Clinical trial results:
A Phase 2a, Multi-centre, Single-arm Trial of the combination of AZD2014 and Weekly Paclitaxel in Patients with Relapsed or Refractory Squamous Non-Small Cell Lung Cancer After at Least One Line of Prior Therapy

Summary

EudraCT number	2015-000159-26
Trial protocol	ES
Global end of trial date	29 December 2016

Results information

Result version number	v1 (current)
This version publication date	12 January 2018
First version publication date	12 January 2018

Trial information

Trial identification

Sponsor protocol code	D2274C00001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02403895
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	151 85, Sodertalje, Sweden,
Public contact	Medical Science Director, AstraZeneca, clinicaltrialtransparency@astrazeneca.com
Scientific contact	Medical Science Director, AstraZeneca, clinicaltrialtransparency@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 December 2016
Global end of trial reached?	Yes
Global end of trial date	29 December 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of the combination of AZD2014 and weekly paclitaxel in patients with squamous cell Non Small Cell Lung Cancer (NSCLC) by evaluation of objective response rate (ORR)

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation Good Clinical Practice and applicable regulatory requirements and the AstraZeneca policy on Bioethics

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 April 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 6
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Spain: 2
Worldwide total number of subjects	11
EEA total number of subjects	5

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	8

From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First subject enrolled: 15 April 2015 Last subject last visit: 29 December 2016 The study was performed at 7 centres: 4 USA, 2 Spain, 1 Germany Patient population: Patients with squamous non-small cell lung cancer with relapsed or refractory disease for whom weekly paclitaxel is an appropriate treatment choice

Pre-assignment

Screening details:

11 patients were enrolled Patients were assigned to treatment if they met all of the inclusion criteria and none of the exclusion criteria

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Open-label AZD2014

Arm description:

Open-label AZD2014 given twice daily 3 days on, 4 days off during weekly paclitaxel

Arm type	Experimental
Investigational medicinal product name	vistusertib
Investigational medicinal product code	AZD2014
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

50mg BD Weekly Intermittent Schedule 3 days on, 4 days off

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

80mg/m2 weekly for 6 weeks of 7 week cycle

Number of subjects in period 1	Open-label AZD2014
Started	11
Completed	11

Baseline characteristics

Reporting groups	
Reporting group title	Open-label AZD2014
Reporting group description:	
Open-label AZD2014 given twice daily 3 days on, 4 days off during weekly paclitaxel	

Reporting group values	Open-label AZD2014	Total	
Number of subjects	11	11	
Age Categorical Units: Subjects			
<=18 years	0	0	
Between 18 and 65 years	8	8	
>=65 years	3	3	
Age continuous Units: years			
median	62.0		
full range (min-max)	49 to 80	-	
Sex: Female, Male Units: Subjects			
Female	1	1	
Male	10	10	
Race Units: Subjects			
White	9	9	
Black or African American	1	1	
Other	1	1	
Ethnic Group Units: Subjects			
Not Hispanic or Latino	11	11	
Height Units: cm			
median	172		
full range (min-max)	154 to 180	-	
Weight Units: kg			
median	70		
full range (min-max)	62 to 125	-	
Body Mass Index (BMI) Units: kg/m2			
median	25.71		
full range (min-max)	20.96 to 39.45	-	

Subject analysis sets	
Subject analysis set title	Evaluable for efficacy
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All dosed patients with a baseline tumour assessment of measurable disease	

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who recieved at least 1 dose of AZD2014

Reporting group values	Evaluable for efficacy	Safety	
Number of subjects	11	11	
Age Categorical Units: Subjects			
<=18 years	0	0	
Between 18 and 65 years	8	8	
>=65 years	3	3	
Age continuous Units: years			
median	62.0	62.0	
full range (min-max)	49 to 80	49 to 80	
Sex: Female, Male Units: Subjects			
Female	1	1	
Male	10	10	
Race Units: Subjects			
White	9	9	
Black or African American	1	1	
Other	1	1	
Ethnic Group Units: Subjects			
Not Hispanic or Latino	11	11	
Height Units: cm			
median	172	172	
full range (min-max)	154 to 180	154 to 180	
Weight Units: kg			
median	70	70	
full range (min-max)	62 to 125	62 to 125	
Body Mass Index (BMI) Units: kg/m2			
median	25.71	25.71	
full range (min-max)	20.96 to 39.45	20.96 to 39.45	

End points

End points reporting groups

Reporting group title	Open-label AZD2014
Reporting group description:	
Open-label AZD2014 given twice daily 3 days on, 4 days off during weekly paclitaxel	
Subject analysis set title	Evaluable for efficacy
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All dosed patients with a baseline tumour assessment of measurable disease	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who recieved at least 1 dose of AZD2014	

Primary: Anti-tumour activity through calculation of the percentage of patients who have a Partial Response or Complete response through measurement of tumour lesion sizes

End point title	Anti-tumour activity through calculation of the percentage of patients who have a Partial Response or Complete response through measurement of tumour lesion sizes
End point description:	
Calculation of the percentage of patient who have a Complete Response or Partial Response to treatment which is confirmed by a repeat assessment 4 weeks later	
End point type	Primary
End point timeframe:	
From first dose until disease progression (Approximately 3 months)	

End point values	Open-label AZD2014	Evaluable for efficacy		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Percent				
number (confidence interval 90%)				
CR	0 (0 to 23.8)	0 (0 to 23.8)		
PR	0 (0 to 23.8)	0 (0 to 23.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis of Objective Response Rate
Statistical analysis description:	
Objective response rate (proportion of subjects with CR or PR) were summarised Two-sided 90% Clopper-Pearson confidence intervals was provided for the objective respoonse rate	
Comparison groups	Open-label AZD2014 v Evaluable for efficacy

Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Estimation of percentage
Point estimate	0
Confidence interval	
level	90 %
sides	2-sided
lower limit	0
upper limit	23.8

Secondary: Number of patients experiencing adverse events (AE) and Serious Adverse Events (SAEs) including chemistry, haematology, vital signs and ECG variables

End point title	Number of patients experiencing adverse events (AE) and Serious Adverse Events (SAEs) including chemistry, haematology, vital signs and ECG variables

End point description:

The safety and tolerability of AZD2014 with weekly paclitaxel will be assessed with the collection of AEs/SAEs, clinical chemistry/haematology/coagulation, vital signs, and ECG parameters

End point type	Secondary

End point timeframe:

Informed consent until end of safety follow up (Approx 10 months if all treatment cycles are completed)

End point values	Open-label AZD2014			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Participants				
Any AE	11			
Any SAE	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Overall Survival

End point title	Duration of Overall Survival

End point description:

Assessment of the duration of overall survival through patient follow-up

End point type	Secondary

End point timeframe:

From first dose until end of life (Approx 9 months)

End point values	Open-label AZD2014			
Subject group type	Reporting group			
Number of subjects analysed	0[1]			
Units: Weeks				
number (not applicable)				

Notes:

[1] - Overall survival not analysed due to early termination of the study after 11 patients enrolled

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-tumour activity through assessment of Best Objective Response by assessment of tumour lesions

End point title	Anti-tumour activity through assessment of Best Objective Response by assessment of tumour lesions

End point description:

Assessment of the best tumour response through assessment of tumour lesions by RECIST 1.1 criteria

End point type	Secondary

End point timeframe:

From Baseline until Disease Progression (Approx 3 months)

End point values	Open-label AZD2014			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Participants				
CR	0			
PR	0			
SD	5			
PD	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-tumour activity through assessment of Duration of Response by assessment of tumour lesions

End point title	Anti-tumour activity through assessment of Duration of Response by assessment of tumour lesions

End point description:

Assessment of the duration of tumour response through assessment of tumour lesions by RECIST 1.1 criteria

End point type	Secondary

End point timeframe:

From date of first documented response until documented progression or end of life in the absence of progression (Approx 3 months)

End point values	Open-label AZD2014			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: Days				
number (not applicable)				

Notes:

[2] - No data for analysis - 0 of 11 subjects responded to treatment

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-tumour activity through assessment of Disease Control Rate by measurement of the number of patients who achieve Partial Response, Complete Response or Stable Disease through assessment of tumour lesions

End point title	Anti-tumour activity through assessment of Disease Control Rate by measurement of the number of patients who achieve Partial Response, Complete Response or Stable Disease through assessment of tumour lesions

End point description:

Assessment of the disease control rate, number of patients who experience a response through assessment of tumour lesions by RECIST 1.1 criteria

End point type	Secondary

End point timeframe:

From first dose until documented progression and at least 7 weeks after the start of treatment for assessment of Stable Disease (Approx 3 months)

End point values	Open-label AZD2014			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Percentage				
number (confidence interval 80%)				
Disease control rate at 6 weeks	45.5 (24.1 to 68.2)			
Disease control rate at 13 weeks	18.2 (4.9 to 41.5)			
Disease control rate at 20 weeks	18.2 (4.9 to 41.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-tumour activity through assessment of percentage change in tumour size by measurement of tumour lesions

End point title	Anti-tumour activity through assessment of percentage change in tumour size by measurement of tumour lesions

End point description:

Assessment of the degree of tumour response through measurement of the change in tumour lesion sizes

End point type	Secondary

End point timeframe:

From baseline until documented progression (Approx 3 months)

End point values	Open-label AZD2014			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: mm				
number (not applicable)				

Notes:

[3] - Anti-tumour activity not analysed due to early termination of study after 11 patients

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-tumour activity through assessment of duration of progression free survival by measurement of tumour lesions

End point title	Anti-tumour activity through assessment of duration of progression free survival by measurement of tumour lesions

End point description:

Assessment of the duration of progression free survival through assessment of tumour lesions by RECIST 1.1 criteria

End point type	Secondary

End point timeframe:

From date of first dose until documented progression or end of life (Approx 3 months)

End point values	Open-label AZD2014			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: Days				
number (not applicable)				

Notes:

[4] - Progression Free Survival not analysed due to early termination of study after 11 patients

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluate the effect of the combination of AZD2014 and paclitaxel on pharmacokinetics which may include assessment of AUC (Area Under Curve) and levels of plasma concentration over time (Cmax, tmax, tlast, Cinf)

End point title	Evaluate the effect of the combination of AZD2014 and paclitaxel on pharmacokinetics which may include assessment of AUC (Area Under Curve) and levels of plasma concentration over time (Cmax, tmax, tlast, Cinf)

End point description:

To determine the effect of co-administration of paclitaxel on the PK of oral AZD2014 and the effect of co administration of oral AZD2014 on the PK of paclitaxel (Group A) by: PK parameters for each in the presence and absence of the other by intensive PK sampling and NCA techniques.

End point type	Secondary

End point timeframe:

Assessment at multiple timepoints in Group A patients. Samples will be taken at pre-dose and at 10 further timepoints on day 1 and at pre-dose and 9 further timepoints on days 3 and 8

End point values	Open-label AZD2014			
Subject group type	Reporting group			
Number of subjects analysed	0[5]			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	()			

Notes:

[5] - Outcome not measured due to early termination of the study - data insufficient

Statistical analyses

No statistical analyses for this end point

Secondary: Estimated pharmacokinetic exposure to AZD2014 through the use of population PK modelling

End point title	Estimated pharmacokinetic exposure to AZD2014 through the use of population PK modelling

End point description:

Group B patients: PK parameters for AZD2014 estimated from a sparse PK sampling regimen and use of population PK modelling techniques (may be reported outside the clinical study report (CSR))

End point type	Secondary

End point timeframe:

Assessment at multiple timepoints in Group B patients between study day 1 and day 3. Samples will be taken at 3 points on day 1 and at predose and at a further 2 points on day 3

End point values	Open-label AZD2014			
Subject group type	Reporting group			
Number of subjects analysed	0[6]			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	()			

Notes:

[6] - Outcome not measured due to early termination of the study - data insufficient

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected from the time of informed consent throughout the treatment period until the end of the follow-up period (28 days after discontinuation of study treatment).

Adverse event reporting additional description:

Adverse events were assessed systematically through clinical review, and collection of laboratory assessment, physical examination, performance status, ECHO/MUGA and ECG. Patients attended the clinic for assessment on a weekly basis

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Open-label AZD2014

Reporting group description:

Open-label AZD2014 given twice daily 3 days on, 4 days off during weekly paclitaxel

Serious adverse events	Open-label AZD2014		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 11 (36.36%)		
number of deaths (all causes)	9		
number of deaths resulting from adverse events	0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

Acute Respiratory Failure			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary Embolism			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Open-label AZD2014		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 11 (100.00%)		
Investigations			
Weight decreased			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Spinal compression fracture			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Nervous system disorders			

Peripheral Neuropathy			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	3		
Headache			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Nerve compression			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	4		
Leukopenia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	4 / 11 (36.36%)		
occurrences (all)	4		
Mucosal Inflammation			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	5		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Abdominal distension			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		

Diarrhoea subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 4		
Dyspepsia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Stomatitis subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Vomiting subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	4 / 11 (36.36%) 5		
Dyspnoea subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2		
Pulmonary Embolism subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Dyspnea exertional subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Haemoptysis subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Hypoxia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Nasal dryness subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Skin and subcutaneous tissue disorders			

Dry Skin subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Papule subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Pruritus subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Rash subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Eating disorder symptom subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Insomnia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 2		
Bone pain subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Spinal Column Stenosis subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Infections and infestations Pneumonia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 2		

Fungal Infection subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1			
Lower Respiratory Tract Infection subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1			
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 2			
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1			
Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1			
Hypercalcaemia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1			
Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1			
Hypoalbuminaemia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1			
Hypokalaemia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1			
Hypomagnesaemia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1			
Hyponatraemia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1			
Increased appetite				

subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 October 2015	Based on emerging data the restriction on CYP2C8 inhibitor or inducer concomitant medications was removed

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
05 February 2016	Sponsor decision to stop further recruitment on the basis of futility due to a lack of response (0 of 11 patients) seen in the 50mg cohort	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Sponsor and Investigator decision was taken to terminate further recruitment into the study due to lack of observed responses rendering it futile to continue. As such, an abbreviated Clinical Study Report was produced based on data from 11 patients.

Notes: