Clinical trial results:
An Open-Label Phase I/II Study of GSK2110183 in Combination with Carboplatin and Paclitaxel in Subjects with Platinum-Resistant Ovarian Cancer

Summary

EudraCT number	2012-002483-27
Trial protocol	GB
Global end of trial date	01 July 2015

Results information

Result version number	v1 (current)
This version publication date	01 March 2017
First version publication date	01 March 2017

Trial information

Trial identification

Sponsor protocol code	PKB116611

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01653912
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Accenture
Sponsor organisation address	1160 W Swedesford Road, Berwyn, United States, PA 19312
Public contact	Study Director, Novartis Pharma AG, 41 613241111,
Scientific contact	Study Director, Novartis Pharma AG, 41 613241111,

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	24 November 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 July 2015
Global end of trial reached?	Yes
Global end of trial date	01 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Phase I
To determine the safety and tolerability of GSK2110183 administered in combination with carboplatin and paclitaxel in subjects with ovarian cancer--which will be used to identify the dosing regimen to be evaluated in Phase II.

Primary Phase II
To evaluate the clinical efficacy (as measured by overall response rate) of GSK2110183 administered in combination with carboplatin and paclitaxel in subjects with recurrent platinum-resistant ovarian cancer.

To evaluate the clinical efficacy (as measured by overall response rate) of GSK2110183 administered in combination with carboplatin and paclitaxel in subjects with platinum refractory ovarian cancer.

Protection of trial subjects:

This clinical study was designed and implemented and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and with the ethical principles laid down in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 July 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 26
Country: Number of subjects enrolled	Russian Federation: 5
Country: Number of subjects enrolled	Australia: 28
Worldwide total number of subjects	59
EEA total number of subjects	26

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)	33
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 10 centers in 3 countries (United Kingdom, Australia, and Russia)

Pre-assignment

Screening details:

A total of 59 subjects (29 subjects in Phase I and 30 subjects in Phase II)

Period 1

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

Blinding implementation details:

This was an open-label study

Arms

Arm title	GSK2110183, Carboplatin and Paclitaxel

Arm description:

Subjects will be treated with a maximum of 6 doses of carboplatin + paclitaxel in combination with continuous daily GSK2110183 followed by GSK2110183 at the single-agent Maximum Tolerated Dose (MTD) of 125 mg or above by mouth daily.
GSK2110183 in combination with carboplatin and paclitaxel: Phase I is a dose escalation evaluation of increasing doses of GSK2110183 administered on a continuous daily schedule in combination with carboplatin Area Under the Curve (AUC) 5 and paclitaxel 175 mg/m2 given every 3 weeks for a maximum 6 cycles. The dosing regimen identified in Phase I will then be evaluated in Phase II, a single arm study focused on clinical efficacy. Treatment with the 3 drugs regimen will continue for a maximum of 6 x 21 day cycles followed by continuous GSK2110183 at the single agent MTD. Subjects may continue on study drug until progression, death or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	GSK2110183
Investigational medicinal product code	GSK2110183
Other name	Afuresertib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

150 mg capsule by mouth daily for 6 months

Investigational medicinal product name	CARBOPLATIN
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Area Under the Curve (AUC) 5

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

Dosage and administration details:

175 mg/m2 intravenously every 3 weeks

Number of subjects in period 1	GSK2110183, Carboplatin and Paclitaxel
Started	59
Completed	47
Not completed	12
Adverse event, non-fatal	4
Clinical Progression	8

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description:

Subjects will be treated with a maximum of six doses of carboplatin + paclitaxel in combination with continuous daily GSK2110183 followed by single agent GSK2110183 at the single-agent MTD of 125 mg or above oral daily.
GSK2110183 in combination with carboplatin and paclitaxel: Phase I is a dose escalation evaluation of increasing doses of GSK2110183 administered on a continuous daily schedule in combination with carboplatin AUC 5 and paclitaxel 175mg/m2 given every three weeks for a maximum 6 cycles. The dosing regimen identified in Phase I will then be evaluated in Phase II, a single arm study focused on clinical efficacy. Treatment with the three drug regimen will continue for a maximum of 6 x 21 day cycles followed by continuous GSK2110183 at the single agent MTD. Subjects may continue on study drug until progression, death or
unacceptable toxicity.

Reporting group values	Overall Study	Total	
Number of subjects	59	59	
Age categorical Units: Subjects			
Adults (18-64 years)	33	33	
From 65-84 years	26	26	
Age continuous Units: years			
arithmetic mean	60.8		
standard deviation	± 9.97	-	
Gender categorical Units: Subjects			
Female	59	59	
Male	0	0	
Ethnicity (NIH/OMB) Units: Subjects			
Not Hispanic or Latino	59	59	
Region of Enrollment Units: Subjects			
Australia	28	28	
United Kingdom	26	26	
Russian Federation	5	5	
Height Units: cm			
arithmetic mean	160.86		
standard deviation	± 6.264	-	
Weight Units: kg			
arithmetic mean	68.74		
standard deviation	± 15.721	-	

End points

End points reporting groups

Reporting group title	GSK2110183, Carboplatin and Paclitaxel

Reporting group description:

Subjects will be treated with a maximum of 6 doses of carboplatin + paclitaxel in combination with continuous daily GSK2110183 followed by GSK2110183 at the single-agent Maximum Tolerated Dose (MTD) of 125 mg or above by mouth daily.
GSK2110183 in combination with carboplatin and paclitaxel: Phase I is a dose escalation evaluation of increasing doses of GSK2110183 administered on a continuous daily schedule in combination with carboplatin Area Under the Curve (AUC) 5 and paclitaxel 175 mg/m2 given every 3 weeks for a maximum 6 cycles. The dosing regimen identified in Phase I will then be evaluated in Phase II, a single arm study focused on clinical efficacy. Treatment with the 3 drugs regimen will continue for a maximum of 6 x 21 day cycles followed by continuous GSK2110183 at the single agent MTD. Subjects may continue on study drug until progression, death or unacceptable toxicity.

Primary: Phase I Tolerability: Number of Subjects With Dose Limiting Toxicity (DLT) Events

End point title	Phase I Tolerability: Number of Subjects With Dose Limiting Toxicity (DLT) Events[1]

End point description:

Dose limiting toxicity: An event was considered a DLT if it had a reasonable causal relationship to study drug and occurs within the first 3 weeks of therapy and met at least one of the following criteria:
• Grade 3 or 4 non-hematologic toxicity as described in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v 4.0, 2009 [NCI, 2009] with the exceptions of Grade 3 electrolyte disturbances that respond to correction within 24 hours; or Grade 3 rash, diarrhea, nausea, vomiting and mucositis that responded to standard medical supportive care within 48 hours).
• Grade 4 neutropenia lasting ≥5 days
• Febrile neutropenia
• Grade 3 thrombocytopenia with bleeding
• Grade 4 thrombocytopenia
• Grade 4 anemia
• Treatment delay of >14 days due to unresolved toxicity
• Alanine aminotransferase (ALT) >3 times upper limit of normal (ULN) with bilirubin >2 times ULN

Analysis Population Description:
All treated Subjects (ATS) in phase I

End point type	Primary

End point timeframe:

Up to Week 3

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Primary endpoint analysis was sequential and was performed adaptively using Bayesian design.

End point values	GSK2110183, Carboplatin and Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: Participants				
Subjects with at Least 1 TEAE of Grade ≥3	26			
Neutropenia	12			
Hypomagnesaemia	6			
Diarrhoea	1			

Rash Maculo-Papular	2			
Vomiting	2			
Anaemia	3			
Rash	2			
Fatigue	1			
Nausea	3			
Neutropenic sepsis	1			
Hyperglycemia	3			

Statistical analyses

No statistical analyses for this end point

Primary: Phase I Safety: Number of Subjects Reporting Adverse Events

End point title	Phase I Safety: Number of Subjects Reporting Adverse

End point description:

Study Treatment refers to GSK2110183 with or without Carboplatin and/or Paclitaxel.

Analysis Population Description:
Phase I ATS population

End point type	Primary

End point timeframe:

Up to Week 3

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical hypothesis was tested in Phase I.

End point values	GSK2110183, Carboplatin and Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: participants				
Treatment Emergent Adverse Events (TEAEs)	29			
Serious TEAEs	14			
GSK2110183 Related Serious TEAEs	7			
GSK2110183 Related TEAEs	29			
Study Treatment Related TEAEs	29			
TEAEs Leading to Discontinuation of GSK2110183	6			
TEAEs Leading to Discontinuation of Study Treatmnt	17			
TEAEs Leading to Dose Modification of GSK2110183	18			
TEAEs Leading to Dose Modification of Study Trtmnt	26			
TEAEs Leading to Death	0			
Dose Limiting Toxicity	3			

Statistical analyses

No statistical analyses for this end point

Primary: Overall Response Rate (ORR) in Phase II Subjects With Recurrent Platinum-resistant Ovarian Cancer (Cohort A)

End point title	Overall Response Rate (ORR) in Phase II Subjects With Recurrent Platinum-resistant Ovarian Cancer (Cohort A)[3]

End point description:

ORR defined as the percentage of subjects with Investigator confirmed complete response (CR) or partial response (PR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria.

Analysis Population Description:
ATS population (Phase II-Cohort A)

End point type	Primary

End point timeframe:

Every 3 weeks up to 6 months

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical hypothesis was tested in Phase I.

End point values	GSK2110183, Carboplatin and Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: participants				
arithmetic mean (confidence interval 95%)	32.1 (15.9 to 52.4)			

Statistical analyses

No statistical analyses for this end point

Primary: ORR in Phase II Subjects With Recurrent Platinum-refractory Ovarian Cancer (Cohort B)

End point title	ORR in Phase II Subjects With Recurrent Platinum-refractory Ovarian Cancer (Cohort B)[4]

End point description:

Due to difficulty in enrolling platinum refractory subjects into Phase II Efficacy-Cohort B, enrollment was stopped prior to having the planned 10-20 subjects enrolled.

End point type	Primary

End point timeframe:

Every 3 weeks up to 6 months

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Primary endpoint analysis was sequential and was performed adaptively using Bayesian design.

End point values	GSK2110183, Carboplatin and Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	0[5]			
Units: Participants				

Notes:

[5] - No analysis done due to difficulty in enrolling Platinum refractory subjects in Cohort B.

Statistical analyses

No statistical analyses for this end point

Secondary: ORR in Phase I Subjects With Recurrent Platinum-resistant Ovarian Cancer

End point title	ORR in Phase I Subjects With Recurrent Platinum-resistant Ovarian Cancer

End point description:

Analysis Population Description:
ATS population

End point type	Secondary

End point timeframe:

Up to Week 3

End point values	GSK2110183, Carboplatin and Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: participants				
arithmetic mean (confidence interval 95%)	24.1 (10.3 to 43.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Tolerability: Number of Subjects With DLT Events During the First 3 Weeks of Combination Therapy

End point title	Phase II Tolerability: Number of Subjects With DLT Events During the First 3 Weeks of Combination Therapy

End point description:

Analysis Population Description:
ATS population

End point type	Secondary
End point timeframe:	
Up to Day 21 (Phase II)	

End point values	GSK2110183, Carboplatin and Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: participants				
Subjects with at Least 1 TEAE of Grade ≥3	26			
Neutropenia	1			
Hypomagnesaemia	3			
Diarrhoea	6			
Rash Maculo-Papular	5			
Vomiting	4			
Anaemia	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Safety: Number of Subjects Reporting Adverse Events

End point title	Phase II Safety: Number of Subjects Reporting Adverse Events
End point description:	
Analysis Population Description: ATS population	
End point type	Secondary
End point timeframe:	
Up to Day 51	

End point values	GSK2110183, Carboplatin and Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: participants				
TEAEs	30			
Serious TEAEs	16			
GSK2110183 Related Serious TEAEs	11			
GSK2110183 Related TEAEs	25			
Study Treatment Related TEAEs	30			
TEAEs Leading to Discontinuation of GSK2110183	9			

TEAEs Leading to Discontinuation of Study Treatmnt	13			
TEAEs Leading to Dose Modification of GSK2110183	17			
TEAEs Leading to Dose Modification of Study Trtmnt	24			
TEAEs Leading to Death	0			
Dose Limiting Toxicity	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II: Response Rate (RR) Defined by Gynecologic Cancer Intergroup (GCIG) CA 125

End point title	Phase II: Response Rate (RR) Defined by Gynecologic Cancer Intergroup (GCIG) CA 125

End point description:

RR as defined by the percentage of phase II subjects with investigator-assessed PR or CR at any time during the study by GCIG cancer antigen (CA) 125

Analysis Population Description:
ATS population

End point type	Secondary

End point timeframe:

From Month 1 to 6

End point values	GSK2110183, Carboplatin and Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: participants				
arithmetic mean (confidence interval 95%)	46.7 (28.3 to 65.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) by RECIST or Clinical Symptomatic Progression of Subjects With Recurrent Platinum-resistant Ovarian Cancer (Phase II-Cohort A)

End point title	Progression Free Survival (PFS) by RECIST or Clinical Symptomatic Progression of Subjects With Recurrent Platinum-resistant Ovarian Cancer (Phase II-Cohort A)

End point description:

PFS is defined as the number of months between date of first GSK2110183 treatment and the earliest date of disease progression by either RECIST or clinical symptomatic progression or death due to any

cause whichever is earlier.

Analysis Population Description:
ATS population

End point type	Secondary

End point timeframe:

After first dose up to Month 6

End point values	GSK2110183, Carboplatin and Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: participants				
arithmetic mean (confidence interval 95%)	6.5 (4.4 to 8.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: PFS by RECIST of Subjects With Recurrent Platinum-resistant Ovarian Cancer (Phase II-Cohort A)

End point title	PFS by RECIST of Subjects With Recurrent Platinum-resistant Ovarian Cancer (Phase II-Cohort A)

End point description:

PFS is defined as the number of months between date of first GSK2110183 treatment and the earliest date of disease progression by RECIST or death due to any cause whichever is earlier.

Analysis Population Description:
ATS population

End point type	Secondary

End point timeframe:

After first dose up to Month 6

End point values	GSK2110183, Carboplatin and Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: participants				
arithmetic mean (confidence interval 95%)	7.1 (6.3 to 9)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Day 51

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	GSK2110183, Carboplatin and Paclitaxel

Reporting group description:

Subjects will be treated with a maximum of 6 doses of carboplatin + paclitaxel in combination with continuous daily GSK2110183 followed by GSK2110183 at the single-agent Maximum Tolerated Dose (MTD) of 125 mg or above by mouth daily.
GSK2110183 in combination with carboplatin and paclitaxel: Phase I is a dose escalation evaluation of increasing doses of GSK2110183 administered on a continuous daily schedule in combination with carboplatin Area Under the Curve (AUC) 5 and paclitaxel 175mg/m2 given every 3 weeks for a maximum 6 cycles. The dosing regimen identified in Phase I will then be evaluated in Phase II, a single arm study focused on clinical efficacy. Treatment with the 3 drugs regimen will continue for a maximum of 6 x 21 day cycles followed by continuous GSK2110183 at the single agent MTD. Subjects may continue on study drug until progression,
death or unacceptable toxicity.

Serious adverse events	GSK2110183, Carboplatin and Paclitaxel		
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 59 (50.85%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Chills			

subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	3 / 59 (5.08%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Influenza Like Illness				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Mucosal Inflammation				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	2 / 59 (3.39%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Drug Hypersensitivity				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypersensitivity				
subjects affected / exposed	2 / 59 (3.39%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Cough				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Dyspnoea				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural Effusion				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Transaminases Increased				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Upper Limb Fracture				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Lethargy				
subjects affected / exposed	1 / 59 (1.69%)			
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	5 / 59 (8.47%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	0 / 0			
Febrile Neutropenia				
subjects affected / exposed	4 / 59 (6.78%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	0 / 0			
Neutropenia				

subjects affected / exposed	2 / 59 (3.39%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	2 / 59 (3.39%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal Pain				
subjects affected / exposed	3 / 59 (5.08%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	2 / 59 (3.39%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Colonic Obstruction				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	8 / 59 (13.56%)			
occurrences causally related to treatment / all	10 / 10			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lip Swelling				

subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Oesophagitis			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Small Intestinal Obstruction			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences causally related to treatment / all	7 / 7		
deaths causally related to treatment / all	0 / 0		
Oesophageal Pain			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash Maculo-Papular			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Renal Failure Acute				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back Pain				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Escherichia Urinary Tract Infection				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis Viral				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lobar Pneumonia				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lower Respiratory Tract Infection				
subjects affected / exposed	2 / 59 (3.39%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Neutropenic Sepsis				
subjects affected / exposed	3 / 59 (5.08%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Oral Infection				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Peritonitis Bacterial			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory Tract Infection Bacterial			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary Tract Infection			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypomagnesaemia			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	GSK2110183, Carboplatin and Paclitaxel		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 59 (100.00%)		
Vascular disorders			
Hot flush			

subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Hypertension			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	5		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	6		
Fatigue			
subjects affected / exposed	37 / 59 (62.71%)		
occurrences (all)	64		
Mucosal inflammation			
subjects affected / exposed	6 / 59 (10.17%)		
occurrences (all)	7		
Oedema peripheral			
subjects affected / exposed	7 / 59 (11.86%)		
occurrences (all)	10		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	9		
Hypersensitivity			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	7		
Reproductive system and breast disorders			
Reproductive system and breast disorders			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	6		
Dyspnoea			

subjects affected / exposed	15 / 59 (25.42%)		
occurrences (all)	20		
Epistaxis			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	4		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	11 / 59 (18.64%)		
occurrences (all)	12		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Blood creatinine increased			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	4		
Platelet count decreased			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	6		
Weight decreased			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
White blood cell count decreased			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	8		
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	5		

Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	8		
Dysgeusia			
subjects affected / exposed	6 / 59 (10.17%)		
occurrences (all)	6		
Headache			
subjects affected / exposed	11 / 59 (18.64%)		
occurrences (all)	15		
Hypoaesthesia			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	9		
Neuropathy peripheral			
subjects affected / exposed	12 / 59 (20.34%)		
occurrences (all)	12		
Neurotoxicity			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	8		
Paraesthesia			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Peripheral sensory neuropathy			
subjects affected / exposed	10 / 59 (16.95%)		
occurrences (all)	13		
Syncope			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 59 (20.34%)		
occurrences (all)	14		
Neutropenia			
subjects affected / exposed	19 / 59 (32.20%)		
occurrences (all)	25		
Thrombocytopenia			

subjects affected / exposed	12 / 59 (20.34%)		
occurrences (all)	18		
Eye disorders			
Eye disorders			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	5		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	6 / 59 (10.17%)		
occurrences (all)	6		
Abdominal pain			
subjects affected / exposed	18 / 59 (30.51%)		
occurrences (all)	26		
Abdominal pain upper			
subjects affected / exposed	10 / 59 (16.95%)		
occurrences (all)	10		
Constipation			
subjects affected / exposed	25 / 59 (42.37%)		
occurrences (all)	34		
Diarrhoea			
subjects affected / exposed	41 / 59 (69.49%)		
occurrences (all)	83		
Dyspepsia			
subjects affected / exposed	11 / 59 (18.64%)		
occurrences (all)	16		
Gastroesophageal Reflux Disease			
subjects affected / exposed	20 / 59 (33.90%)		
occurrences (all)	36		
Mouth ulceration			
subjects affected / exposed	6 / 59 (10.17%)		
occurrences (all)	8		
Nausea			
subjects affected / exposed	39 / 59 (66.10%)		
occurrences (all)	73		
Stomatitis			

subjects affected / exposed	12 / 59 (20.34%)		
occurrences (all)	18		
Vomiting			
subjects affected / exposed	35 / 59 (59.32%)		
occurrences (all)	66		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	32 / 59 (54.24%)		
occurrences (all)	34		
Dry skin			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	6		
Pruritus			
subjects affected / exposed	14 / 59 (23.73%)		
occurrences (all)	15		
Rash			
subjects affected / exposed	17 / 59 (28.81%)		
occurrences (all)	26		
Rash maculo-papular			
subjects affected / exposed	13 / 59 (22.03%)		
occurrences (all)	14		
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	12		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	17 / 59 (28.81%)		
occurrences (all)	29		
Back pain			
subjects affected / exposed	7 / 59 (11.86%)		
occurrences (all)	8		
Myalgia			
subjects affected / exposed	12 / 59 (20.34%)		
occurrences (all)	16		
Pain in extremity			

subjects affected / exposed	6 / 59 (10.17%)		
occurrences (all)	8		
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Oral candidiasis			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	6		
Upper respiratory tract infection			
subjects affected / exposed	6 / 59 (10.17%)		
occurrences (all)	6		
Urinary tract infection			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	30 / 59 (50.85%)		
occurrences (all)	49		
Dehydration			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	5		
Hyperglycaemia			
subjects affected / exposed	6 / 59 (10.17%)		
occurrences (all)	7		
Hypokalaemia			
subjects affected / exposed	7 / 59 (11.86%)		
occurrences (all)	8		
Hypomagnesaemia			
subjects affected / exposed	17 / 59 (28.81%)		
occurrences (all)	18		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 October 2012	Amendment 1: Addition of EudraCT number; Addition of safety evaluation to objectives and endpoints for Phase II; Addition of ability to increase afuresertib dose beyond 125 mg in dose escalation based on emerging data from afuresertib program which resulted in an increase in the number of subjects that could potentially enroll the Phase I part of the study; Removal of eligibility criteria based on restriction of number of prior therapies; Clarification of timing of select assessments in Time and Events Table; Removal of bone scans as method of disease assessment; Clarification of formula for calculation of creatinine clearance; Update of recommendations for managing hyperglycemia; Clarification of monitoring required for carboplatin and paclitaxel specific toxicities; Clarification of carboplatin and paclitaxel sourcing, Addition of specific dose modification guidelines for conduction disorders; Additional QTc stopping criteria added; Insulin monitoring added; Clarification of birth control requirements.
16 May 2013	Amendment 2: Addition of secondary efficacy objectives and endpoints for Phase I; Clarification of cohort 1.5; Removal of requirement for documented response on platinum therapy prior to enrolment for Phase II; Addition of window for time period of progression after most recent therapy for patients eligible for Phase II; Clarification on exclusion criteria for electrocardiogram (ECG) abnormalities; Clarification on Paclitaxel and Carboplatin sourcing; Clarification that Fridericia's formula should be used for QTc; Clarification of timing for 1,5 Ag, PK and CA 125 assessments in Time and Events Table; Removal of urinalysis for lab assessments.
19 November 2013	Amendment 3: Addition of platinum-refractory patient population includes changes in the introduction, objectives, endpoints, study design, number of study subjects, eligibility criteria, data analysis and specifications; Update of data for study PKB115125 to justify use of 150 mg dose of afuresertib in maintenance portion of study drug administration; Addition of optional fresh tumor biopsies for exploratory pharmacodynamic analysis includes changes to objectives, endpoint, time and events table, assessments and data analysis; Update of eligibility criteria focused on enrolment of diabetic subjects based on evaluation of emerging safety data; Update of afuresertib dosage and administration to allow study drug to be taken in the fed or fasted state on non – PK days; Clarification of dose modification recommendations; Update on management of mucositis recommendations; Update of hyperglycemia supportive care recommendations based on review of currently available safety data; Update on dyspepsia supportive care recommendations to include the ability to take afuresertib with a meal; Addition of rash supportive care management guidelines based on review of currently available safety data; Update of meals and dietary recommendations to allow administration of afuresertib with food. Clarification on adverse event (AE) and serious adverse event (SAE) reporting and follow up time period as well as updated SAE Email address and Fax number.

20 March 2014	Amendment 4: Change in target overall response rate for platinum resistant ovarian cancer patient population based on review of published literature evaluating clinical efficacy in similar patient populations. Addition of details regarding interim analysis of median PFS at 6 months. Modification of eligibility criteria for Cohort A to facilitate enrolment. Modification of dispensing of afuresertib every 3 weeks throughout the study. Clarification of how changes in eligibility criteria for Cohort B will be communicated to sites and the study team. Clarification of fasting instructions for subjects undergoing PK sampling to correct internal protocol inconsistencies. Correction of internal consistencies regarding references to investigational product, i.e., replacement of afuresertib with GSK2110183. Clarification of timing of circulating biomarker sample collection so that subjects in Phase II don't have to return to clinic on Cycle 1, Days 8 and 15 just for biomarker sampling.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported