Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled Phase II Trial of Neoadjuvant Carboplatin and Paclitaxel, With or Without Debio 1143 in Patients With Newly Diagnosed Advanced Epithelial Ovarian Cancer.

Summary

EudraCT number	2015-005137-42
Trial protocol	ES BE FR IT
Global end of trial date	03 January 2018

Results information

Result version number	v1 (current)
This version publication date	20 December 2018
First version publication date	20 December 2018

Trial information

Trial identification

Sponsor protocol code	Debio1143-EOC-203

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Debiopharm International, S.A.
Sponsor organisation address	Case postale 5911, Chemin Messidor 5-7, Lausanne, Switzerland, 1002
Public contact	Clinical Department, Debiopharm International, 0041 21 3210 111, ClinicalTrials@debiopharm.com
Scientific contact	Clinical Department, Debiopharm International, 0041 21 3210 111, ClinicalTrials@debiopharm.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	03 January 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 January 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the antitumour activity according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria of paclitaxel + carboplatin with or without Debio 1143 at the end of neoadjuvant treatment (prior to interval debulking surgery) in subjects with newly diagnosed epithelial ovarian cancer (EOC).

Protection of trial subjects:

Written approval of the study protocol and the informed consent was obtained from the independent ethics committee (IEC), prior to initiation of the study. The study was conducted in accordance with local regulations, Good Clinical Practice (GCP), International Council for Harmonisation (ICH) notes for GCP (ICH/CPMP/135/95), and ethical principles that have their origin in the Declaration of Helsinki and its amendments.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 June 2016
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	Spain: 8
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Italy: 12
Worldwide total number of subjects	35
EEA total number of subjects	35

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)	24
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted from 16 June 2017 to 03 Jan 2018 in France, Italy, Spain and Belgium.

Pre-assignment

Screening details:

A total of 46 subjects were screened. Out of 46, 36 subjects were randomised and 35 were treated.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Debio 1143

Arm description:

Debio 1143 was administered orally at a dose of 200 milligram (mg) once daily on Days 1 to 5 of every 21-day cycle in combination with intravenous (IV) paclitaxel 135 milligram per meter square (mg/m^2) and carboplatin administered on Day 1 of every 21-day cycle for 4 cycles.

Arm type	Experimental
Investigational medicinal product name	Debio 1143
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Debio 1143 was administered orally at a dose of 200 mg once daily on Days 1 to 5 of every 21-day cycle.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel 135 mg/m^2 was administered intravenously on Day 1 of every 21-cycle of 4 cycles.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin was administered intravenously on Day 1 of every 21-cycle of 4 cycles.

Arm title	Placebo

Arm description:

Matching placebo to Debio 1143 was administered orally once daily on Days 1 to 5 of every 21-day cycle in combination with standard 3-hour IV paclitaxel 175 mg/m^2 and carboplatin administered on Day 1 of every 21-day cycle for 4 cycles.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Matching placebo to Debio 1143 was administered orally once daily on Days 1 to 5 of every 21-day cycle.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel 175 mg/m^2 was administered intravenously on Day 1 of every 21-cycle of 4 cycles.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin was administered intravenously on Day 1 of every 21-cycle of 4 cycles.

Number of subjects in period 1	Debio 1143	Placebo
Started	22	13
Completed	18	13
Not completed	4	0
Death	1	-
Non-compliance with study drug	1	-
Adverse event	1	-
Progressive disease	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Debio 1143
Reporting group description:	
Debio 1143 was administered orally at a dose of 200 milligram (mg) once daily on Days 1 to 5 of every 21-day cycle in combination with intravenous (IV) paclitaxel 135 milligram per meter square (mg/m^2) and carboplatin administered on Day 1 of every 21-day cycle for 4 cycles.	
Reporting group title	Placebo
Reporting group description:	
Matching placebo to Debio 1143 was administered orally once daily on Days 1 to 5 of every 21-day cycle in combination with standard 3-hour IV paclitaxel 175 mg/m^2 and carboplatin administered on Day 1 of every 21-day cycle for 4 cycles.	

Reporting group values	Debio 1143	Placebo	Total
Number of subjects	22	13	35
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 58.91 ± 8.12	 59.46 ± 9.88	 -
Gender categorical Units: Subjects			
Female	22	13	35
Male	0	0	0

End points

End points reporting groups

Reporting group title	Debio 1143

Reporting group description:

Debio 1143 was administered orally at a dose of 200 milligram (mg) once daily on Days 1 to 5 of every 21-day cycle in combination with intravenous (IV) paclitaxel 135 milligram per meter square (mg/m^2) and carboplatin administered on Day 1 of every 21-day cycle for 4 cycles.

Reporting group title	Placebo

Reporting group description:

Matching placebo to Debio 1143 was administered orally once daily on Days 1 to 5 of every 21-day cycle in combination with standard 3-hour IV paclitaxel 175 mg/m^2 and carboplatin administered on Day 1 of every 21-day cycle for 4 cycles.

Subject analysis set title	Before Surgery: Debio 1143
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Debio 1143 was administered orally at a dose of 200 mg once daily on Days 1 to 5 of every 21-day cycle in combination with intravenous (IV) paclitaxel 135 mg/m^2 and carboplatin administered on Day 1 of every 21-day cycle for 4 cycles.

Subject analysis set title	Before Surgery: Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Matching placebo to Debio 1143 was administered orally once daily on Days 1 to 5 of every 21-day cycle in combination with standard 3-hour IV paclitaxel 175 mg/m^2 and carboplatin administered on Day 1 of every 21-day cycle for 4 cycles.

Subject analysis set title	After Surgery: Debio 1143
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Debio 1143 was administered orally at a dose of 200 mg once daily on Days 1 to 5 of every 21-day cycle in combination with intravenous (IV) paclitaxel 135 mg/m^2 and carboplatin administered on Day 1 of every 21-day cycle for 4 cycles.

Subject analysis set title	After Surgery: Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Matching placebo to Debio 1143 was administered orally once daily on Days 1 to 5 of every 21-day cycle in combination with standard 3-hour IV paclitaxel 175 mg/m^2 and carboplatin administered on Day 1 of every 21-day cycle for 4 cycles.

Primary: Response Rate (RR) Assessed by Central Independent Radiology Committee (CIRC)

End point title	Response Rate (RR) Assessed by Central Independent Radiology Committee (CIRC)[1]

End point description:

Response rate is estimated by complete or partial response based on RECIST v1.1. According to RECIST v1.1, complete response (CR) is defined as disappearance of all target lesions. Any pathological lymph nodes had to have reduction in short axis to less than (<) 10 millimeter (mm). CR had to be confirmed by repeat assessments performed no less than 28 days after the criteria for response were first met to qualify as CR. Partial response (PR) is defined as at least a 30 percent (%) decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameter. PR had to be confirmed by repeat assessments performed no less than 28 days after the criteria for response were first met to qualify as PR. The intent-to-treat (ITT) analysis set included all correctly randomized subjects.

End point type	Primary

End point timeframe:

Cycle 2 (Days 15-21), Cycle 4 (Days 15-21), and at end of study (28 days post surgery); Up to approximately 18 months

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: Only descriptive statistical analysis was planned to be reported for this endpoint.

End point values	Debio 1143	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	13		
Units: percentage of subjects				
number (not applicable)	54.5	23.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Surgical Complete Resection (sCR)

End point title	Rate of Surgical Complete Resection (sCR)

End point description:

Rate of surgical complete resection is defined as no macroscopic residual tumor at time of interval debulking surgery. The ITT analysis set included all correctly randomized subjects.

End point type	Secondary

End point timeframe:

Cycle 2 (Days 15-21), Cycle 4 (Days 15-21), and at end of study (28 days post surgery); Up to approximately 18 months

End point values	Debio 1143	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	13		
Units: percentage of subjects				
number (confidence interval 95%)	88.2 (63.6 to 98.5)	90.9 (58.7 to 99.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Radiological Complete Response (CR)

End point title	Rate of Radiological Complete Response (CR)

End point description:

The rate of radiological CR before and after debulking surgery is reported. The ITT analysis set included all correctly randomized subjects. Here, 'n' signifies the total number of subjects analyzed at specific timepoint.

End point type	Secondary

End point timeframe:

Cycle 2 (Days 15-21), Cycle 4 (Days 15-21), end of treatment (28 days) and at end of study (28 days

End point values	Debio 1143	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	13		
Units: percentage of subjects				
number (confidence interval 95%)				
Before Surgery (n =20, 13) After Surgery (n =14, 8)	0 (0 to 16.8) 78.6 (49.2 to 95.3)	0 (0 to 24.7) 62.5 (24.5 to 91.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Pathological Complete Response (pCR)

End point title	Rate of Pathological Complete Response (pCR)

End point description:

Rate of pathological response (pCR) is defined as no residual invasive cancer at the time of debulking surgery. The ITT analysis set included all correctly randomized subjects.

End point type	Secondary

End point timeframe:

Cycle 2 (Days 15-21), Cycle 4 (Days 15-21), and at end of study (28 days post surgery); Up to approximately 18 months

End point values	Debio 1143	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[2]	11[3]		
Units: percentage of subjects				
number (confidence interval 95%)	5.9 (0.1 to 28.7)	9.1 (0.2 to 41.3)		

Notes:

[2] - Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

[3] - Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Response Rate of Radiological Response

End point title	Response Rate of Radiological Response

End point description:

The ITT analysis set included all correctly randomized subjects. Here 'n' signifies total number of subjects analyzed at specific timepoint. Here, 99999 indicates number and 95%confidence interval for Placebo arm as it is not estimable, since number of subjects analysed was 0.

End point type	Secondary

End point timeframe:

Cycle 2, 4 and 6: Day 15, end of treatment (28 days) and at end of study (28 days post surgery); Up to approximately 18 months

End point values	Debio 1143	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	13		
Units: percentage of subjects				
number (confidence interval 95%)				
Cycle 2 Day 15 (n =20, 13)	40.0 (19.1 to 63.9)	38.5 (13.9 to 68.4)		
Cycle 4 Day 15 (n =16, 9)	75.0 (47.6 to 92.7)	77.8 (40.0 to 97.2)		
Cycle 6 Day 15 (n =1, 0)	0.0 (0.0 to 97.5)	99999 (99999 to 99999)		
End of treatment (n =4, 3)	50.0 (6.8 to 93.2)	100.0 (29.2 to 100.0)		
Early Discontinuation (n =15, 9)	86.7 (59.5 to 98.3)	88.9 (51.8 to 99.7)		
End of study after Post-surgery treatment (n =3,3)	100.0 (29.2 to 100.0)	100.0 (29.2 to 100.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Surgical Intervention

End point title	Duration of Surgical Intervention

End point description:

End point type	Secondary

End point timeframe:

Approximately 28 days

End point values	Debio 1143	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: hours				

Notes:

[4] - Due to premature discontinuation of the study, this endpoint was not analyzed.

[5] - Due to premature discontinuation of the study, this endpoint was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Peri-operative Serious Complications Within the First 28 Days

End point title	Rate of Peri-operative Serious Complications Within the First 28 Days

End point description:

End point type	Secondary

End point timeframe:

First 28 days

End point values	Debio 1143	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: percentage of subjects				
number (not applicable)				

Notes:

[6] - Due to premature discontinuation of the study, this endpoint was not analyzed.

[7] - Due to premature discontinuation of the study, this endpoint was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Post-Operative Death [Less Than (<) 28 days]

End point title	Rate of Post-Operative Death [Less Than (<) 28 days]

End point description:

The ITT analysis set included all correctly randomized subjects.

End point type	Secondary

End point timeframe:

Less than 28 days

End point values	Debio 1143	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	13		
Units: percentage of subjects				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Hospitalization for Debulking Surgery

End point title	Duration of Hospitalization for Debulking Surgery

End point description:

End point type	Secondary

End point timeframe:

From day of surgery to day of discharge (approximately 28 days)

End point values	Debio 1143	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: hours				

Notes:

[8] - Due to premature discontinuation of the study, this endpoint was not analyzed.

[9] - Due to premature discontinuation of the study, this endpoint was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Adverse Events (AEs) and Serious Adverse Events (SAES)

End point title	Number of Subjects with Adverse Events (AEs) and Serious Adverse Events (SAES)

End point description:

An AE was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. An SAE is an AE resulting in any of the following outcomes or deemed significant for any other reason: death; Initial or prolonged in-patient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent were events between first dose of study drug to the end of study that were absent before treatment or that worsened relative to pre-treatment state. AEs and SAEs are assessed by National Cancer Institute Common Terminology Criteria Adverse Events (NCI-CTCAE) v4.03. Safety population included all subjects who received any dose of one of the study drugs.

End point type	Secondary

End point timeframe:

Up to 18 months

End point values	Before Surgery: Debio 1143	Before Surgery: Placebo	After Surgery: Debio 1143	After Surgery: Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	22	13	22	13
Units: subjects				
AEs	22	13	3	1
SAEs	1	1	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve From Time Zero Extrapolated to Infinite time (AUCinf) of Debio 1143 and Debio 1143-MET1

End point title	Area Under the Curve From Time Zero Extrapolated to Infinite time (AUCinf) of Debio 1143 and Debio 1143-MET1[10]

End point description:

Pharmacokinetic (PK) population included all subjects for whom valid PK parameters could be estimated. Here, 99999 indicates geometric mean and geometric co-efficient of variation as it was not estimable, since number of subjects analysed was '0'.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 3.5, 6.5-8h Day 1 Cycle 1

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to report data for only Debio 1143 reporting arm.

End point values	Debio 1143			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: hour*milligram per Litre (h*mg/L)				
geometric mean (geometric coefficient of variation)				
Debio 1143 (n =20) Debio 1143-MET1 (n =0)	15.97 (± 27.66) 99999 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve (AUC) From Time Zero to Time tau (AUC0-tau 24 hour) of Debio 1143 and Debio 1143-MET1

End point title	Area Under the Curve (AUC) From Time Zero to Time tau (AUC0-tau 24 hour) of Debio 1143 and Debio 1143-MET1[11]

End point description:

PK population included all subjects for whom valid PK parameters could be estimated.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 3.5, 6.5-8h Day 1 Cycle 1

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to report data for only Debio 1143 reporting arm.

End point values	Debio 1143			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: h*mg/L				
geometric mean (geometric coefficient of variation)				
Debio 1143 Debio 1143-MET1	12.70 (± 25.78) 10.90 (± 50.54)			

Statistical analyses

No statistical analyses for this end point

Secondary: Metabolite Ratio of Area Under the Curve From Time Zero to Time tau (MR AUCtau 24 hour)

End point title	Metabolite Ratio of Area Under the Curve From Time Zero to Time tau (MR AUCtau 24 hour)[12]

End point description:

PK population included all subjects for whom valid PK parameters could be estimated. Here, 99999 indicates geometric mean and geometric co-efficient of variation as it was not estimable, since number of subjects analysed was '0'.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 3.5, 6.5-8h Day 1 Cycle 1

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to report data for only Debio 1143 reporting arm.

End point values	Debio 1143			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Ratio				
geometric mean (geometric coefficient of variation)				
Debio 1143 (n =20) Debio 1143-MET1 (n =0)	0.86 (± 43.66) 99999 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Debio 1143 and Debio 1143-MET1

End point title	Maximum Observed Plasma Concentration (Cmax) of Debio 1143 and Debio 1143-MET1[13]

End point description:

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 3.5, 6.5-8h Day 1 Cycle 1

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to report data for only Debio 1143 reporting arm.

End point values	Debio 1143			
Subject group type	Reporting group			
Number of subjects analysed	0[14]			
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)	()			

Notes:

[14] - Due to change in the planned analysis, data for this endpoint was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration (Ctrough) of Debio 1143 and Debio 1143-MET1

End point title	Trough Concentration (Ctrough) of Debio 1143 and Debio 1143-MET1[15]

End point description:

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 3.5, 6.5-8h Day 1 Cycle 1

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to report data for only Debio 1143 reporting arm.

End point values	Debio 1143			
Subject group type	Reporting group			
Number of subjects analysed	0[16]			
Units: microgram per milliliter (mcg/mL)				
geometric mean (geometric coefficient of variation)	()			

Notes:

[16] - Due to change in the planned analysis, data for this endpoint was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Average Concentration (Cavg) of Debio 1143 and Debio 1143-MET1

End point title	Average Concentration (Cavg) of Debio 1143 and Debio 1143-MET1[17]

End point description:

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 3.5, 6.5-8h Day 1 Cycle 1

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to report data for only Debio 1143 reporting arm.

End point values	Debio 1143			
Subject group type	Reporting group			
Number of subjects analysed	0[18]			
Units: millilitre (mL)				
geometric mean (geometric coefficient of variation)	()			

Notes:

[18] - Due to change in the planned analysis, data for this endpoint was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Clearance (CL/F) of Debio 1143 and Debio 1143-MET1

End point title	Apparent Clearance (CL/F) of Debio 1143 and Debio 1143-MET1[19]

End point description:

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 3.5, 6.5-8h Day 1 Cycle 1

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to report data for only Debio 1143 reporting arm.

End point values	Debio 1143			
Subject group type	Reporting group			
Number of subjects analysed	0[20]			
Units: Liter per hour (L/h)				
geometric mean (geometric coefficient of variation)	()			

Notes:

[20] - Due to change in the planned analysis, data for this endpoint was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution of Debio 1143 and Debio 1143-MET1

End point title	Volume of Distribution of Debio 1143 and Debio 1143-MET1[21]

End point description:

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 3.5, 6.5-8h Day 1 Cycle 1

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to report data for only Debio 1143 reporting arm.

End point values	Debio 1143			
Subject group type	Reporting group			
Number of subjects analysed	0[22]			
Units: Litre (L)				
geometric mean (geometric coefficient of variation)	()			

Notes:

[22] - Due to change in the planned analysis, data for this endpoint was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Terminal Elimination Half-Life (t1/2) of Debio 1143 and Debio 1143-MET1

End point title	Apparent Terminal Elimination Half-Life (t1/2) of Debio 1143 and Debio 1143-MET1[23]

End point description:

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 3.5, 6.5-8h Day 1 Cycle 1

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to report data for only Debio 1143 reporting arm.

End point values	Debio 1143			
Subject group type	Reporting group			
Number of subjects analysed	0[24]			
Units: hour				
geometric mean (geometric coefficient of variation)	()			

Notes:

[24] - Due to change in the planned analysis, data for this endpoint was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve From Time Zero Extrapolated to Infinite time (AUCinf) of Paclitaxel

End point title	Area Under the Curve From Time Zero Extrapolated to Infinite time (AUCinf) of Paclitaxel

End point description:

PK population included all subjects for whom valid PK parameters could be estimated.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 3.5, 6.5-8h Day 1 Cycle 1

End point values	Debio 1143	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	12		
Units: h*mg/L				
geometric mean (geometric coefficient of variation)	10.81 (± 26.45)	17.23 (± 36.21)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve (AUC) From Time Zero to Time tau (AUC0-tau 24 hour) of Paclitaxel

End point title	Area Under the Curve (AUC) From Time Zero to Time tau (AUC0-tau 24 hour) of Paclitaxel

End point description:

PK population included all subjects for whom valid PK parameters could be estimated.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 3.5, 6.5-8h Day 1 Cycle 1

End point values	Debio 1143	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	12		
Units: h*mg/L				
geometric mean (geometric coefficient of variation)	9.29 (± 22.32)	13.65 (± 34.70)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve (AUC) From Time Zero to Time tau (AUC0-tau 26 hour) of Paclitaxel

End point title	Area Under the Curve (AUC) From Time Zero to Time tau (AUC0-tau 26 hour) of Paclitaxel

End point description:

PK population included all subjects for whom valid PK parameters could be estimated.

End point type	Secondary

End point timeframe:

Pre-dose, 3.5, 6.5-8h Day 1 Cycle 1

End point values	Debio 1143	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	12		
Units: h*mg/L				
geometric mean (geometric coefficient of variation)	9.37 (± 22.41)	13.75 (± 34.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve (AUC) From Time Zero to Time tau (AUC0-tau 31 hour) of Paclitaxel

End point title	Area Under the Curve (AUC) From Time Zero to Time tau (AUC0-tau 31 hour) of Paclitaxel

End point description:

PK population included all subjects for whom valid PK parameters could be estimated.

End point type	Secondary

End point timeframe:

Pre-dose, 3.5, 6.5-8h Day 1 Cycle 1

End point values	Debio 1143	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	12		
Units: h*mg/L				
geometric mean (geometric coefficient of variation)	9.52 (± 22.58)	13.98 (± 34.38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Tc>0.05 micromoles per Litre (mcgmol/L) for Paclitaxel

End point title	Tc>0.05 micromoles per Litre (mcgmol/L) for Paclitaxel

End point description:

PK population included all subjects for whom valid PK parameters could be estimated.

End point type	Secondary

End point timeframe:

Pre-dose, 3.5, 6.5-8h Day 1 Cycle 1

End point values	Debio 1143	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	12		
Units: hour				
geometric mean (geometric coefficient of variation)	24.17 (± 23.34)	29.44 (± 48.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance for Paclitaxel

End point title	Clearance for Paclitaxel

End point description:

PK population included all subjects for whom valid PK parameters could be estimated.

End point type	Secondary

End point timeframe:

Pre-dose, 3.5, 6.5-8h Day 1 Cycle 1

End point values	Debio 1143	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	12		
Units: Litre per hour (L/h)				
geometric mean (geometric coefficient of variation)	20.57 (± 26.33)	16.84 (± 36.40)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve From Time Zero Extrapolated to Infinite time (AUCinf) of Free Carboplatin

End point title	Area Under the Curve From Time Zero Extrapolated to Infinite time (AUCinf) of Free Carboplatin

End point description:

PK population included all subjects for whom valid PK parameters could be estimated.

End point type	Secondary

End point timeframe:

Pre-dose, 3.5, 6.5-8h Day 1 Cycle 1

End point values	Debio 1143	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[25]	11[26]		
Units: minute*milligram per millilitre				
geometric mean (geometric coefficient of variation)	4.51 (± 24.71)	4.81 (± 23.56)		

Notes:

[25] - Here "number of subjects analyzed" signifies total number of subjects analyzed for this endpoint.

[26] - Here "number of subjects analyzed" signifies total number of subjects analyzed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Free Carboplatin

End point title	Maximum Observed Plasma Concentration (Cmax) of Free Carboplatin

End point description:

PK population included all subjects for whom valid PK parameters could be estimated. Here, 'n' signifies total number of subjects analyzed at specific timepoint.

End point type	Secondary

End point timeframe:

Pre-dose, 4, 6.5-8h post-dose Day 1 Cycle 1; Pre-dose, 4h post-dose Day 1 Cycle 2

End point values	Debio 1143	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	12		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1 (n =20, 12)	28614.46 (± 29.61)	27026.82 (± 20.05)		
Cycle 2 Day 1 (n =17, 12)	31396.28 (± 20.58)	29989.05 (± 47.28)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time of Maximum Observed Plasma Concentration (tmax) of Free Carboplatin

End point title	Time of Maximum Observed Plasma Concentration (tmax) of Free Carboplatin

End point description:

PK population included all subjects for whom valid PK parameters could be estimated. Here, 'n' signifies total number of subjects analyzed at specific timepoint.

End point type	Secondary

End point timeframe:

Pre-dose, 4, 6.5-8h post-dose Day 1 Cycle 1; Pre-dose, 4h post-dose Day 1 Cycle 2

End point values	Debio 1143	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	12		
Units: hour				
median (full range (min-max))				
Cycle 1 Day 1 (n =20, 12)	1.00 (0.42 to 1.33)	1.01 (0.50 to 1.35)		
Cycle 2 Day 1 (n =17, 12)	1.00 (0.42 to 1.33)	1.02 (0.00 to 1.20)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 18 months	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Before Surgery: Debio 1143
Reporting group description:	
Debio 1143 was administered orally at a dose of 200 mg once daily on Days 1 to 5 of every 21-day cycle in combination with intravenous (IV) paclitaxel 135 milligram per meter square (mg/m^2) and carboplatin administered on Day 1 of every 21-day cycle for 4 cycles.	
Reporting group title	Before Surgery: Placebo
Reporting group description:	
Matching placebo to Debio 1143 was administered orally once daily on Days 1 to 5 of every 21-day cycle in combination with standard 3-hour IV paclitaxel 175 mg/m^2 and carboplatin administered on Day 1 of every 21-day cycle for 4 cycles.	
Reporting group title	After Surgery: Debio 1143
Reporting group description:	
Debio 1143 was administered orally at a dose of 200 mg once daily on Days 1 to 5 of every 21-day cycle in combination with intravenous (IV) paclitaxel 135 milligram per meter square (mg/m^2) and carboplatin administered on Day 1 of every 21-day cycle for 4 cycles.	
Reporting group title	After Surgery: Placebo
Reporting group description:	
Matching placebo to Debio 1143 was administered orally once daily on Days 1 to 5 of every 21-day cycle in combination with standard 3-hour IV paclitaxel 175 mg/m^2 and carboplatin administered on Day 1 of every 21-day cycle for 4 cycles.	

Serious adverse events	Before Surgery: Debio 1143	Before Surgery: Placebo	After Surgery: Debio 1143
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 22 (4.55%)	1 / 13 (7.69%)	1 / 22 (4.55%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	0 / 22 (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
Pulmonary embolism			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (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

Serious adverse events	After Surgery: Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			

subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Before Surgery: Debio 1143	Before Surgery: Placebo	After Surgery: Debio 1143
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 22 (100.00%)	13 / 13 (100.00%)	3 / 22 (13.64%)
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Hot flush			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Venous thrombosis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 22 (27.27%)	5 / 13 (38.46%)	0 / 22 (0.00%)
occurrences (all)	8	7	0
Asthenia			
subjects affected / exposed	5 / 22 (22.73%)	5 / 13 (38.46%)	0 / 22 (0.00%)
occurrences (all)	6	8	0
Pyrexia			
subjects affected / exposed	1 / 22 (4.55%)	2 / 13 (15.38%)	0 / 22 (0.00%)
occurrences (all)	1	2	0
Mucosal inflammation			
subjects affected / exposed	1 / 22 (4.55%)	1 / 13 (7.69%)	0 / 22 (0.00%)
occurrences (all)	1	1	0

Oedema peripheral			
subjects affected / exposed	1 / 22 (4.55%)	1 / 13 (7.69%)	0 / 22 (0.00%)
occurrences (all)	1	1	0
Mucosal dryness			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	2	0	0
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Genital haemorrhage			
subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	0 / 22 (0.00%)
occurrences (all)	0	2	0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 22 (4.55%)	1 / 13 (7.69%)	0 / 22 (0.00%)
occurrences (all)	2	2	0
Dyspnoea			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Pulmonary embolism			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 22 (13.64%)	1 / 13 (7.69%)	0 / 22 (0.00%)
occurrences (all)	3	1	0
Anxiety			

subjects affected / exposed	0 / 22 (0.00%)	2 / 13 (15.38%)	0 / 22 (0.00%)
occurrences (all)	0	2	0
Emotional disorder			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 22 (22.73%)	2 / 13 (15.38%)	0 / 22 (0.00%)
occurrences (all)	5	3	0
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 22 (9.09%)	1 / 13 (7.69%)	0 / 22 (0.00%)
occurrences (all)	2	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 22 (0.00%)	2 / 13 (15.38%)	0 / 22 (0.00%)
occurrences (all)	0	2	0
Weight decreased			
subjects affected / exposed	0 / 22 (0.00%)	2 / 13 (15.38%)	0 / 22 (0.00%)
occurrences (all)	0	2	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Blood bilirubin increased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Blood creatinine increased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Lipase increased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Neutrophil count decreased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Platelet count decreased			

subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	0 / 22 (0.00%)
occurrences (all)	0	2	0
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	4 / 22 (18.18%)	3 / 13 (23.08%)	0 / 22 (0.00%)
occurrences (all)	4	3	0
Procedural nausea			
subjects affected / exposed	1 / 22 (4.55%)	2 / 13 (15.38%)	0 / 22 (0.00%)
occurrences (all)	1	2	0
Infusion related reaction			
subjects affected / exposed	2 / 22 (9.09%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	4	0	0
Procedural vomiting			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Wound complication			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	2
Neurotoxicity			
subjects affected / exposed	4 / 22 (18.18%)	1 / 13 (7.69%)	0 / 22 (0.00%)
occurrences (all)	6	3	0
Paraesthesia			
subjects affected / exposed	2 / 22 (9.09%)	2 / 13 (15.38%)	0 / 22 (0.00%)
occurrences (all)	2	2	0
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 22 (9.09%)	2 / 13 (15.38%)	0 / 22 (0.00%)
occurrences (all)	2	2	0
Headache			

subjects affected / exposed	2 / 22 (9.09%)	1 / 13 (7.69%)	0 / 22 (0.00%)
occurrences (all)	3	1	0
Neuropathy peripheral			
subjects affected / exposed	3 / 22 (13.64%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	4	0	0
Burning sensation			
subjects affected / exposed	2 / 22 (9.09%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	2	0	0
Dizziness			
subjects affected / exposed	2 / 22 (9.09%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	2	0	0
Dysaesthesia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 13 (7.69%)	0 / 22 (0.00%)
occurrences (all)	1	2	0
Dysgeusia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 13 (7.69%)	0 / 22 (0.00%)
occurrences (all)	1	1	0
Migraine			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Neuralgia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Presyncope			
subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	13 / 22 (59.09%)	9 / 13 (69.23%)	0 / 22 (0.00%)
occurrences (all)	19	16	0
Anaemia			
subjects affected / exposed	5 / 22 (22.73%)	9 / 13 (69.23%)	0 / 22 (0.00%)
occurrences (all)	9	14	0
Leukopenia			
subjects affected / exposed	4 / 22 (18.18%)	4 / 13 (30.77%)	0 / 22 (0.00%)
occurrences (all)	8	6	0

Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	7 / 22 (31.82%)	8 / 13 (61.54%)	1 / 22 (4.55%)
occurrences (all)	10	9	1
Nausea			
subjects affected / exposed	5 / 22 (22.73%)	8 / 13 (61.54%)	0 / 22 (0.00%)
occurrences (all)	6	8	0
Vomiting			
subjects affected / exposed	4 / 22 (18.18%)	6 / 13 (46.15%)	0 / 22 (0.00%)
occurrences (all)	6	6	0
Abdominal pain			
subjects affected / exposed	1 / 22 (4.55%)	3 / 13 (23.08%)	0 / 22 (0.00%)
occurrences (all)	1	6	0
Diarrhoea			
subjects affected / exposed	2 / 22 (9.09%)	1 / 13 (7.69%)	1 / 22 (4.55%)
occurrences (all)	2	1	1
Abdominal pain upper			
subjects affected / exposed	0 / 22 (0.00%)	2 / 13 (15.38%)	1 / 22 (4.55%)
occurrences (all)	0	2	1
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 22 (4.55%)	1 / 13 (7.69%)	0 / 22 (0.00%)
occurrences (all)	1	1	0
Stomatitis			
subjects affected / exposed	2 / 22 (9.09%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	2	0	0
Encapsulating peritoneal sclerosis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Haemorrhoids			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Odynophagia			

subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	7 / 22 (31.82%)	5 / 13 (38.46%)	0 / 22 (0.00%)
occurrences (all)	7	7	0
Pruritus			
subjects affected / exposed	1 / 22 (4.55%)	2 / 13 (15.38%)	0 / 22 (0.00%)
occurrences (all)	1	2	0
Erythema			
subjects affected / exposed	1 / 22 (4.55%)	1 / 13 (7.69%)	0 / 22 (0.00%)
occurrences (all)	1	1	0
Rash			
subjects affected / exposed	2 / 22 (9.09%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	2	0	0
Dry skin			
subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Nail disorder			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Rash maculo-papular			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	2	0	0
Urticaria			
subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Urinary tract pain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 22 (27.27%)	4 / 13 (30.77%)	1 / 22 (4.55%)
occurrences (all)	7	5	1
Myalgia			

subjects affected / exposed	2 / 22 (9.09%)	2 / 13 (15.38%)	1 / 22 (4.55%)
occurrences (all)	4	2	1
Back pain			
subjects affected / exposed	1 / 22 (4.55%)	1 / 13 (7.69%)	1 / 22 (4.55%)
occurrences (all)	1	1	1
Bone pain			
subjects affected / exposed	1 / 22 (4.55%)	1 / 13 (7.69%)	0 / 22 (0.00%)
occurrences (all)	1	1	0
Groin pain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	2	0	0
Pain in extremity			
subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Sepsis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	2 / 22 (9.09%)	2 / 13 (15.38%)	1 / 22 (4.55%)
occurrences (all)	2	3	1
Hypomagnesaemia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 13 (7.69%)	0 / 22 (0.00%)
occurrences (all)	1	1	0

Non-serious adverse events	After Surgery: Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 13 (7.69%)		
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Hot flush			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Venous thrombosis			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Asthenia			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Mucosal inflammation			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Oedema peripheral			

subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Mucosal dryness			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Genital haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Pulmonary embolism			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Anxiety			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		

Emotional disorder			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Blood bilirubin increased			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Blood creatinine increased			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Lipase increased			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Neutrophil count decreased			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Platelet count decreased			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			

Procedural pain subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Procedural nausea subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Infusion related reaction subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Procedural vomiting subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Wound complication subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Nervous system disorders Syncope subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Neurotoxicity subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Paraesthesia subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Headache subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Neuropathy peripheral			

subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Burning sensation subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Dizziness subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Dysaesthesia subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Dysgeusia subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Migraine subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Neuralgia subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Presyncope subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	 0 / 13 (0.00%) 0		
Anaemia subjects affected / exposed occurrences (all)	 0 / 13 (0.00%) 0		
Leukopenia subjects affected / exposed occurrences (all)	 0 / 13 (0.00%) 0		
Eye disorders Vision blurred			

subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Stomatitis			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Encapsulating peritoneal sclerosis			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Haemorrhoids			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Odynophagia			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		

Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Erythema			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Dry skin			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Nail disorder			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Rash maculo-papular			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Urticaria			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Urinary tract pain			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		

Back pain			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Bone pain			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Groin pain			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Respiratory tract infection			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Sepsis			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Hypomagnesaemia			

subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 October 2016	1. Clarified, adjusted, and reorganized the objectives. 2. Modified the statistical method for the analysis of the primary endpoint by biomarker category. 3. Adjusted the derived efficacy parameters and efficacy assessments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
03 November 2017	Sponsor decided to discontinue the study based on the paclitaxel underexposure observed in the investigational arm (Debio 1143 + paclitaxel 135 mg/m2 + carboplatin) reported by the IDMC members during the PK/safety analysis.	-

Notes:

Limitations and caveats

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

Due to the early termination of the study, less number of subjects were randomized.

Notes: