Clinical trial results:
Preoperative window-of-opportunity (WoO) study of Debio 1143 with or without cisplatin (CDDP) in patients with resectable squamous cell carcinoma of the head and neck.

Summary

EudraCT number	2014-004655-31
Trial protocol	FR
Global end of trial date	18 July 2018

Results information

Result version number	v1 (current)
This version publication date	14 August 2019
First version publication date	14 August 2019

Trial information

Trial identification

Sponsor protocol code	Debio 1143-SCCHN-202

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,
Public contact	Vice President Clinical Research & Development, Debiopharm International S.A., 41 213210111, info-international@debiopharm.com
Scientific contact	Vice President Clinical Research & Development, Debiopharm International S.A., 41 213210111, info-international@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	18 July 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the pharmacodynamic (PDy) activity of Debio 1143 alone and Debio 1143 combined with cisplatin (CDDP), in subjects with squamous cell carcinoma of the head and neck (SCCHN)

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	11 August 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 26
Worldwide total number of subjects	26
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)	19

From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in France from 11 August 2015 to 18 Jul 2018.

Pre-assignment

Screening details:

Subjects with newly diagnosed resectable SCCHN who were candidates for primary surgical treatment were administered either Debio 1143 or Debio 1143 in combination with cisplatin or cisplatin alone pre-operatively.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Debio 1143

Arm description:

Subjects were administered Debio 1143 once daily for 15 (± 2) days until surgery, and the last dose was administered on the day of surgery.

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

Dosage and administration details:

Debio 1143 was administered at a dose of 200 milligram (mg) per oral (PO) once daily for 15 (± 2) days until surgery. The last dose was to be administered on the day of surgery.

Arm title	Debio 1143 + Cisplatin

Arm description:

Subjects were administered Debio 1143 once daily for 15 (± 2) days until surgery, and the last dose was administered on the day of surgery. Cisplatin was administered once weekly on study Days 1 and 8.

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

Dosage and administration details:

Debio 1143 was administered at a dose of 200 mg PO once daily for 15 (± 2) days until surgery. The last dose was to be administered on the day of surgery.

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

Dosage and administration details:

Cisplatin was administered at a dose of 40 milligrams per square metre (mg/m^2) intravenous (IV) infusion once weekly on study Days 1 and 8.

Arm title	Cisplatin

Arm description:

Cisplatin was administered once weekly on study Days 1 and 8.

Arm type	Experimental
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin was administered at a dose of 40 mg/m^2 IV infusion once weekly on study Days 1 and 8.

Number of subjects in period 1	Debio 1143	Debio 1143 + Cisplatin	Cisplatin
Started	13	6	7
Completed	12	6	6
Not completed	1	0	1
Surgery cancelled after Serious Adverse Event	-	-	1
Subject postponed surgery	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Debio 1143
Reporting group description:	
Subjects were administered Debio 1143 once daily for 15 (± 2) days until surgery, and the last dose was administered on the day of surgery.	
Reporting group title	Debio 1143 + Cisplatin
Reporting group description:	
Subjects were administered Debio 1143 once daily for 15 (± 2) days until surgery, and the last dose was administered on the day of surgery. Cisplatin was administered once weekly on study Days 1 and 8.	
Reporting group title	Cisplatin
Reporting group description:	
Cisplatin was administered once weekly on study Days 1 and 8.	

Reporting group values	Debio 1143	Debio 1143 + Cisplatin	Cisplatin
Number of subjects	13	6	7
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	60.23	59.83	57.29
standard deviation	± 10.89	± 7.03	± 7.16
Gender categorical			
Units: Subjects			
Female	3	1	1
Male	10	5	6

Reporting group values	Total		
Number of subjects	26		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	5		
Male	21		

End points

End points reporting groups

Reporting group title	Debio 1143
Reporting group description:	
Subjects were administered Debio 1143 once daily for 15 (± 2) days until surgery, and the last dose was administered on the day of surgery.	
Reporting group title	Debio 1143 + Cisplatin
Reporting group description:	
Subjects were administered Debio 1143 once daily for 15 (± 2) days until surgery, and the last dose was administered on the day of surgery. Cisplatin was administered once weekly on study Days 1 and 8.	
Reporting group title	Cisplatin
Reporting group description:	
Cisplatin was administered once weekly on study Days 1 and 8.	

Primary: Effect of Debio 1143 Alone and Debio 1143 Combined With CDDP on cIAP-1 Levels in Subjects With Squamous Cell Carcinoma of the Head and Neck (SCCHN)

End point title	Effect of Debio 1143 Alone and Debio 1143 Combined With CDDP on cIAP-1 Levels in Subjects With Squamous Cell Carcinoma of the Head and Neck (SCCHN)[1][2]
End point description:	
The assessment of the levels of cIAP-1 in tumor biopsies was performed using a validated immunohistochemistry (IHC) assay. The assay was developed using a mouse monoclonal anti-cIAP-1. Per protocol (PP) population was defined as all subjects included in the intent to treat (ITT) population, but excluding those who did not receive the study drugs, did not undergo a pre-treatment and post-treatment PDy assessment, received non-permitted concomitant treatments, violated clinically relevant inclusion/non-inclusion criteria, did not receive at least 75% of the planned Debio 1143 dose, did not receive at least 50% of the planned CDDP dose or did not receive Debio 1143 the day before surgery and on the day of surgery.	
End point type	Primary
End point timeframe:	
Pre-dose (Day 1) and At time of surgery (Day 15)	

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 statistics was planned to be reported for this endpoint.

[2] - 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 be reported for the reporting arms Debio 1143 and Debio 1143 + Cisplatin.

End point values	Debio 1143	Debio 1143 + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	5		
Units: H-score				
arithmetic mean (standard deviation)				
Pre-dose (Day 1)	73.33 (± 86.69)	93.80 (± 131.09)		
At time of surgery (Day 15)	25.25 (± 30.69)	71.40 (± 114.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Vital Sign Weight Over Time

End point title	Change From Baseline in Vital Sign Weight Over Time

End point description:

Safety population was defined as subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP). For arm Debio 1143 + Cisplatin at change at follow-up 1 day post-surgery, 99999 indicates standard deviation, as number of subjects evaluated was 1. For arm Cisplatin at change at follow-up 1 day post-surgery, 99999 indicates arithmetic mean and standard deviation as no subject was evaluated.

End point type	Secondary

End point timeframe:

Baseline, Day 8, Day of surgery (Day 15), follow-up 1 day post-surgery and follow-up 4 weeks post-surgery

End point values	Debio 1143	Debio 1143 + Cisplatin	Cisplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	6	7	
Units: kilogram (kg)				
arithmetic mean (standard deviation)				
Baseline (n=13,6,7)	69.23 (± 9.14)	78.83 (± 17.17)	73.29 (± 16.25)	
Change at Day 8 (n=12,6,6)	0.58 (± 2.61)	0.17 (± 1.33)	-1.50 (± 1.52)	
Change on Day of surgery (Day 15) (n=5,5,3)	0.40 (± 0.55)	0.60 (± 2.07)	-0.33 (± 2.31)	
Change at follow-up 1 day post-surgery (n=6,1,0)	0.67 (± 1.75)	-1.00 (± 99999)	99999 (± 99999)	
Change at follow-up 4weeks post-surgery (n=11,6,7)	-4.00 (± 2.68)	-3.33 (± 1.21)	-4.00 (± 3.27)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Vital Sign Body Surface Area Over Time

End point title	Change From Baseline in Vital Sign Body Surface Area Over Time

End point description:

Safety population was defined as subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP). For arm Debio 1143 + Cisplatin at change at follow-up 1 day post-surgery, 99999 indicates standard deviation, as number of subjects evaluated was 1. For arm Cisplatin at change at

follow-up 1 day post-surgery, 99999 indicates arithmetic mean and standard deviation as no subject was evaluated.

End point type	Secondary

End point timeframe:

Baseline, Day 8, Day of surgery (Day 15), Follow-up 1 day post-surgery and Follow-up 4 weeks post-surgery

End point values	Debio 1143	Debio 1143 + Cisplatin	Cisplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	6	7	
Units: metre square (m^2)				
arithmetic mean (standard deviation)				
Baseline (n=13,6,7)	1.82 (± 0.14)	1.95 (± 0.26)	1.86 (± 0.24)	
Change at day 8 (n=12,6,6)	0.01 (± 0.03)	0.00 (± 0.02)	-0.02 (± 0.02)	
Change at Day of surgery (Day 15) (n=5,5,3)	0.01 (± 0.01)	0.01 (± 0.03)	-0.01 (± 0.03)	
Change at follow-up 1 day post-surgery (n=6,1,0)	0.01 (± 0.03)	-0.01 (± 99999)	99999 (± 99999)	
Change at follow-up 4weeks post-surgery (n=11,6,7)	-0.05 (± 0.03)	-0.04 (± 0.01)	-0.05 (± 0.04)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Vital Sign Heart Rate Over Time

End point title	Change From Baseline in Vital Sign Heart Rate Over Time

End point description:

Safety population was defined as subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP).

End point type	Secondary

End point timeframe:

Baseline, Day 8, Day of surgery (Day 15), Follow-up 1 day post-surgery and Follow-up 4 weeks post-surgery

End point values	Debio 1143	Debio 1143 + Cisplatin	Cisplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	6	7	
Units: beats/min				
arithmetic mean (standard deviation)				
Baseline (n=13,6,7)	74.23 (± 12.84)	69.17 (± 9.37)	70.71 (± 10.92)	
Change at Day 8 (n=12,6,6)	4.75 (± 13.82)	-1.00 (± 6.81)	9.33 (± 10.91)	
Change at Day of surgery (Day 15) (n=8,5,4)	-2.13 (± 9.25)	0.80 (± 8.76)	-0.50 (± 12.87)	

Change at follow-up 1 day post-surgery (n=9,5,2)	6.44 (± 23.75)	19.60 (± 13.01)	26.00 (± 11.31)	
Change at follow-up 4weeks post-surgery (n=12,6,6)	4.50 (± 18.05)	21.33 (± 11.89)	16.33 (± 18.74)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Vital Sign Systolic Blood Pressure Over Time

End point title	Change From Baseline in Vital Sign Systolic Blood Pressure Over Time

End point description:

Safety population was defined as subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP).

End point type	Secondary

End point timeframe:

Baseline, Day 8, Day of surgery (Day 15), Follow-up 1 day post-surgery and Follow-up 4 weeks post-surgery

End point values	Debio 1143	Debio 1143 + Cisplatin	Cisplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	6	7	
Units: millimetre of mercury (mmHg)				
arithmetic mean (standard deviation)				
Baseline (n=13,6,7)	142.31 (± 20.17)	153.67 (± 15.97)	130.00 (± 26.45)	
Change at Day 8 (n=12,6,6)	-11.92 (± 17.12)	-18.00 (± 17.84)	4.33 (± 22.74)	
Change on Day of surgery (Day 15) (n=8,5,4)	-20.25 (± 18.20)	-10.60 (± 9.50)	3.00 (± 29.47)	
Change at follow-up 1 day post-surgery (n=9,5,2)	-15.78 (± 21.79)	-19.60 (± 16.71)	-19.00 (± 9.90)	
Change at follow-up 4weeks post-surgery (n=12,6,6)	-17.50 (± 24.22)	-20.67 (± 21.44)	-13.33 (± 22.10)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Vital Sign Diastolic Blood Pressure Over Time

End point title	Change From Baseline in Vital Sign Diastolic Blood Pressure Over Time

End point description:

Safety population was defined as subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP).

End point type	Secondary

End point timeframe:

Baseline, Day 8, Day of surgery, Follow-up 1 day post-surgery and Follow-up 4 weeks post-surgery

End point values	Debio 1143	Debio 1143 + Cisplatin	Cisplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	6	7	
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline (n=13,6,7)	84.69 (± 11.75)	82.83 (± 14.46)	79.57 (± 12.99)	
Change at Day 8 (n=12,6,6)	-3.83 (± 12.84)	-6.50 (± 15.71)	-3.67 (± 6.35)	
Change on Day of surgery (Day 15) (n=8,5,4)	-13.50 (± 8.65)	3.20 (± 20.97)	-0.50 (± 17.60)	
Change at follow-up 1 day post-surgery (n=9,5,2)	-23.22 (± 14.03)	-18.60 (± 13.97)	-23.50 (± 7.78)	
Change at follow-up 4weeks post-surgery (n=12,6,6)	-8.08 (± 9.34)	-2.83 (± 20.13)	-1.67 (± 12.55)	

Statistical analyses

No statistical analyses for this end point

Secondary: Eastern Cooperative Oncology Group performance status (ECOG PS) Over Time

End point title	Eastern Cooperative Oncology Group performance status (ECOG PS) Over Time

End point description:

Per the inclusion criteria, subjects that had ECOG PS of 0-1 were analysed. Grade 0: Fully active, able to carry on all pre-disease performance without restriction; Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; Grade 2: Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours. Safety population was defined as subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP).

End point type	Secondary

End point timeframe:

Baseline and Follow-up 4 Weeks Post-Surgery (FUPS-4wks)

End point values	Debio 1143	Debio 1143 + Cisplatin	Cisplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	6	7	
Units: subjects				
Baseline-Fully active (n=13,6,7)	9	6	6	
Baseline-Light work (n=13,6,7)	4	0	1	
FUPS-4wks-Fully active (n=11,5,6)	2	2	4	
FUPS-4wks-Light work (n=11,5,6)	8	3	2	

FUPS-4wks-Unable to work (n=11,5,6)	1	0	0	

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

A serious adverse event any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. The safety population included subjects who received a dose of any of the study drugs (Debio 1143 and/or Cisplatin).

End point type	Secondary

End point timeframe:

Screening up to 43 days

End point values	Debio 1143	Debio 1143 + Cisplatin	Cisplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	6	7	
Units: subjects	1	0	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects and Severity of AEs Graded According to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) v4 Criteria

End point title	Number of Subjects and Severity of AEs Graded According to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) v4 Criteria

End point description:

The NCI CTCAE is a descriptive terminology which can be utilized for adverse event (AE) reporting. A grading (severity) scale is provided for each AE term. The CTCAE displays Grades 1 through 5. Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). Grade 3: Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL. Grade 4: Life-threatening consequences; urgent intervention indicated. Grade 5: Death related to AE. Safety population was defined as subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP).

End point type	Secondary

End point timeframe:

Screening up to 43 days

End point values	Debio 1143	Debio 1143 + Cisplatin	Cisplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	6	7	
Units: subjects				
Grade 1	11	5	7	
Grade 2	8	3	6	
Grade 3	2	2	6	
Grade 4	0	0	1	
Unknown	3	1	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects and Severity of Laboratory Abnormalities Graded According to the NCI-CTCAE v4 Criteria

End point title	Number of Subjects and Severity of Laboratory Abnormalities Graded According to the NCI-CTCAE v4 Criteria

End point description:

Laboratory parameters included haematology (activated partial thromboplastin time prolonged [APTT], fibrinogen decreased, haemoglobin increased, anaemia, neutrophil count decreased, platelet count decreased, leukocytosis and white blood cell decreased), clinical chemistry (increased alkaline phosphatase [ALP], increased alanine aminotransferase [ALT], increased aspartate aminotransferase [AST], increased blood bilirubin and increased creatinine). Data for total grades (1-4) has been reported. Safety population was defined as subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP). 99999 indicates that abnormalities were not observed for that arm and specified time point.

End point type	Secondary

End point timeframe:

Before surgery (screening) and On-treatment period (Day 1 up to Day 15)

End point values	Debio 1143	Debio 1143 + Cisplatin	Cisplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	6	7	
Units: subjects				
Before surgery: APTT	99999	99999	99999	
Before surgery: Fibrinogen decreased	6	2	3	
Before surgery: Hemoglobin increased	99999	99999	99999	
Before surgery: Anaemia	6	4	3	
Before surgery: Neutrophil count decreased	99999	99999	99999	

Before surgery: Platelet count decreased	99999	3	99999	
Before surgery: Leukocytosis	99999	99999	99999	
Before surgery: White blood cell decreased	99999	99999	99999	
On-treatment: APTT	99999	99999	99999	
On-treatment: Fibrinogen decreased	6	2	3	
On-treatment: Hemoglobin increased	99999	99999	99999	
On-treatment: Anaemia	13	6	3	
On-treatment: Neutrophil count decreased	99999	99999	99999	
On-treatment: Platelet count decreased	99999	4	99999	
On-treatment: Leukocytosis	99999	99999	99999	
On-treatment: White blood cell decreased	99999	99999	99999	
Before surgery: Increased ALP	2	99999	1	
Before surgery: Increased ALT	1	3	99999	
Before surgery: Increased AST	1	2	99999	
Before surgery: Increased blood bilirubin	99999	1	99999	
Before surgery: Increased creatinine	11	6	2	
On-treatment: Increased ALP	2	99999	1	
On-treatment: Increased ALT	1	3	99999	
On-treatment: Increased AST	3	3	99999	
On-treatment: Increased blood bilirubin	1	2	99999	
On-treatment: Increased creatinine	12	6	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Severe Post-operative Bleeding

End point title	Number of Subjects With Severe Post-operative Bleeding

End point description:

Severe post-operative bleeding was defined as decrease of haemoglobin (Hb) > 2 gram per decilitre (g/dL) and clinical evidence of blood loss (e.g. melena, hematuria or surgical wound bleeding). Safety population included subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP).

End point type	Secondary

End point timeframe:

During 4 weeks post-surgery (up to Day 28 post surgery)

End point values	Debio 1143	Debio 1143 + Cisplatin	Cisplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	6	7	
Units: subjects	1	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Delayed Wound Healing

End point title	Number of Subjects With Delayed Wound Healing

End point description:

Delayed wound healing was defined as presence of surgical wound or surgical wound healing complications at 3-4 weeks from surgery as per the Surgeon's judgment. Safety population included subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP).

End point type	Secondary

End point timeframe:

During 4 weeks post-surgery (up to Day 28 post surgery)

End point values	Debio 1143	Debio 1143 + Cisplatin	Cisplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	6	7	
Units: subjects	2	2	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of Debio 1143 Alone or Combined with CDDP and CDDP Alone on Apoptosis Using Serum Samples

End point title	Effect of Debio 1143 Alone or Combined with CDDP and CDDP Alone on Apoptosis Using Serum Samples

End point description:

Serum samples were obtained from subjects at baseline, during and after treatment with Debio 1143 for the detection (by ELISA) of caspase-cleaved cytokeratin (CK) 18 fragment M30 antigen (CK18-M30), which is a marker of epithelial cellular apoptosis. PP population was defined as all subjects included in ITT population, but excluding those who did not receive the study drugs, did not undergo a pre-treatment and post-treatment PDy assessment, received non-permitted concomitant treatments, violated clinically relevant inclusion/non-inclusion criteria, did not receive at least 75% of the planned Debio 1143 dose, did not receive at least 50% of the planned CDDP dose or did not receive Debio 1143 the day before surgery and on the day of surgery.

End point type	Secondary

End point timeframe:

Day 1-Pre Dose, Day 1 - 4 Hours Post-Dose, Day of Surgery (Day 15) - Pre-Dose, Day of Surgery (Day 15) - 4 Hours Post-Dose and End of Study - 4 Weeks Post-Dose

End point values	Debio 1143	Debio 1143 + Cisplatin	Cisplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	5	6	
Units: units per litre (U/L)				
arithmetic mean (standard deviation)				
CK18-M30: Day 1 - Pre-Dose (n=9,5,6)	225.60 (± 93.63)	232.78 (± 228.00)	179.00 (± 66.29)	
CK18-M30: Day 1 - 4 Hours Post-Dose (n=9,5,6)	218.45 (± 73.38)	224.51 (± 198.89)	146.16 (± 28.89)	
CK18-M30: Day of Surgery - Pre-Dose (n=8,5,5)	273.4 (± 92.84)	260.67 (± 180.50)	173.51 (± 89.05)	
CK18-M30:Day of Surgery-4Hours Post-Dose (n=9,5,6)	270.00 (± 73.56)	304.17 (± 254.60)	152.65 (± 32.92)	
CK18-M30:End of Study-4 Weeks Post-Dose (n=9,4,4)	198.37 (± 65.11)	160.87 (± 90.16)	148.86 (± 40.94)	

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of Debio 1143 Alone or Combined with CDDP and CDDP Alone on Apoptosis Using Tumor Samples

End point title	Effect of Debio 1143 Alone or Combined with CDDP and CDDP Alone on Apoptosis Using Tumor Samples

End point description:

The effect of treatment on apoptosis was evaluated based on the levels of cleaved caspase-3, given that inhibitor of apoptosis protein suppress apoptosis by blocking caspases. PP population was defined as all subjects included in ITT population, but excluding those who did not receive the study drugs, did not undergo a pre-treatment and post-treatment PDy assessment, received non-permitted concomitant treatments, violated clinically relevant inclusion/non-inclusion criteria, did not receive at least 75% of the planned Debio 1143 dose, did not receive at least 50% of the planned CDDP dose or did not receive Debio 1143 the day before surgery and on the day of surgery.

End point type	Secondary

End point timeframe:

Pre dose (Day 1) and at time of surgery (Day 15)

End point values	Debio 1143	Debio 1143 + Cisplatin	Cisplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	5	6	
Units: per millimetre square (/mm²)				
arithmetic mean (standard deviation)				
Cleaved Caspase-3 Positive Cells: Pre dose (Day 1)	0.67 (± 1.15)	0.00 (± 0.00)	0.00 (± 0.00)	
Cleaved Caspase-3Positive Cells:At time of surgery	1.50 (± 1.98)	0.00 (± 0.00)	0.00 (± 0.00)	

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of Debio 1143 Alone or Combined with CDDP and CDDP Alone on Necrosis

End point title	Effect of Debio 1143 Alone or Combined with CDDP and CDDP Alone on Necrosis

End point description:

PP population was defined as all subjects included in ITT population, but excluding those who did not receive the study drugs, did not undergo a pre-treatment and post-treatment PDy assessment, received non-permitted concomitant treatments, violated clinically relevant inclusion/non-inclusion criteria, did not receive at least 75% of the planned Debio 1143 dose, did not receive at least 50% of the planned CDDP dose or did not receive Debio 1143 the day before surgery and on the day of surgery.

End point type	Secondary

End point timeframe:

Pre dose (Day 1) and at time of surgery (Day 15)

End point values	Debio 1143	Debio 1143 + Cisplatin	Cisplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	5	6	
Units: percent				
arithmetic mean (standard deviation)				
Pre dose (Day 1)	0.83 (± 2.89)	0.00 (± 0.00)	0.00 (± 0.00)	
At time of surgery (Day 15)	1.67 (± 5.77)	0.00 (± 0.00)	0.00 (± 0.00)	

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of Debio 1143 Alone or Combined with CDDP and CDDP Alone on Proliferation Markers in Tumors

End point title	Effect of Debio 1143 Alone or Combined with CDDP and CDDP Alone on Proliferation Markers in Tumors

End point description:

The expression of the Ki67 protein was used as a proliferation marker. PP population was defined as all subjects included in ITT population, but excluding those who did not receive the study drugs, did not undergo a pre-treatment and post-treatment PDy assessment, received non-permitted concomitant treatments, violated clinically relevant inclusion/non-inclusion criteria, did not receive at least 75% of the planned Debio 1143 dose, did not receive at least 50% of the planned CDDP dose or did not receive Debio 1143 the day before surgery and on the day of surgery.

End point type	Secondary

End point timeframe:

Pre dose (Day 1) and At time of surgery (Day 15)

End point values	Debio 1143	Debio 1143 + Cisplatin	Cisplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	5	6	
Units: percent				
arithmetic mean (standard deviation)				
Pre dose (Day 1)	64.17 (± 23.53)	91.00 (± 2.24)	40.83 (± 34.84)	
At time of surgery (Day 15)	70.83 (± 25.12)	67.00 (± 26.4)	61.67 (± 27.87)	

Statistical analyses

No statistical analyses for this end point

Secondary: Measurement of any Early Biological Response to Debio 1143 Alone or Combined With CDDP and CDDP Alone by 18F-FDG PET

End point title	Measurement of any Early Biological Response to Debio 1143 Alone or Combined With CDDP and CDDP Alone by 18F-FDG PET

End point description:

The biological response was assessed by treatment cohort as the standardised uptake value (SUV) percentage change from baseline to Day -1 prior to surgery (S-1). PP population was defined as all subjects included in ITT population, but excluding those who did not receive the study drugs, did not undergo a pre-treatment and post-treatment PDy assessment, received non-permitted concomitant treatments, violated clinically relevant inclusion/non-inclusion criteria, did not receive at least 75% of the planned Debio 1143 dose, did not receive at least 50% of the planned CDDP dose or did not receive Debio 1143 the day before surgery and on the day of surgery.

End point type	Secondary

End point timeframe:

From baseline to Day -1 prior to surgery (Day 14)

End point values	Debio 1143	Debio 1143 + Cisplatin	Cisplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	5	4	
Units: percent change				
arithmetic mean (standard deviation)	6.47 (± 26.90)	-8.75 (± 41.19)	24.29 (± 58.42)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Pre-dose for Cytokine and Chemokine

End point title	Percent Change From Pre-dose for Cytokine and Chemokine

End point description:

The downstream effects of IAP inhibition by Debio 1143 on NF-κB signaling were assessed by measuring level of cytokines and chemokines using multiplex assay, which allows detection of 30 biomarkers. PP population was defined as all subjects included in ITT population, but excluding those who did not receive the study drugs, did not undergo a pre-treatment and post-treatment PDy assessment, received non-permitted concomitant treatments, violated clinically relevant inclusion/non-inclusion criteria, did not receive at least 75% of the planned Debio 1143 dose, did not receive at least 50% of the planned CDDP dose or did not receive Debio 1143 the day before surgery and on the day of surgery.

End point type	Secondary

End point timeframe:

Day of surgery (Day 15)

End point values	Debio 1143	Debio 1143 + Cisplatin	Cisplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	5	6	
Units: percent change				
arithmetic mean (standard deviation)				
Tumor necrosis factor alpha (TNFα) (n= 10, 1, 2)	26.68 (± 21.01)	14.86 (± 99999)	1.17 (± 16.84)	
Monocyte chemoattractant protein-1 (n=11, 2, 0)	31.79 (± 17.6)	53.63 (± 10.67)	99999 (± 99999)	
CK18-M30 (n=8,5,5)	53.92 (± 94.02)	37.49 (± 50.96)	-0.49 (± 26.63)	
Interferon gamma (IFNg) (n=11,2,3)	38.5 (± 118.06)	0 (± 0)	-26.01 (± 45.05)	
Eotaxin-1 (n=10,2,0)	1.64 (± 25.19)	13.96 (± 38.01)	99999 (± 99999)	
Eotaxin-3 (n=9,2,0)	0 (± 0)	7.69 (± 10.88)	99999 (± 99999)	
GMCSF (n=2,0,2)	0 (± 0)	99999 (± 99999)	0 (± 0)	
Interleukin (IL) 10 (n=10,4,3)	0 (± 0)	0 (± 0)	0 (± 0)	
IL12 IL23p40 (n=11,5,5)	138.47 (± 64.92)	40.28 (± 95.68)	-32.61 (± 17.27)	
IL12p70 (n=5,1,2)	0 (± 0)	0 (± 9999)	0 (± 0)	
IL13 (n=6,3,0)	0 (± 0)	0 (± 0)	99999 (± 99999)	
IL15 (n=9,5,5)	73.16 (± 64.83)	28.72 (± 14.19)	1.33 (± 10.19)	
IL16 (n=11,5,5)	26.16 (± 47.46)	-15.32 (± 28.72)	35.05 (± 81.44)	
IL17 (n=2,4,5)	0 (± 0)	29.26 (± 58.53)	0 (± 0)	
IL1a (n=0,1,0)	99999 (± 99999)	0 (± 99999)	99999 (± 99999)	
IL1b (n=0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	
IL2 (n=3,1,1)	0 (± 0)	0 (± 99999)	0 (± 99999)	
IL4 (n=4,1,1)	0 (± 0)	0 (± 99999)	0 (± 99999)	

IL5 (n=2,4,0)	0 (± 0)	0 (± 0)	99999 (± 99999)	
IL6 (n=11,5,5)	0 (± 0)	-14.10 (± 31.53)	36.86 (± 121.5)	
IL7 (n=11,5,5)	-18.5 (± 38.99)	-47.57 (± 21.82)	-30.12 (± 33.45)	
IL8 HA (n=0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	
IL8 LA (n=11,2,2)	51.25 (± 118.15)	-16.33 (± 15.26)	23.44 (± 19.97)	
Interferon inducible protein10 (IP10) (n=11,2,0)	14.01 (± 36.35)	27.16 (± 11.80)	99999 (± 99999)	
Monocyte chemoattractant protein-4 (n=11,2,0)	27.02 (± 43.33)	29.02 (± 29.16)	99999 (± 99999)	
Macrophage derived chemokine (MDC) (n=11,2,0)	46.47 (± 34.97)	7.13 (± 42.13)	99999 (± 99999)	
Macrophage inflammatory protein 1 alpha (n=3,1,0)	0 (± 0)	0 (± 99999)	99999 (± 99999)	
Macrophage inflammatory protein 1 beta (n=11,2,0)	-2.21 (± 16.79)	1.12 (± 48)	99999 (± 99999)	
TARC (n=11,2,0)	88.73 (± 85.30)	50.65 (± 69.25)	99999 (± 99999)	
TNFβ (n=3,3,1)	0 (± 0)	0 (± 0)	0 (± 99999)	
Vascular endothelial growth factor (n=10,5,5)	3.20 (± 32.48)	-15.53 (± 29.33)	-10.21 (± 33.74)	
CK18-M65 (n=10,5,5)	234.56 (± 304.57)	96.23 (± 189.02)	29.76 (± 70.65)	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) of Debio 1143 and Metabolite D 1143-MET1 in Plasma

End point title	Maximum Plasma Concentration (Cmax) of Debio 1143 and Metabolite D 1143-MET1 in Plasma[3]

End point description:

Safety population was defined as subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP).

End point type	Secondary

End point timeframe:

Day 1 and Day 8

Notes:

[3] - 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 be reported for the reporting arms Debio 1143 and Debio 1143 + Cisplatin.

End point values	Debio 1143	Debio 1143 + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	6		
Units: nanogram/millilitre (ng/mL)				
geometric mean (geometric coefficient of variation)				

Debio 1143: Day 1 (n=13,6)	1999.84 (± 68.08)	2039.25 (± 24.43)		
Debio 1143: Day 8 (n=13,3)	2129.74 (± 50.91)	1743.57 (± 27.26)		
Debio 1143 Metabolite: Day 1 (n=13,6)	979.63 (± 49.07)	855.65 (± 31.32)		
Debio 1143 Metabolite: Day 8 (n=13,3)	1400.79 (± 43.99)	878.97 (± 19.94)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Concentration (Tmax) Debio 1143 and Metabolite D 1143-MET1 in Plasma

End point title	Time to Maximum Concentration (Tmax) Debio 1143 and Metabolite D 1143-MET1 in Plasma[4]

End point description:

Safety population was defined as subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP).

End point type	Secondary

End point timeframe:

Day 1 and Day 8

Notes:

[4] - 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 be reported for the reporting arms Debio 1143 and Debio 1143 + Cisplatin.

End point values	Debio 1143	Debio 1143 + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	6		
Units: hour (h)				
median (full range (min-max))				
Debio 1143: Day 1 (n=13,6)	1.50 (0.38 to 3.10)	1.09 (0.45 to 1.58)		
Debio 1143: Day 8 (n=13,3)	1.50 (0.47 to 4.25)	1.75 (1.50 to 3.03)		
Debio 1143 Metabolite: Day 1 (n=13,6)	3.02 (1.50 to 23.60)	2.98 (1.50 to 7.67)		
Debio 1143 Metabolite: Day 8 (n=13,3)	3.00 (1.58 to 6.00)	6.12 (1.50 to 6.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration-time curve (AUC) on the Dosing Interval Debio 1143 and Metabolite D 1143-MET1 in Plasma

End point title	Area under the plasma concentration-time curve (AUC) on the Dosing Interval Debio 1143 and Metabolite D 1143-MET1 in

	Plasma[5]

End point description:

Safety population was defined as subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP).

End point type	Secondary

End point timeframe:

Day 1 and Day 8

Notes:

[5] - 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 be reported for the reporting arms Debio 1143 and Debio 1143 + Cisplatin.

End point values	Debio 1143	Debio 1143 + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	6		
Units: hour*nanogram per millilitre (h*ng/mL)				
geometric mean (geometric coefficient of variation)				
Debio 1143: Day 1 (n=13,6)	8037.79 (± 57.94)	8484.93 (± 40.83)		
Debio 1143: Day 8 (n=13,3)	9643.20 (± 44.77)	7621.50 (± 40.05)		
Debio 1143 Metabolite: Day 1 (n=11,5)	11114.70 (± 47.60)	8812.51 (± 32.66)		
Debio 1143 Metabolite: Day 8 (n=11,2)	17471.39 (± 53.10)	11200.00 (± 0.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: T1/2 Debio 1143 and Metabolite D 1143-MET1 in Plasma

End point title	T1/2 Debio 1143 and Metabolite D 1143-MET1 in Plasma[6]

End point description:

Safety population included subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP). For arm Debio 1143 + Cisplatin at Day 8 for Debio 1143 Metabolite, 99999 indicates standard deviation, as number of subjects evaluated was 0.

End point type	Secondary

End point timeframe:

Day 1 and Day 8

Notes:

[6] - 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 be reported for the reporting arms Debio 1143 and Debio 1143 + Cisplatin.

End point values	Debio 1143	Debio 1143 + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	6		
Units: hour				
geometric mean (geometric coefficient of variation)				
Debio 1143: Day 1 (n=12,6)	6.2 (± 9.9)	6.11 (± 14.58)		
Debio 1143: Day 8 (n=13,3)	6.82 (± 18.71)	6.96 (± 6.79)		
Debio 1143 Metabolite: Day 1 (n=7,2)	7.43 (± 22.24)	6.3 (± 11.58)		
Debio 1143 Metabolite: Day 8 (n=4,0)	6.17 (± 13.4)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Ctrough Debio 1143 and Metabolite D 1143-MET1 in Plasma

End point title	Ctrough Debio 1143 and Metabolite D 1143-MET1 in Plasma[7]

End point description:

Safety population was defined as subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP).

End point type	Secondary

End point timeframe:

Day 2, Day 8, Day 9, Day of Surgery (Day 15), Follow-up (FU) 1 Day Post-Surgery (Day 16)

Notes:

[7] - 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 be reported for the reporting arms Debio 1143 and Debio 1143 + Cisplatin.

End point values	Debio 1143	Debio 1143 + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	6		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Debio 1143: Day 2 (n=13,6)	51.39 (± 81.17)	53.44 (± 54.49)		
Debio 1143: Day 8 (n=12,4)	65.03 (± 72.79)	63.20 (± 9.13)		
Debio 1143: Day 9 (n=13,4)	71.18 (± 61.49)	63.53 (± 49.25)		
Debio 1143: Day of Surgery (n=12,6)	93.32 (± 71.11)	56.84 (± 87.95)		
Debio 1143: FU 1 Day Post-Surgery (n=12,6)	88.49 (± 86.08)	63.04 (± 39.50)		
Debio 1143 Metabolite: Day 2 (n=13,6)	201.89 (± 79.11)	124.71 (± 37.49)		
Debio 1143 Metabolite: Day 8 (n=12,4)	317.00 (± 106.60)	257.13 (± 27.74)		
Debio 1143 Metabolite: Day 9 (n=13,4)	301.12 (± 123.64)	191.73 (± 101.92)		

Debio 1143 Metabolite: Day of Surgery (n=12,6)	331.18 (± 99.44)	87.04 (± 243.05)		
Debio 1143 Metabolite:FU 1Day Post-Surgery(n=12,6)	332.68 (± 115.35)	102.61 (± 95.10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Average Concentration (Cav) Debio 1143 and Metabolite D 1143-MET1 in Plasma

End point title	Average Concentration (Cav) Debio 1143 and Metabolite D 1143-MET1 in Plasma[8]

End point description:

Safety population was defined as subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP).

End point type	Secondary

End point timeframe:

Day 8

Notes:

[8] - 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 be reported for the reporting arms Debio 1143 and Debio 1143 + Cisplatin.

End point values	Debio 1143	Debio 1143 + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	6		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Debio 1143: Day 8 (n=13,3)	401.49 (± 44.73)	317.87 (± 40.03)		
Debio 1143 Metabolite: Day 8 (n=11,2)	727.71 (± 53.06)	467.00 (± 0.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation Ratio Based on Cmax (ARCmax) Debio 1143 and Metabolite D 1143-MET1 in Plasma

End point title	Accumulation Ratio Based on Cmax (ARCmax) Debio 1143 and Metabolite D 1143-MET1 in Plasma[9]

End point description:

Accumulation ratio based on Cmax is calculated as Cmax(Day 8)/Cmax(Day 1). Safety population was defined as subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP).

End point type	Secondary

End point timeframe:

Day 8

Notes:

[9] - 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 be reported for the reporting arms Debio 1143 and Debio 1143 + Cisplatin.

End point values	Debio 1143	Debio 1143 + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	6		
Units: ratio				
geometric mean (geometric coefficient of variation)				
Debio 1143: Day 8 (n=13,3)	1.07 (± 44.07)	0.90 (± 28.18)		
Debio 1143 Metabolite: Day 8 (n=13,3)	1.43 (± 56.23)	1.20 (± 22.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation Ratio Based on AUC (ARAUC) Debio 1143 and Metabolite D 1143-MET1 in Plasma

End point title	Accumulation Ratio Based on AUC (ARAUC) Debio 1143 and Metabolite D 1143-MET1 in Plasma[10]

End point description:

ARAUCt was calculated as AUCτ(Day 8)/AUCτ(Day 1). Safety population was defined as subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP).

End point type	Secondary

End point timeframe:

Day 8

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 be reported for the reporting arms Debio 1143 and Debio 1143 + Cisplatin.

End point values	Debio 1143	Debio 1143 + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	6		
Units: ratio				
geometric mean (geometric coefficient of variation)				
Debio 1143: Day 8 (n=13,3)	1.20 (± 37.41)	1.01 (± 29.81)		
Debio 1143 Metabolite: Day 8 (n=10,2)	1.39 (± 55.40)	1.26 (± 7.28)		

Statistical analyses

No statistical analyses for this end point

Secondary: Linearity Index Based on AUC (LIAUC) Debio 1143 and Metabolite D 1143-MET1 in Plasma

End point title	Linearity Index Based on AUC (LIAUC) Debio 1143 and Metabolite D 1143-MET1 in Plasma[11]

End point description:

LIAUC, calculated as AUCτ(Day 8)/AUC(Day 1). Safety population was defined as subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP). For arm Debio 1143 + Cisplatin, Debio 1143 metabolite category, 99999 indicates geometric mean and geometric CV as no subject was evaluated at the specified time point.

End point type	Secondary

End point timeframe:

Day 8

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 be reported for the reporting arms Debio 1143 and Debio 1143 + Cisplatin.

End point values	Debio 1143	Debio 1143 + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	6		
Units: ratio				
geometric mean (geometric coefficient of variation)				
Debio 1143: Day 8 (n=12,3)	1.15 (± 39.02)	0.96 (± 27.80)		
Debio 1143 Metabolite: Day 8 (n=5,0)	0.85 (± 48.01)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation Index (AI) Debio 1143 and Metabolite D 1143-MET1 in Plasma

End point title	Accumulation Index (AI) Debio 1143 and Metabolite D 1143-MET1 in Plasma[12]

End point description:

AI calculated as 1/|1-e- λ|. Safety population was defined as subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP). For arm Debio 1143 + Cisplatin, Debio 1143 metabolite category, 99999 indicates geometric mean and geometric CV, as no subject was evaluated at the specified time point.

End point type	Secondary

End point timeframe:

Day 8

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 be reported for the reporting arms Debio 1143 and Debio 1143 + Cisplatin.

End point values	Debio 1143	Debio 1143 + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	6		
Units: ratio				
geometric mean (geometric coefficient of variation)				
Debio 1143: Day 8 (n=13,3)	1.10 (± 4.25)	1.10 (± 1.82)		
Debio 1143 Metabolite: Day 8 (n=4,0)	1.07 (± 3.06)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Total Body Clearance (CL/F) Debio 1143 in Plasma

End point title	Apparent Total Body Clearance (CL/F) Debio 1143 in Plasma[13]

End point description:

Apparent total body clearance (oral clearance) to be calculated as dose/AUC∞. Safety population was defined as subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP).

End point type	Secondary

End point timeframe:

Day 1 and Day 8

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 be reported for the reporting arms Debio 1143 and Debio 1143 + Cisplatin.

End point values	Debio 1143	Debio 1143 + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	6		
Units: litre per hour (L/h)				
geometric mean (geometric coefficient of variation)				
Debio 1143: Day 1 (n=12,6)	23.91 (± 61.96)	22.28 (± 41.39)		
Debio 1143: Day 8 (n=13,3)	20.74 (± 44.64)	26.22 (± 40.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution During the Terminal Phase (V/F) of Debio 1143 Alone

End point title	Apparent Volume of Distribution During the Terminal Phase (V/F) of Debio 1143 Alone[14]

End point description:

Apparent volume of distribution during the terminal phase to be calculated as (CL/F)/λz. Safety population was defined as subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP).

End point type	Secondary

End point timeframe:

Day 1 and Day 8

Notes:

[14] - 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 be reported for the reporting arms Debio 1143 and Debio 1143 + Cisplatin.

End point values	Debio 1143	Debio 1143 + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	6		
Units: litre(s)				
geometric mean (geometric coefficient of variation)				
Debio 1143: Day 1 (n=12,6)	213.92 (± 58.58)	196.40 (± 41.63)		
Debio 1143: Day 8 (n=13,3)	204.23 (± 47.82)	263.49 (± 33.94)		

Statistical analyses

No statistical analyses for this end point

Secondary: Tumor Concentration Distribution of Debio 1143 Based on an Appropriate Mass Spectrometry Method

End point title	Tumor Concentration Distribution of Debio 1143 Based on an Appropriate Mass Spectrometry Method[15]

End point description:

The molecular distribution of Debio 1143 in tumour biopsies was assessed by matrix-assisted laser desorption/ionization (MALDI) imaging. The different histological regions were identified on stained sections adjacent to the ones used for Quantitative Mass Spectrometry Imaging, leading to a specific quantification integrating the biological characterization of the tumour heterogeneity. Safety population was defined as subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP).

End point type	Secondary

End point timeframe:

Day of surgery (Day 15)

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 be reported for the reporting arms Debio 1143 and Debio 1143 + Cisplatin.

End point values	Debio 1143	Debio 1143 + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	6		
Units: microgram per gram (mcg/g)				
arithmetic mean (standard deviation)				
Day of surgery (n=10,5)	11.83 (± 11.03)	26.50 (± 18.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: AUClast: Free and Total CDDP in Plasma

End point title	AUClast: Free and Total CDDP in Plasma[16]

End point description:

Total and free CDDP were determined in plasma and ultracentrifuged plasma, respectively, using a validated inductively coupled plasma mass spectrometry (ICP/MS) method. Safety population was defined as subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP). For arm Cisplatin, 99999 indicates geometric mean and geometric CV, as no subject was evaluated at the specified time point.

End point type	Secondary

End point timeframe:

Day 1 and Day 8

Notes:

[16] - 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 be reported for the reporting arms Debio 1143 + Cisplatin and Cisplatin.

End point values	Debio 1143 + Cisplatin	Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	7		
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)				
Cisplatin Free: Day 1 (n=3,3)	2870.80 (± 124.57)	2163.09 (± 21.65)		
Cisplatin Free: Day 8 (n=2,0)	3718.47 (± 17.01)	99999 (± 99999)		
Cisplatin Total: Day 1 (n=6,5)	41102.10 (± 24.13)	8902.75 (± 61.38)		
Cisplatin Total: Day 8 (n=3,0)	53968.44 (± 5.99)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: CL/F: Free and Total CDDP in Plasma

End point title	CL/F: Free and Total CDDP in Plasma[17]

End point description:

Total and free CDDP were determined in plasma and ultracentrifuged plasma, respectively, using a validated inductively coupled plasma mass spectrometry (ICP/MS) method. Safety population was defined as subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP). For arm Cisplatin, 99999 indicates geometric mean and geometric CV, as no subject was evaluated at the specified time point.

End point type	Secondary

End point timeframe:

Day 1 and Day 8

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 be reported for the reporting arms Debio 1143 + Cisplatin and Cisplatin.

End point values	Debio 1143 + Cisplatin	Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	7		
Units: L/h				
geometric mean (geometric coefficient of variation)				
Cisplatin Free: Day 1 (n=2,4)	31.81 (± 36.32)	52.44 (± 51.81)		
Cisplatin Free: Day 8 (n=3,0)	48.22 (± 27.36)	99999 (± 99999)		
Cisplatin Total: Day 1 (n=4,6)	17.18 (± 27.73)	22.32 (± 44.74)		
Cisplatin Total: Day 8 (n=5,0)	21.60 (± 2.00)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clast: Free and Total CDDP in Plasma

End point title	Clast: Free and Total CDDP in Plasma[18]

End point description:

Total and free CDDP were determined in plasma and ultracentrifuged plasma, respectively, using a validated inductively coupled plasma mass spectrometry (ICP/MS) method. Safety population was defined as subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP). For arm Cisplatin at Day 8, 99999 indicates geometric mean and geometric CV, as no subject was evaluated at the specified time point.

End point type	Secondary

End point timeframe:

Day 1 and Day 8

Notes:

[18] - 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 be reported for the reporting arms Debio 1143 + Cisplatin and Cisplatin.

End point values	Debio 1143 + Cisplatin	Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	7		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cisplatin Free: Day 1 (n=3,3)	48.30 (± 54.01)	55.39 (± 18.09)		
Cisplatin Free: Day 8 (n=2,0)	50.31 (± 21.81)	99999 (± 99999)		
Cisplatin Total: Day 1 (n=6,5)	1881.87 (± 35.88)	1989.84 (± 20.10)		
Cisplatin Total: Day 8 (n=3,0)	2071.62 (± 8.59)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Css: Free and Total CDDP in Plasma

End point title	Css: Free and Total CDDP in Plasma[19]

End point description:

Total and free CDDP were determined in plasma and ultracentrifuged plasma, respectively, using a validated inductively coupled plasma mass spectrometry (ICP/MS) method. Safety population was defined as subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP). For arm Cisplatin at Day 8, 99999 indicates geometric mean and geometric CV, as no subject was evaluated at the specified time point.

End point type	Secondary

End point timeframe:

Day 1 and Day 8

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 be reported for the reporting arms Debio 1143 + Cisplatin and Cisplatin.

End point values	Debio 1143 + Cisplatin	Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	7		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cisplatin Free: Day 1 (n=3,4)	339.99 (± 20106.07)	1206.91 (± 39.20)		
Cisplatin Free: Day 8 (n=3,0)	1647.45 (± 40.35)	99999 (± 99999)		
Cisplatin Total: Day 1 (n=6,7)	385.37 (± 53779.14)	1155.60 (± 2410.79)		
Cisplatin Total: Day 8 (n=5,0)	3647.98 (± 11.79)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Visual Predictive Check of Relationships Between Selected Pharmacokinetic (PK) Parameters and Pharmacodynamic (PDy) and Pharmacogenetics (PGx) Markers

End point title	Visual Predictive Check of Relationships Between Selected Pharmacokinetic (PK) Parameters and Pharmacodynamic (PDy) and Pharmacogenetics (PGx) Markers[20]

End point description:

End point type	Secondary

End point timeframe:

Day of surgery (Day 15)

Notes:

[20] - 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 be reported for the reporting arms Debio 1143 and Debio 1143 + Cisplatin.

End point values	Debio 1143	Debio 1143 + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[21]	0[22]		
Units: units				
arithmetic mean (standard deviation)	()	()		

Notes:

[21] - Data collected was too premature to make a conclusion on this endpoint – hence no data shown.

[22] - Data collected was too premature to make a conclusion on this endpoint – hence no data shown.

Statistical analyses

No statistical analyses for this end point

Secondary: Association of Predictive Markers With a Pdy Activity of Debio 1143

End point title	Association of Predictive Markers With a Pdy Activity of Debio 1143[23]

End point description:

End point type	Secondary

End point timeframe:

Baseline, Day of surgery (Day 15)

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 be reported for the reporting arm Debio 1143.

End point values	Debio 1143			
Subject group type	Reporting group			
Number of subjects analysed	0[24]			
Units: units				
arithmetic mean (standard deviation)	()			

Notes:

[24] - Data collected was too premature to make a conclusion on this endpoint – hence no data shown.

Statistical analyses

No statistical analyses for this end point

Secondary: Genetic Variations in Drug Metabolizing Enzyme and Transporter (DMET) Genes Associated With Differences in the PK Disposition of Debio 1143

End point title	Genetic Variations in Drug Metabolizing Enzyme and Transporter (DMET) Genes Associated With Differences in the PK Disposition of Debio 1143[25]

End point description:

End point type	Secondary

End point timeframe:

Day of surgery (Day 15)

Notes:

[25] - 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 be reported for the reporting arm Debio 1143.

End point values	Debio 1143			
Subject group type	Reporting group			
Number of subjects analysed	0[26]			
Units: units				
arithmetic mean (standard deviation)	()			

Notes:

[26] - Data was not summarised as no association signal was identified.

Statistical analyses

No statistical analyses for this end point

Secondary: Exploration of Relationships Between 18F-FDG PET Imaging Results and PK/PDy Markers if Deemed Appropriate

End point title	Exploration of Relationships Between 18F-FDG PET Imaging Results and PK/PDy Markers if Deemed Appropriate

End point description:

End point type	Secondary

End point timeframe:

Baseline, Day of surgery (Day 15)

End point values	Debio 1143	Debio 1143 + Cisplatin	Cisplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[27]	0[28]	0[29]	
Units: units				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[27] - Data was not summarised as no clear trend was observed.

[28] - Data was not summarised as no clear trend was observed.

[29] - Data was not summarised as no clear trend was observed.

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of CDDP Alone on cIAP-1 Levels in Subjects With SCCHN

End point title	Effect of CDDP Alone on cIAP-1 Levels in Subjects With

End point description:

The assessment of the levels of cIAP-1 in tumor biopsies was performed using a validated IHC assay. The assay was developed using a mouse monoclonal anti-cIAP-1. PP population was defined as all subjects included in ITT population, but excluding those who did not receive the study drugs, did not undergo a pre-treatment and post-treatment PDy assessment, received non-permitted concomitant treatments, violated clinically relevant inclusion/non-inclusion criteria, did not receive at least 75% of the planned Debio 1143 dose, did not receive at least 50% of the planned CDDP dose or did not receive Debio 1143 the day before surgery and on the day of surgery.

End point type	Secondary

End point timeframe:

Pre-dose (Day 1) and At time of surgery (Day 15)

Notes:

[30] - 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 be reported for the reporting arm Cisplatin.

End point values	Cisplatin			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: H-Score				
arithmetic mean (standard deviation)				
Pre-dose (Day 1)	100.83 (± 108.74)			
At time of surgery (Day 15)	106.67 (± 116.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Pre-dose for Programmed Cell Death Protein 1 (PD1), Programmed Death-Ligand 1 (PDL-1), Cluster of Differentiation (CD) 3, CD4 and CD8

End point title	Percent Change From Pre-dose for Programmed Cell Death Protein 1 (PD1), Programmed Death-Ligand 1 (PDL-1), Cluster of Differentiation (CD) 3, CD4 and CD8

End point description:

PP population population was defined as all subjects included in ITT population, but excluding those who did not receive the study drugs, did not undergo a pre-treatment and post-treatment PDy assessment, received non-permitted concomitant treatments, violated clinically relevant inclusion/non-inclusion criteria, did not receive at least 75% of the planned Debio 1143 dose, did not receive at least 50% of the planned CDDP dose or did not receive Debio 1143 the day before surgery and on the day of surgery.

End point type	Secondary

End point timeframe:

At time of surgery (Day 15)

End point values	Debio 1143	Debio 1143 + Cisplatin	Cisplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	5	6	
Units: percent change				
arithmetic mean (standard deviation)				
PD1 (n=7,5,5)	435.71 (± 546.74)	121.33 (± 223.66)	4024.00 (± 8875.63)	
CD3 (n=11,5,6)	3.90 (± 30.99)	127.00 (± 266.26)	70.37 (± 158.80)	
CD4 (n=11,5,6)	7.79 (± 29.26)	100.48 (± 227.31)	80.65 (± 152.11)	
CD8 (n=11,5,6)	203.99 (± 564.58)	23.33 (± 95.45)	210.42 (± 369.83)	
PDL-1 (n=8,5,6)	137.5 (± 159.8)	380 (± 334.66)	183.33 (± 278.69)	

Statistical analyses

No statistical analyses for this end point

Secondary: AUC From Time 0 Extrapolated to Infinity Debio 1143 and Metabolite D 1143-MET1 in Plasma

End point title	AUC From Time 0 Extrapolated to Infinity Debio 1143 and Metabolite D 1143-MET1 in Plasma[31]

End point description:

Safety population was defined as subjects who received a dose of any of the study drugs (Debio 1143 and/or CDDP).

End point type	Secondary

End point timeframe:

Day 1

Notes:

[31] - 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 be reported for the reporting arms Debio 1143 and Debio

1143 + Cisplatin.

End point values	Debio 1143	Debio 1143 + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	6		
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)				
Debio 1143: Day 1 (n=12,6)	8362.60 (± 61.88)	8978.54 (± 41.32)		
Debio 1143 Metabolite: Day 1 (n=4,2)	13927.38 (± 37.91)	12299.59 (± 1.15)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Screening up to 43 days	
Adverse event reporting additional description:	
The safety population included subjects who received a dose of any of the study drugs (Debio 1143 and/or Cisplatin).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Debio 1143
Reporting group description:	
Subjects were administered Debio 1143 once daily for 15 (± 2) days until surgery, and the last dose was administered on the day of surgery.	
Reporting group title	Debio 1143 + Cisplatin
Reporting group description:	
Subjects were administered Debio 1143 once daily for 15 (± 2) days until surgery, and the last dose was administered on the day of surgery. Cisplatin was administered once weekly on study Days 1 and 8.	
Reporting group title	Cisplatin
Reporting group description:	
Cisplatin was administered once weekly on study Days 1 and 8.	

Serious adverse events	Debio 1143	Debio 1143 + Cisplatin	Cisplatin
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	2 / 7 (28.57%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 13 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Laryngeal repair			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (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
Infections and infestations			

Pneumonia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Debio 1143	Debio 1143 + Cisplatin	Cisplatin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 13 (92.31%)	6 / 6 (100.00%)	7 / 7 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Dry gangrene			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	0 / 13 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Thrombophlebitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 13 (23.08%)	2 / 6 (33.33%)	2 / 7 (28.57%)
occurrences (all)	3	2	2
Pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 6 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	2
Pyrexia			

subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	2
Chills			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Face oedema			
subjects affected / exposed	0 / 13 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
First bite syndrome			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hyperthermia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Impaired healing			
subjects affected / exposed	0 / 13 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	0 / 13 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Stenosis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 13 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Bronchial obstruction			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hypoxia			

subjects affected / exposed	0 / 13 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 13 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 13 (7.69%)	2 / 6 (33.33%)	0 / 7 (0.00%)
occurrences (all)	1	2	0
Insomnia			
subjects affected / exposed	3 / 13 (23.08%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	3	0	0
Agitation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Confusional state			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Investigations			
Weight decreased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 6 (16.67%)	2 / 7 (28.57%)
occurrences (all)	0	1	2
Lipase increased			
subjects affected / exposed	1 / 13 (7.69%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	1	2	0
Alanine aminotransferase increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Aspiration tracheal			
subjects affected / exposed	0 / 13 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Blood creatinine decreased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Crystal urine			

subjects affected / exposed	0 / 13 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Procedural pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Seroma			
subjects affected / exposed	0 / 13 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Skin flap necrosis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Tracheostomy malfunction			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Vasoplegia syndrome			
subjects affected / exposed	0 / 13 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Wound complication			
subjects affected / exposed	0 / 13 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 13 (7.69%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Dysarthria			

subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hypoaesthesia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Neuralgia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
VIIth nerve paralysis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 13 (30.77%)	1 / 6 (16.67%)	2 / 7 (28.57%)
occurrences (all)	5	2	4
Thrombocytopenia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 13 (7.69%)	3 / 6 (50.00%)	1 / 7 (14.29%)
occurrences (all)	1	3	1
Nausea			
subjects affected / exposed	2 / 13 (15.38%)	2 / 6 (33.33%)	1 / 7 (14.29%)
occurrences (all)	2	2	1
Diarrhoea			
subjects affected / exposed	2 / 13 (15.38%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	3	0	2
Dyspepsia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Leukoplakia oral			

subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Oral mucosal discolouration			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Oral pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Salivary hypersecretion			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Stomatitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Stomatitis necrotising			
subjects affected / exposed	0 / 13 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Tooth discolouration			
subjects affected / exposed	0 / 13 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 13 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 13 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	2 / 13 (15.38%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Acne			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Pain of skin			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0

Pruritus			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	0 / 13 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Skin necrosis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 13 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Decreased nasolabial fold			
subjects affected / exposed	0 / 13 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Fistula			
subjects affected / exposed	0 / 13 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Abscess neck			
subjects affected / exposed	2 / 13 (15.38%)	0 / 6 (0.00%)	2 / 7 (28.57%)
occurrences (all)	2	0	2
Bronchitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Fungal infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0

Fungal skin infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Postoperative wound infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 13 (7.69%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Abnormal loss of weight			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Hyperkalaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 April 2016	• The interim analysis was conducted on the first 8 subjects in the Debio 1143 monotherapy cohort (Step 1) instead of the planned 12 subjects. • Screening period was extended from 14 to 28 days. • Human immunodeficiency virus (HIV)-positive subjects were excluded due to newly published in vitro data suggesting that Smac mimetics may have the ability to reverse HIV-1 latency by activating NF-κB. • Subjects with squamous cell carcinoma of the nasopharynx, nasal cavity, and paranasal sinuses were allowed into the study. • Previously excluded subjects with prior malignancies were allowed into the study provided there was no demonstrated evidence of the recurrence of the disease. • Pancreatic enzyme testing (amylase and lipase) was added following 3 cases of asymptomatic and reversible amylase and lipase increases in subjects receiving Debio 1143 combined with CDDP and radiotherapy in study 2013-000044-25.
04 April 2017	• Treatment allocation in Step 2 was modified. Instead of all 12 subjects in Step 2 receiving Debio 1143 in combination with CDDP, the subjects were to be split into two subcohorts of 6 subjects. One cohort of 6 subjects (Step 2a) would receive Debio 1143 in combination with CDDP, and the second cohort of 6 subjects (Step 2b) would receive CDDP alone. The rationale for this change was to better discriminate between the effect due to CDDP alone vs Debio 1143 in combination with CDDP. As a result of these changes, the primary and secondary objectives as well as the corresponding endpoints were updated to include the CDDP monotherapy cohort. This was considered a substantial amendment to the protocol. • Other changes included removing blood sampling for flow cytometry and saliva sampling in Step 2 based on unreliable results from these tests at Step 1 interim analysis. In addition a more sensitive analytical method was implemented for CDDP sample analysis.
19 July 2017	• The CDDP monotherapy cohort was removed from the primary objective and primary endpoint. The assessment of cIAP in the CDDP monotherapy cohort was added as a secondary objective and endpoint. • Guidelines for the management of febrile neutropenia/neutropenia were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported