECHO) data, electrocardiogram (ECG) data, and Eastern Cooperative Oncology Group performance status. All safety analyses were performed on the Safety Analysis Set. Data were presented separately for patients who crossed over to savolitinib plus osimertinib upon investigator assessed PD per RECIST version 1.1 on savolitinib plus placebo. Safety data were presented using descriptive statistics unless otherwise specified.

Study Population

A total of 116 patients were enrolled (signed informed consent) in 21 study centres across 6 countries (Argentina, India, Taiwan, Thailand, Vietnam, and the United States). The first patient was randomised into the study on 04 November 2020, and the last patient was randomised on 21 March 2022.

Of the 116 patients who entered pre-screening or screening, 30 patients were randomised in a 1:1 ratio to either savolitinib plus osimertinib (14 patients) or savolitinib plus placebo (16 patients) and received treatment.

At data cut-off (DCO; 21 December 2022), 18 (60.0%) patients were ongoing in the study: 9 (64.3%) patients in the savolitinib plus osimertinib arm and 9 (56.3%) patients in the savolitinib plus placebo arm. Twelve (40.0%) patients had terminated the study at DCO: 5 (35.7%) patients in the savolitinib plus osimertinib arm and 7 (43.8%) patients in the savolitinib plus placebo arm. Of these 12 patients, 11 patients were terminated from the study due to death as obtained from public records or survival follow-up and one patient terminated the study due to 'other' reasons. The 'other' reason was recorded as 'death due to disease progression'.

At DCO, of the 14 patients randomised to the savolitinib plus osimertinib arm, 4 (28.6%) patients were ongoing both savolitinib and osimertinib treatment and 10 (71.4%) patients had discontinued both savolitinib and osimertinib treatment at DCO. The most common reason for discontinuing both savolitinib and osimertinib treatment was 'condition under investigation worsened' (savolitinib: 42.9% of patients; osimertinib: 50.0% of patients).

At DCO, all 16 patients randomised to the savolitinib plus placebo arm discontinued their initial randomised treatment (ie, both savolitinib and placebo). Of these patients, 10 (62.5%) crossed over and therefore went on to receive savolitinib plus osimertinib. The most common reason for discontinuing their randomised treatment was 'other' (savolitinib: 6 [37.5%] patients; placebo: 7 [43.8%] patients), including patients' decision to cross over at the time of study unblinding.

At DCO, 5/10 (50.0%) cross-over patients were ongoing savolitinib and osimertinib treatment. The most common reason for discontinuing savolitinib and osimertinib treatment after cross-over was 'condition under investigation worsened' (40.0% of patients). At DCO, 8 (80.0%) cross-over patients were ongoing in the study and 2 (20.0%) patients had discontinued the study due to death related to disease under investigation.

Overall, patients had a median age of 61 years (range: 37 to 78 years), 46.7% of patients were male and 53.3% of patients were female, and the majority (90.0%) were Asian, due to most patients having been enrolled in centres in India, Taiwan, Thailand, and Vietnam. The demographic, disease, prior therapy, and concomitant medication characteristics of the study population were in general well balanced between the study treatment arms. The enrolled patients were representative of the intended study population, except in terms of race distribution.

Summary of Efficacy Results

Due to early study recruitment termination, only 30 patients were randomised into the study in total (savolitinib plus osimertinib:14 patients; and savolitinib plus placebo: 16 patients), rather than the planned 56 randomised patients. Therefore, efficacy data should be interpreted with caution due to the small sample size. Given the lower than planned study sample size, no statistical comparison was undertaken.

In all randomised patients in the savolitinib plus osimertinib treatment arm, an objective response per RECIST version 1.1 according to investigator assessment was reported in 8 out of 14 randomised patients, corresponding to an ORR of 57.1% (95% CI: 28.86%, 82.34%;). A lower ORR was observed in the savolitinib plus placebo treatment arm (12.5%; 95% CI: 1.55%, 38.35%), with 2 out of 16 randomised patients achieving a response.

No patients had a complete response. Of the patients who responded to treatment, all responses were PRs. The best objective response of progression was observed in one patient (7.1%) in the savolitinib plus osimertinib treatment arm, whereas 8 patients (50%) had progression as best response in the savolitinib plus placebo treatment arm.

CCI

Median PFS in the savolitinib plus osimertinib arm was 7.36 months (95% CI: 5.55 months, not calculated [NC]) and 1.64 months (95% CI: 1.28, 4.07 months) in the savolitinib plus placebo arm. At the time of the DCO, the median duration of follow-up in censored patients was 9.53 months (range: 1.4 to 16.6 months) in the savolitinib plus osimertinib arm and 9.03 months (range: 0 to 10.9 months) in the savolitinib plus placebo arm.

CCI

As of the DCO, 5 of the 8 responding patients (62.5%) in the savolitinib plus osimertinib arm had progressed or died, and the median DoR was 30.6 weeks (95% CI: 18.9 weeks, NC). Median DoR was not calculable in the savolitinib plus placebo arm as only one of the 2 responding patients had died or progressed at the time of the DCO.

CCI

CCI

For OS, 5 deaths (35.7%) had occurred in the savolitinib plus osimertinib arm and 7 (43.8%) in the savolitinib plus placebo arm. Median OS for the savolitinib plus osimertinib arm was not attained (95% CI: 9.56 months, NC) and was 13.37 months (95% CI: 7.82 months, NC) for the savolitinib plus placebo arm. The survival rate at 12 months was 78.6% (95% CI: 47.2%, 92.5%) in the savolitinib plus osimertinib arm and 58.9% (95% CI: 29.1%, 79.7%) in the savolitinib plus placebo arm.

CCI

Median percentage change in TL summed diameters at 12 weeks was a 47.1% decrease (range: -67%, 18%) in the savolitinib plus osimertinib arm and 0% (range: -48, 85) in the savolitinib plus placebo arm. The median best percentage change from baseline in TL size was a 48.0% decrease (range: -87% to 14%) in the savolitinib plus osimertinib arm and a 7.7% increase (range: -48% to 85%) in the savolitinib plus placebo arm.

Summary of Pharmacokinetic Results

- Savolitinib and metabolites (M2 and M3):
  - Savolitinib tss,max values were similar when administered with placebo and with osimertinib (approximately 3 hours post-dose).
  - The AUCss and Css,max values of savolitinib in this study were consistent with other studies.
  - There was no evidence of accumulation of savolitinib with time after multiple dosing.
  - The ratio of plasma exposure of metabolite M2 and M3 in comparison to savolitinib were approximately 30% and 11%, respectively.

- Osimertinib and its metabolite:
  - Osimertinib median tss,max was 4 hours.
  - The Css,max and AUCss of osimertinib were consistent with other osimertinib studies.
  - There was no evidence of accumulation of osimertinib with time following multiple doses.
  - The ratio of osimertinib metabolite to osimertinib plasma exposure was approximately 8%.

CCI

CCI

[redacted]

Summary of Safety Results

Median total treatment duration was longer in the savolitinib plus osimertinib arm (7.2 months [range: 2.0 to 17.3 months] for savolitinib and 8.3 months [range: 1.8 to 17.3 months] for osimertinib) than in the savolitinib plus placebo arm (1.9 months [range: 0.9 to 8.3 months] for savolitinib and 1.8 months [range: 0.9 to 8.3 months]) for placebo). This may be partially due to patients in the savolitinib plus placebo arm crossing over to open-label savolitinib plus osimertinib treatment at study unblinding rather than staying on their initial randomised treatment assignment until PD. Median actual treatment duration, ie, total treatment duration minus duration of dose interruptions, was generally similar to median total treatment duration and was shorter by no more than 0.6 months in both arms. Overall, the median relative dose intensity was 100% for each drug in each treatment arm, and the lower limit of the interquartile range was > 96% for each drug in each treatment arm.

All patients experienced at least one AE. Overall, an AE possibly related to savolitinib only was reported in 11 patients (36.7%): 7 patients (50.0%) in the savolitinib plus osimertinib arm and 4 patients (25.0%) in the savolitinib plus placebo arm. With the exception of nausea (5 patients [16.7%]), and vomiting, oedema peripheral, and amylase increased (all 2 patients [6.7%]), all AEs possibly related to savolitinib only were reported in one patient each. Overall, an AE possibly related to osimertinib or placebo only was reported in 2 patients (6.7%; one patient in each arm). None of the AEs possibly related to osimertinib or placebo only were reported in more than one patient. Overall, an AE possibly related to both savolitinib and osimertinib or placebo was reported in 12 patients (40.0%): 9 patients (64.3%) in the savolitinib plus osimertinib arm and 3 patients (18.8%) in the savolitinib plus placebo arm. With the exception of amylase increased (3 patients [10.0%]), and dermatitis acneiform, fatigue, nausea, and paronychia (all 2 patients [6.7%]), all AEs possibly related to savolitinib and osimertinib or placebo were reported in one patient each.

The majority of patients (73.3%) experienced AEs of maximum Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2 in severity. Adverse events of CTCAE Grade 3 or higher were reported in 3 (21.4%) patients in the savolitinib plus osimertinib arm and 5 (31.3%) patients in the savolitinib plus placebo arm. Adverse events of CTCAE Grade 3 or higher reported in more than one patient were pneumonia (3 patients, 10.0%) and amylase increased (2 patients, 6.7%). Treatment-related CTCAE Grade 3 or higher AEs were reported in 2 patients (6.7%). Both events were amylase increased and occurred in the savolitinib plus placebo arm.

Overall, adverse events of special interest (AESIs) were reported in 7 patients (23.3%), with 5 patients (35.7%) in the savolitinib plus osimertinib arm and 2 patients (12.5%) in the savolitinib plus placebo arm. Hypoalbuminaemia was reported as an AESI in 5 patients (16.7%): 3 patients (21.4%) in the savolitinib plus osimertinib arm and 2 patients (12.5%) in the savolitinib plus placebo arm. For one patient in the savolitinib plus osimertinib arm, the AESI of hypoalbuminaemia was considered by the investigator to be related to both savolitinib and osimertinib treatment. Pyrexia was reported as an AESI in 2 patients (14.3%); both in the savolitinib plus osimertinib arm. The AESIs of alanine aminotransferase increased and aspartate aminotransferase increased (both CTCAE Grade 2 and considered by the investigator to be related to both savolitinib and osimertinib treatment), and transaminases increased (Grade 1) were reported in one patient. The AESI of hepatic enzyme increased (Grade 2) was reported in one patient following cross-over to the savolitinib plus osimertinib arm and was considered by the investigator to be related to savolitinib treatment only.

Deaths due to AEs were reported in one patient (7.1%) in the savolitinib plus osimertinib arm and 3 patients (18.8%) in the savolitinib plus placebo arm. The AEs were pneumonia, septic shock, diabetes mellitus, and hypertension. None of the AEs with an outcome of death were considered related to study treatment by the investigator.

Serious AEs were reported in 7 patients (23.3%) in total (4 patients [28.6%] and 3 patients [18.8%] in the savolitinib plus osimertinib arm and savolitinib plus placebo arm, respectively). With the exception of pneumonia (3 patients [10.0%] in the savolitinib plus placebo arm), all SAEs (savolitinib plus osimertinib arm: deep vein thrombosis, diabetes mellitus, haematuria, hepatic enzyme increased, hypernatremia, hypertension, pyrexia, sepsis, and wound necrosis; savolitinib plus placebo arm: septic shock, toxicity to various agents, and upper gastrointestinal haemorrhage) were reported in one patient each. An SAE (Grade 2 hepatic enzyme increased) considered to be related to savolitinib was reported for one patient in the savolitinib plus osimertinib arm. As a result, osimertinib was interrupted and savolitinib was permanently discontinued. The event resolved and was reported as an AESI. No SAEs were considered related to osimertinib or placebo and no SAEs were considered related to both savolitinib and osimertinib/placebo.

A total of 3 patients discontinued one or both study drugs due to AEs: one patient (7.1%) was in the savolitinib plus osimertinib arm and the other 2 patients (12.5%) were in the savolitinib plus placebo arm. Two of the AEs were considered to be related to savolitinib: a Grade 2 event of hepatic enzyme increased and a Grade 3 event of amylase increased. Two patients, one in each treatment arm, had their savolitinib dose reduced. The AEs that led to savolitinib dose reductions were oedema peripheral and transaminases increased; neither was considered to be related to study treatment. No osimertinib dose reductions occurred due to AEs. There were no AEs leading to dose interruption of savolitinib only. Adverse events led to the interruption of osimertinib only in 2 patients in the savolitinib plus osimertinib arm; the AEs were hepatic enzyme increased and transaminases increased. Adverse events led to the interruption of both savolitinib and osimertinib/placebo in 5 patients (16.7%): 2 patients (14.3%) in the savolitinib plus osimertinib arm and 3 patients (18.8%) in the savolitinib plus placebo arm. An AE of vomiting led to dose interruption of both savolitinib and osimertinib/placebo in 2 patients. Adverse events of sepsis, headache, and pyrexia led to dose interruption of both savolitinib and osimertinib/placebo in one patient each.

No clinically relevant trends in laboratory data, vital signs, ECG, or physical findings were evident during the study.

Conclusion(s)

Due to early study recruitment termination, only 30 patients were randomised into the study in total (savolitinib plus osimertinib:14 patients; and savolitinib plus placebo: 16 patients). Therefore, all study data should be interpreted with caution due to the small sample size.

- The efficacy outcomes (ie, ORR, PFS) were higher in the savolitinib plus osimertinib arm compared with the savolitinib plus placebo arm. CCI [redacted] No statistical comparisons were undertaken due to the small sample size resulting from the early discontinuation of recruitment to the study and the data should be interpreted with caution.
- Savolitinib administered in combination with osimertinib and administered as monotherapy was generally well tolerated, and the safety profile in each arm was overall considered consistent with the established profile of each drug. No new safety signals were identified in this study.
- Pharmacokinetic parameters (Css,max and AUCss) for savolitinib and osimertinib were consistent with other savolitinib and/or osimertinib studies and there was no evidence of accumulation of either savolitinib or osimertinib with time following multiple doses.