Clinical trial results:
A Randomised three-arm, open label, Phase II study of continuous Selumetinib versus continuous or interrupted Selumetinib in combination with weekly Paclitaxel in metastatic Uveal Melanoma

Summary

EudraCT number	2014-004437-22
Trial protocol	GB DE
Global end of trial date	04 August 2020

Results information

Result version number	v1 (current)
This version publication date	19 September 2021
First version publication date	19 September 2021

Trial information

Trial identification

Sponsor protocol code	UoL001077

Additional study identifiers

ISRCTN number	ISRCTN29621851
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Liverpool
Sponsor organisation address	Research Support Office, 2nd Floor Block D, Waterhouse Building, 3 Brownlow Street, Liverpool, United Kingdom, L69 3GL
Public contact	Charlotte Rawcliffe, Liverpool Clinical Trials Centre - University of Liverpool, +44 151 794 8167, c.rawcliffe@liv.ac.uk
Scientific contact	Charlotte Rawcliffe, Liverpool Clinical Trials Centre - University of Liverpool, +44 151 794 8167, c.rawcliffe@liv.ac.uk

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	11 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 June 2020
Global end of trial reached?	Yes
Global end of trial date	04 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess progression-free survival time between selumetinib alone or combination selumetinib in either a continuous or intermittent schedule with weekly paclitaxel.

Protection of trial subjects:

Consent was obtained prior to each patient participating in the trial, after a full explanation had been given of the treatment options, including the conventional and generally accepted methods of treatment. All risks and potential benefits were explained to the patients, and all patients were provided with Patient Information Sheets prior to consent. Patients were given the right to refuse their consent to participate in the trial, and to withdraw at any time.
The study also had a Trial Steering Committee (TSC) and Data Monitoring Comittee (DMC) that provided overall supervision of the trial, particularly focusing on the progress of the trial, adherence to the protocol, patient safety and consideration of new
information. The TSC included experienced diabetes and sleep respiratory experts and clinical trialists. Meetings were held annually, but additional meetings could have been held if required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	United Kingdom: 72
Worldwide total number of subjects	77
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)	37
From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment took place over 36 months from 14 recruiting centres, the first patient was randomised on and the last patient was screened on 24th November 2015 and the 25th October 2018.

Pre-assignment

Screening details:

112 patients were screened prior to randomisation. 35 patients did not enter the study, 25 of which were due to not meeting the inclusion/exclusion criteria and 10 were due to 'Other' reasons

Period 1

Period 1 title	Intervention Phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Are arms mutually exclusive?	Yes
Arm title	Selumetinib alone

Arm description:

75gm twice daily - continuous

Arm type	Active comparator
Investigational medicinal product name	Selumetinib
Investigational medicinal product code	AZD6244
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Given as 3 25mg tables

Arm title	Selumetinib (Continuous) plus Paclitaxel

Arm description:

PO Selumetinib - 75mg twice daily - continuous
IV Paclitaxel - 80mg/m2 administered on day 1, 8 and 15 (for 6 cycles)

Arm type	Experimental
Investigational medicinal product name	Selumetinib
Investigational medicinal product code	AZD6244
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Given as 3 25mg tables

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	L01CD01
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel will be supplied and prepared according to local policy. Paclitaxel must be handled and

stored according to the instructions within the corresponding Summary of Products Characteristics (Please refer to current paclitaxel SmPCs supplied by the appropriate manufacturer).
Dose banding may be performed as per local practice.
Paclitaxel should be labelled as per standard hospital labelling procedures. For the purposes of this study an Annex 13 compliant label is required.
80mg/m2 paclitaxel should be administered through an in-line filter with a microporous membrane ≤0.22µm.
All patients must be premedicated with corticosteroids, antihistamines, and H2 antagonists prior to paclitaxel therapy.
Paclitaxel should be given under the supervision of a physician with experience in using cancer chemotherapeutic agents. Appropriate equipment for emergency treatment should be available.

Arm title	Selumetinib plus Paclitaxel

Arm description:

PO Selumetinib - 75mg twice daily - 2 days off prior to (and morning of) each paclitaxel
IV Paclitaxel - 80mg/m2 administered on day 1, 8 and 15 (for 6 cycles)

Arm type	Experimental
Investigational medicinal product name	Selumetinib
Investigational medicinal product code	AZD6244
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Given as 3 25mg tables - 2 days off prior to (and morning of) each Paclitaxel administration

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	L01CD01
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

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All patients must be premedicated with corticosteroids, antihistamines, and H2 antagonists prior to paclitaxel therapy.
Paclitaxel should be given under the supervision of a physician with experience in using cancer chemotherapeutic agents. Appropriate equipment for emergency treatment should be available.

Number of subjects in period 1	Selumetinib alone	Selumetinib (Continuous) plus Paclitaxel	Selumetinib plus Paclitaxel
Started	26	26	25
Completed	21	19	19
Not completed	5	7	6
Adverse event, serious fatal	-	1	-
Adverse event, non-fatal	5	6	6

Baseline characteristics

Reporting groups	
Reporting group title	Selumetinib alone
Reporting group description:	
75gm twice daily - continuous	
Reporting group title	Selumetinib (Continuous) plus Paclitaxel
Reporting group description:	
PO Selumetinib - 75mg twice daily - continuous IV Paclitaxel - 80mg/m2 administered on day 1, 8 and 15 (for 6 cycles)	
Reporting group title	Selumetinib plus Paclitaxel
Reporting group description:	
PO Selumetinib - 75mg twice daily - 2 days off prior to (and morning of) each paclitaxel IV Paclitaxel - 80mg/m2 administered on day 1, 8 and 15 (for 6 cycles)	

Reporting group values	Selumetinib alone	Selumetinib (Continuous) plus Paclitaxel	Selumetinib plus Paclitaxel
Number of subjects	26	26	25
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	65.5	65	65
inter-quartile range (Q1-Q3)	56 to 72	61 to 70	58.5 to 71
Gender categorical Units: Subjects			
Female	14	11	12
Male	12	15	13
ECOG Units: Subjects			
ECOG 0	12	15	12
ECOG 1	13	10	11
ECOG 2	1	1	2

Reporting group values	Total		
Number of subjects	77		
Age categorical Units: Subjects			
In utero	0		

Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
median			
inter-quartile range (Q1-Q3)	-		
Gender categorical			
Units: Subjects			
Female	37		
Male	40		
ECOG			
Units: Subjects			
ECOG 0	39		
ECOG 1	34		
ECOG 2	4		

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

Set on the Intention to treat principle retaining patients in their randomised groups irrespective of any protocol deviations

Reporting group values	Full Analysis Set		
Number of subjects	77		
Age categorical			
Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Units: years			
median	65		
inter-quartile range (Q1-Q3)	58 to 71		

Gender categorical Units: Subjects			
Female	37		
Male	40		
ECOG Units: Subjects			
ECOG 0	39		
ECOG 1	34		
ECOG 2	4		

End points

End points reporting groups

Reporting group title	Selumetinib alone
Reporting group description:	
75gm twice daily - continuous	
Reporting group title	Selumetinib (Continuous) plus Paclitaxel
Reporting group description:	
PO Selumetinib - 75mg twice daily - continuous IV Paclitaxel - 80mg/m2 administered on day 1, 8 and 15 (for 6 cycles)	
Reporting group title	Selumetinib plus Paclitaxel
Reporting group description:	
PO Selumetinib - 75mg twice daily - 2 days off prior to (and morning of) each paclitaxel IV Paclitaxel - 80mg/m2 administered on day 1, 8 and 15 (for 6 cycles)	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
Set on the Intention to treat principle retaining patients in their randomised groups irrespective of any protocol deviations	

Primary: Progression Free Survival

End point title	Progression Free Survival
End point description:	
End point type	Primary
End point timeframe:	
Randomisation until disease progression	

End point values	Selumetinib alone	Selumetinib (Continuous) plus Paclitaxel	Selumetinib plus Paclitaxel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	26	25	
Units: Months				
median (confidence interval 95%)	3.45 (2.04 to 4.96)	4.80 (3.45 to 8.25)	4.96 (4.01 to 6.27)	

Statistical analyses

Statistical analysis title	PFS
Comparison groups	Selumetinib alone v Selumetinib (Continuous) plus Paclitaxel v Selumetinib plus Paclitaxel

Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0447 [1]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6074
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.4
upper limit	0.91
Variability estimate	Standard error of the mean
Dispersion value	0.2483

Notes:

[1] - Dispersion value about log hazard ratio (-0.4986)

Secondary: Time To Treatment Failure

End point title	Time To Treatment Failure
End point description:	
End point type	Secondary
End point timeframe:	
Randomisation until time to treatment failure	

End point values	Selumetinib alone	Selumetinib (Continuous) plus Paclitaxel	Selumetinib plus Paclitaxel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	26	25	
Units: Months				
median (confidence interval 95%)	3.45 (2.04 to 5.42)	5.32 (3.45 to 8.67)	5.58 (4.96 to 11.33)	

Statistical analyses

Statistical analysis title	TTF
Comparison groups	Selumetinib alone v Selumetinib (Continuous) plus Paclitaxel v Selumetinib plus Paclitaxel
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022 [2]
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.541

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.347
upper limit	0.842
Variability estimate	Standard error of the mean
Dispersion value	0.269

Notes:

[2] - Standard error about log hazard ratio presented (-0.615)

Secondary: Overall Survival

End point title	Overall Survival

End point description:

End point type	Secondary

End point timeframe:

From Randomisation until Death by any cause

End point values	Selumetinib alone	Selumetinib (Continuous) plus Paclitaxel	Selumetinib plus Paclitaxel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	26	25	
Units: Months				
median (confidence interval 95%)	11.17 (6.73 to 16.5)	8.94 (6.93 to 12.6)	9.10 (5.49 to 15.0)	

Statistical analyses

Statistical analysis title	OS
Comparison groups	Selumetinib alone v Selumetinib (Continuous) plus Paclitaxel v Selumetinib plus Paclitaxel
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.354 [3]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.276
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.828
upper limit	1.967
Variability estimate	Standard error of the mean
Dispersion value	0.263

Notes:
[3] - Dispersion parameter presented about log hazard ratio (0.2439)

Secondary: Response Rate

End point title	Response Rate

End point description:

End point type	Secondary

End point timeframe:
Full study period

End point values	Selumetinib alone	Selumetinib (Continuous) plus Paclitaxel	Selumetinib plus Paclitaxel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	26	25	
Units: Patients	0	4	2	

Statistical analyses

Statistical analysis title	ORR

Statistical analysis description:
Analysis performed on overall response rate

Comparison groups	Selumetinib alone v Selumetinib (Continuous) plus Paclitaxel v Selumetinib plus Paclitaxel
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0866
Method	Fisher exact
Parameter estimate	NA due to zero value
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.642
Variability estimate	Standard error of the mean

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Full study period	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	5

Reporting groups	
Reporting group title	Selumetinib
Reporting group description: -	
Reporting group title	Selumetinib (cont) plus Paclitaxel
Reporting group description: -	
Reporting group title	Selumetinib plus Paclitaxel
Reporting group description: -	

Serious adverse events	Selumetinib	Selumetinib (cont) plus Paclitaxel	Selumetinib plus Paclitaxel
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 26 (42.31%)	15 / 26 (57.69%)	9 / 25 (36.00%)
number of deaths (all causes)	24	22	20
number of deaths resulting from adverse events	0	1	0
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 26 (3.85%)	2 / 26 (7.69%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	2 / 2	0 / 0
Investigations - Other, specify			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 26 (3.85%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Alanine aminotransferase increased			

subjects affected / exposed	1 / 26 (3.85%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood Bilirubin Increased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Vasovagal reaction			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thromboembolic Event			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Haematoma			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Muscle Weakness left-sided			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Headache			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Facial Muscle Weakness			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Seizure			

subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	1 / 26 (3.85%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Paresthesia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
General disorders and administration site conditions			
Fever			
subjects affected / exposed	3 / 26 (11.54%)	6 / 26 (23.08%)	4 / 25 (16.00%)
occurrences causally related to treatment / all	0 / 3	2 / 8	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Fatigue			
subjects affected / exposed	1 / 26 (3.85%)	3 / 26 (11.54%)	2 / 25 (8.00%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pain			
subjects affected / exposed	1 / 26 (3.85%)	2 / 26 (7.69%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Vomiting			
subjects affected / exposed	2 / 26 (7.69%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Malaise			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Odema			

subjects affected / exposed	0 / 26 (0.00%)	2 / 26 (7.69%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Eye infection			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 26 (3.85%)	2 / 26 (7.69%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Constipation			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Nausea			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal distension			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Mucositis oral			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	3 / 26 (11.54%)	2 / 26 (7.69%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 3	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 0
Productive Cough			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Infection			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	1 / 26 (3.85%)	1 / 26 (3.85%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sore Throat			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders			
Akute Kidney Injury			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders - other, specify			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Fracture			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone Pain			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
muscle weakness lower limb			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Chills			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			

subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 26 (0.00%)	2 / 26 (7.69%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Selumetinib	Selumetinib (cont) plus Paclitaxel	Selumetinib plus Paclitaxel
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 26 (96.15%)	24 / 26 (92.31%)	23 / 25 (92.00%)
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 26 (23.08%)	4 / 26 (15.38%)	1 / 25 (4.00%)
occurrences (all)	16	5	2
Alanine aminotransferase increased			
subjects affected / exposed	7 / 26 (26.92%)	7 / 26 (26.92%)	2 / 25 (8.00%)
occurrences (all)	22	7	2
GGT Increased			
subjects affected / exposed	3 / 26 (11.54%)	3 / 26 (11.54%)	0 / 25 (0.00%)
occurrences (all)	3	5	0
Neutrophil count decreased			
subjects affected / exposed	0 / 26 (0.00%)	6 / 26 (23.08%)	3 / 25 (12.00%)
occurrences (all)	0	15	6
Creatinine increased			
subjects affected / exposed	0 / 26 (0.00%)	3 / 26 (11.54%)	1 / 25 (4.00%)
occurrences (all)	0	5	1
Blood bilirubin increased			
subjects affected / exposed	2 / 26 (7.69%)	0 / 26 (0.00%)	2 / 25 (8.00%)
occurrences (all)	3	0	6
Alkaline phosphatase increased			

subjects affected / exposed	2 / 26 (7.69%)	1 / 26 (3.85%)	1 / 25 (4.00%)
occurrences (all)	2	1	2
White Blood Cell Decreased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	3 / 25 (12.00%)
occurrences (all)	0	0	5
Lymphoblast count decreased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	4
Vascular disorders			
Thromboembolic Event			
subjects affected / exposed	0 / 26 (0.00%)	4 / 26 (15.38%)	1 / 25 (4.00%)
occurrences (all)	0	4	2
Epistaxis			
subjects affected / exposed	2 / 26 (7.69%)	5 / 26 (19.23%)	4 / 25 (16.00%)
occurrences (all)	2	7	6
Hypertenstion			
subjects affected / exposed	7 / 26 (26.92%)	9 / 26 (34.62%)	5 / 25 (20.00%)
occurrences (all)	15	18	6
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 26 (3.85%)	9 / 26 (34.62%)	9 / 25 (36.00%)
occurrences (all)	1	11	9
Headache			
subjects affected / exposed	4 / 26 (15.38%)	4 / 26 (15.38%)	1 / 25 (4.00%)
occurrences (all)	4	9	1
Peripheral sensorimotor neuropathy			
subjects affected / exposed	1 / 26 (3.85%)	8 / 26 (30.77%)	8 / 25 (32.00%)
occurrences (all)	1	11	14
Paresthesia			
subjects affected / exposed	2 / 26 (7.69%)	2 / 26 (7.69%)	1 / 25 (4.00%)
occurrences (all)	2	2	1
Dizzyness			
subjects affected / exposed	2 / 26 (7.69%)	4 / 26 (15.38%)	1 / 25 (4.00%)
occurrences (all)	3	4	1
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	12 / 26 (46.15%)	15 / 26 (57.69%)	11 / 25 (44.00%)
occurrences (all)	13	29	20
Oedema			
subjects affected / exposed	6 / 26 (23.08%)	8 / 26 (30.77%)	7 / 25 (28.00%)
occurrences (all)	12	10	8
Pain			
subjects affected / exposed	9 / 26 (34.62%)	10 / 26 (38.46%)	9 / 25 (36.00%)
occurrences (all)	14	18	14
Infusion related reaction			
subjects affected / exposed	0 / 26 (0.00%)	3 / 26 (11.54%)	1 / 25 (4.00%)
occurrences (all)	0	3	1
Fever			
subjects affected / exposed	1 / 26 (3.85%)	1 / 26 (3.85%)	6 / 25 (24.00%)
occurrences (all)	1	2	9
Flu like sypmtoms			
subjects affected / exposed	0 / 26 (0.00%)	4 / 26 (15.38%)	2 / 25 (8.00%)
occurrences (all)	0	5	2
Lethargy			
subjects affected / exposed	2 / 26 (7.69%)	7 / 26 (26.92%)	2 / 25 (8.00%)
occurrences (all)	2	8	2
Edema Limbs			
subjects affected / exposed	2 / 26 (7.69%)	0 / 26 (0.00%)	1 / 25 (4.00%)
occurrences (all)	3	0	1
Eye disorders			
Blurred Vision			
subjects affected / exposed	2 / 26 (7.69%)	3 / 26 (11.54%)	3 / 25 (12.00%)
occurrences (all)	4	3	3
Eye disorders - other, specify			
subjects affected / exposed	1 / 26 (3.85%)	4 / 26 (15.38%)	1 / 25 (4.00%)
occurrences (all)	1	4	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 26 (34.62%)	17 / 26 (65.38%)	15 / 25 (60.00%)
occurrences (all)	13	32	30
Constipation			

subjects affected / exposed	2 / 26 (7.69%)	8 / 26 (30.77%)	10 / 25 (40.00%)
occurrences (all)	3	12	12
Vomiting			
subjects affected / exposed	3 / 26 (11.54%)	7 / 26 (26.92%)	10 / 25 (40.00%)
occurrences (all)	4	13	15
Abdominal pain			
subjects affected / exposed	2 / 26 (7.69%)	4 / 26 (15.38%)	3 / 25 (12.00%)
occurrences (all)	4	5	3
Nausea			
subjects affected / exposed	4 / 26 (15.38%)	14 / 26 (53.85%)	16 / 25 (64.00%)
occurrences (all)	5	17	23
Mucositosis oral			
subjects affected / exposed	3 / 26 (11.54%)	10 / 26 (38.46%)	13 / 25 (52.00%)
occurrences (all)	4	18	21
Gastroesophageal reflux disease			
subjects affected / exposed	2 / 26 (7.69%)	4 / 26 (15.38%)	2 / 25 (8.00%)
occurrences (all)	2	4	3
Dry Mouth			
subjects affected / exposed	3 / 26 (11.54%)	1 / 26 (3.85%)	4 / 25 (16.00%)
occurrences (all)	3	1	4
Dyspepsia			
subjects affected / exposed	1 / 26 (3.85%)	5 / 26 (19.23%)	3 / 25 (12.00%)
occurrences (all)	2	7	4
Abdominal distension			
subjects affected / exposed	1 / 26 (3.85%)	1 / 26 (3.85%)	1 / 25 (4.00%)
occurrences (all)	2	1	1
Sore throat			
subjects affected / exposed	2 / 26 (7.69%)	3 / 26 (11.54%)	0 / 25 (0.00%)
occurrences (all)	2	3	0
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	2 / 26 (7.69%)	6 / 26 (23.08%)	7 / 25 (28.00%)
occurrences (all)	3	8	10
Cough			

subjects affected / exposed	3 / 26 (11.54%)	5 / 26 (19.23%)	4 / 25 (16.00%)
occurrences (all)	3	5	5
Hepatobiliary disorders			
Hypoalbuminaemia			
subjects affected / exposed	1 / 26 (3.85%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences (all)	1	3	0
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	14 / 26 (53.85%)	16 / 26 (61.54%)	10 / 25 (40.00%)
occurrences (all)	44	41	20
Alopecia			
subjects affected / exposed	1 / 26 (3.85%)	8 / 26 (30.77%)	10 / 25 (40.00%)
occurrences (all)	1	12	12
Rash Aceniform			
subjects affected / exposed	6 / 26 (23.08%)	10 / 26 (38.46%)	6 / 25 (24.00%)
occurrences (all)	13	27	13
Rash Generalized			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	4 / 25 (16.00%)
occurrences (all)	1	0	4
Dry Skin			
subjects affected / exposed	3 / 26 (11.54%)	2 / 26 (7.69%)	2 / 25 (8.00%)
occurrences (all)	3	3	2
Nail discolouration			
subjects affected / exposed	0 / 26 (0.00%)	3 / 26 (11.54%)	3 / 25 (12.00%)
occurrences (all)	0	3	3
Papulopustular rash			
subjects affected / exposed	0 / 26 (0.00%)	2 / 26 (7.69%)	0 / 25 (0.00%)
occurrences (all)	0	10	0
Rash pustular			
subjects affected / exposed	2 / 26 (7.69%)	1 / 26 (3.85%)	1 / 25 (4.00%)
occurrences (all)	3	1	1
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 26 (3.85%)	5 / 26 (19.23%)	1 / 25 (4.00%)
occurrences (all)	1	7	2
Rash Macular			

subjects affected / exposed	0 / 26 (0.00%)	2 / 26 (7.69%)	1 / 25 (4.00%)
occurrences (all)	0	6	1
Pruritus			
subjects affected / exposed	2 / 26 (7.69%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences (all)	2	2	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	2 / 25 (8.00%)
occurrences (all)	0	3	3
Infections and infestations			
Infections and Infestations - Other			
subjects affected / exposed	1 / 26 (3.85%)	4 / 26 (15.38%)	3 / 25 (12.00%)
occurrences (all)	1	7	5
Upper respiratory infection			
subjects affected / exposed	0 / 26 (0.00%)	4 / 26 (15.38%)	1 / 25 (4.00%)
occurrences (all)	0	4	1
Eye Infection			
subjects affected / exposed	2 / 26 (7.69%)	2 / 26 (7.69%)	1 / 25 (4.00%)
occurrences (all)	3	2	1
Paronychia			
subjects affected / exposed	0 / 26 (0.00%)	2 / 26 (7.69%)	1 / 25 (4.00%)
occurrences (all)	0	4	1
Mucosal Infection			
subjects affected / exposed	4 / 26 (15.38%)	0 / 26 (0.00%)	0 / 25 (0.00%)
occurrences (all)	4	0	0
Lung Infection			
subjects affected / exposed	0 / 26 (0.00%)	2 / 26 (7.69%)	2 / 25 (8.00%)
occurrences (all)	0	2	2
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	2 / 26 (7.69%)	7 / 26 (26.92%)	9 / 25 (36.00%)
occurrences (all)	4	10	12
Hypokalemia			
subjects affected / exposed	3 / 26 (11.54%)	0 / 26 (0.00%)	1 / 25 (4.00%)
occurrences (all)	6	0	2
Hypophosphatemia			

subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 2	1 / 26 (3.85%) 3	1 / 25 (4.00%) 5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 March 2015	Original approved version, with updates as requested by the competent authority.
20 July 2016	a. Addition of ISRCTN and EudraCT number and update to trial contact details. b. Update to UK Registration statement to document the HRA Approval process. c. Update to trial background to include SUMIT study findings. d. Inclusion criteria: change in reporting units for haemoglobin and creatinine. e. Exclusion criteria: point 2 and point 6 consolidated to avoid repetition i.e. leptomeningeal metastases added to list in point 2 - exclusion for patients who have a known or suspected brain or leptomeningeal metastases, or spinal cord compression, unless asymptomatic. f. Exclusion criteria: point 11, update to wording, effective methods of contraception rather than method. g. Clarification for arm C dosing schedule, selumetinib is to be omitted 2 days prior to (and the morning of) each paclitaxel infusion. h. Addition of information for the preparation of paclitaxel. i. Addition of information for the continued provision of selumetinib. j. Addition of liver MRI as a technique for radiological disease assessment. k. Scan and LVEF assessment times to be performed from the treatment start date. l. Update to the schedule of procedures for clarification only; to clarify screening assessment timeframes, visits for arm A patients, visits and procedures for cycle 7 onwards (continuous selumetinib) and the allowed window for 8 weekly (±3 days) scans and 12 weekly (±14 days) LVEF assessments. m. Medical history review to be carried out at screening & baseline only. n. If a patient has progressed clinic visits will be as per standard of care until death. o. Biopsy procedures to be performed under ultrasound or CT-guidance. p. Update to contraception advice; two reliable methods of contraception required. q. Addition of the use of participant identification centres for the SelPac study. r. Updates to statistical considerations with more detail about planned analyses. s. Update to the statement of indemnity, UoL holds appropriate insurance for the design

24 January 2018	a. Addition of sponsor protocol reference number and update to trial contact details, including named trial statistician. b. Further detail on the rationale for IMP doses provided. c. Retinal vein occlusion added to the list of identified risks with selumetinib use. d. Inclusion criteria: point 7, updated to consider endocrinopathies treated with hormone replacement. e. Inclusion criteria: point 10, requirement for written informed consent added for clarification. f. Exclusion criteria: point 5 updated, statement concerning toxicities from previous treatments removed as this is defined in the inclusion criteria. g. Exclusion criteria: point 7 updated, caveat added for hypertension criteria concerning German-patients only. h. Exclusion criteria: point 12 added, German-patients who are placed on administrative order in an institution or are dependant from the sponsor or study doctor are excluded from the study. i. Further clarification on follow up visit schedule provided. j. Pregnancy test information updated, urine or serum testing is permitted. k. Biochemistry information updated, GGT test is not required on day 8 and 15 of each cycle. Phosphate test added. l. Clarification provided on arm B and C selumetinib dosing following paclitaxel discontinuation. m. Update to selumetinib specific restrictions advice for consistency with the main trial PIS. Patients should avoid consuming grapefruits, Seville oranges, or any other products that may contain these fruits. n. Update to the schedule of procedures for clarification only; to clarify end of treatment, follow-up and end of study visit timeframes. o. Pregnancy testing (for women of child bearing potential only) should be performed at screening and as clinically indicated. p. SAE reporting instructions for site, wording updated for clarity. q. Miscellaneous administrative and formatting changes.
04 July 2018	a. Update to the statistical design, planned sample size and overall study duration. b. Update to the primary analysis method (removal of post stratification factors). c. Removal of the futility analysis. d. Wording for translational sample chain of custody added for clarification purposes. e. Miscellaneous administrative and formatting changes.
22 March 2019	Update to the statistical analysis section for clarification purposes; wording updated to allow analyses to be undertaken with statistical software other than Stata, exploratory translational outcomes paragraph separated into a subsection and wording corrected for final analysis trigger.
13 May 2020	a. Contact details updated. b. Paragraph added to provide information on trials unit merger. c. Update to translational sample storage location. d. Update to the wording for LPLV and trial closure. e. Update to statistical section 10.4 for consistency with LPLV statement.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported