Clinical trial results:
A Phase I/II randomized study to determine the maximum tolerated dose, safety, pharmacokinetics and antitumor activity of Debio 1143 combined with concurrent Chemo-Radiation Therapy in patients with locally advanced squamous cell carcinoma of the head and neck

Summary

EudraCT number	2013-000044-25
Trial protocol	FR
Global end of trial date	28 April 2022

Results information

Result version number	v1 (current)
This version publication date	26 March 2023
First version publication date	26 March 2023

Trial information

Trial identification

Sponsor protocol code	1143-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02022098
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 S.A., +41 213210111, clinicaltrials@debiopharm.com
Scientific contact	Clinical Department, Debiopharm S.A., +41 213210111, 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	28 April 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 April 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part A: To determine the maximum tolerated dose (MTD) of Debio1143 in combination with concurrent chemoradiotherapy (CRT) in subjects with locally advanced squamous cell cancer of the head and neck (LA-SCCHN).
Part B: To evaluate the anti-tumour activity of Debio1143 in comparison with placebo when added to standard concurrent CRT in subjects with LA-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:

Concomitant chemo-radiation therapy (CRT) including cisplatin, 100 mg/m^2, 1-hour intravenous (IV) infusion, once on Day 2 in each 21-day cycle for 3 cycles i.e., on Days 2, 23 and 44 and standard fraction radiotherapy (RT) of 2 gray (Gy), daily for 5 days per week up to 7 weeks.

Evidence for comparator: -

Actual start date of recruitment	16 September 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 105
Country: Number of subjects enrolled	Switzerland: 5
Worldwide total number of subjects	110
EEA total number of subjects	105

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)	88
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Parts A and B of the study were conducted at 23 study centres in France and Switzerland from 16 September 2013 to 28 April 2022.

Pre-assignment

Screening details:

A total of 110 subjects were enrolled, 14 subjects into Part A and 96 subjects were randomised into Part B. Out of 96 randomised subjects from Part B, 95 received Debio 1143 or matching placebo.

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, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Double blind for Part B only.

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A: Debio 1143 100 mg + CRT

Arm description:

Subjects were assigned Debio 1143 100 milligram (mg), oral solution, once daily for 14 days in each 21-day cycle for 3 cycles, i.e., on Days 1-14, 22-35 and 43-56 along with concomitant CRT [cisplatin, 100 mg/m^2, 1-hour IV infusion, once on Day 2 in a 21-day cycle for 3 cycles i.e., on Days 2, 23 and 44 and standard fraction RT of 2 Gy, daily for 5 days per week, up to 7 weeks].

Arm type	Experimental
Investigational medicinal product name	Debio 1143
Investigational medicinal product code	
Other name	Xevinapant
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

100 mg administered orally, once daily for 14 days in a 21-day cycle for 3 cycles.

Arm title	Part A: Debio 1143 200mg + CRT

Arm description:

Subjects were assigned Debio 1143 200 mg, oral solution, once daily for 14 days in each 21-day cycle for 3 cycles, i.e., on Days 1-14, 22-35 and 43-56 along with concomitant CRT [cisplatin, 100 mg/m^2, 1-hour IV infusion, once on Day 2 in a 21-day cycle for 3 cycles i.e., on Days 2, 23 and 44 and standard fraction RT of 2 Gy, daily for 5 days per week, up to 7 weeks].

Arm type	Experimental
Investigational medicinal product name	Debio 1143
Investigational medicinal product code	
Other name	Xevinapant
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

200 mg administered orally, once daily for 14 days in a 21-day cycle for 3 cycles.

Arm title	Part A: Debio 1143 300mg + CRT

Arm description:

Subjects were assigned Debio 1143 300 mg, oral solution, once daily for 14 days in each 21-day cycle

for 3 cycles, i.e., on Days 1-14, 22-35 and 43-56 along with concomitant CRT [cisplatin, 100 mg/m^2, 1-hour IV infusion, once on Day 2 in a 21-day cycle for 3 cycles i.e., on Days 2, 23 and 44 and standard fraction RT of 2 Gy, daily for 5 days per week, up to 7 weeks].

Arm type	Experimental
Investigational medicinal product name	Debio 1143
Investigational medicinal product code	
Other name	Xevinapant
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

300 mg administered orally, once daily for 14 days in a 21-day cycle for 3 cycles.

Arm title	Part B: Debio 1143 200mg + CRT

Arm description:

Subjects were assigned Debio 1143 200 mg, oral solution, once daily for 14 days in each 21-day cycle for 3 cycles, i.e., on Days 1-14, 22-35 and 43-56 along with concomitant CRT [cisplatin, 100 mg/m^2, 1-hour IV infusion once on Day 2 in a 21-day cycle for 3 cycles i.e., on Days 2, 23 and 44 and standard fraction RT of 2 Gy, daily for 5 days per week, up to 7 weeks].

Arm type	Experimental
Investigational medicinal product name	Debio 1143
Investigational medicinal product code	
Other name	Xevinapant
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

200 mg administered orally, once daily for 14 days in a 21-day cycle for 3 cycles.

Arm title	Part B: Placebo + CRT

Arm description:

Subjects were assigned Debio 1143 matching placebo, oral solution, once daily for 14 days in each 21-day cycle for 3 cycles, i.e., on Days 1-14, 22-35 and 43-56 along with concomitant CRT [cisplatin, 100 mg/m^2, 1-hour IV infusion once on Day 2 in a 21-day cycle for 3 cycles i.e., on Days 2, 23 and 44 and standard fraction RT of 2 Gy, daily for 5 days per week, up to 7 weeks].

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Debio 1143 matching placebo administered orally, once daily for 14 days in a 21-day cycle for 3 cycles.

Number of subjects in period 1	Part A: Debio 1143 100 mg + CRT	Part A: Debio 1143 200mg + CRT	Part A: Debio 1143 300mg + CRT
Started	5	6	3
Completed	2	5	1
Not completed	3	1	2
Subject lost to follow-up	-	-	-
Subject non-compliance	-	-	-
Subject not in physical capacity for end of study	-	-	1
Adverse event	-	1	1

Investigator Decision	-	-	-
Reason not specified	-	-	-
Disease Progression	-	-	-
Withdrawal of Consent	-	-	-
Subject followed in another hospital	1	-	-
Did not enter extended efficacy follow-up	-	-	-
Death	-	-	-
Progressive disease	2	-	-
Prohibited Medication	-	-	-

Number of subjects in period 1	Part B: Debio 1143 200mg + CRT	Part B: Placebo + CRT
Started	48	48
Completed	19	8
Not completed	29	40
Subject lost to follow-up	1	1
Subject non-compliance	1	-
Subject not in physical capacity for end of study	-	-
Adverse event	4	3
Investigator Decision	2	-
Reason not specified	5	1
Disease Progression	11	18
Withdrawal of Consent	2	4
Subject followed in another hospital	-	-
Did not enter extended efficacy follow-up	2	4
Death	1	8
Progressive disease	-	-
Prohibited Medication	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Part A: Debio 1143 100 mg + CRT
Reporting group description:	
Subjects were assigned Debio 1143 100 milligram (mg), oral solution, once daily for 14 days in each 21-day cycle for 3 cycles, i.e., on Days 1-14, 22-35 and 43-56 along with concomitant CRT [cisplatin, 100 mg/m^2, 1-hour IV infusion, once on Day 2 in a 21-day cycle for 3 cycles i.e., on Days 2, 23 and 44 and standard fraction RT of 2 Gy, daily for 5 days per week, up to 7 weeks].	
Reporting group title	Part A: Debio 1143 200mg + CRT
Reporting group description:	
Subjects were assigned Debio 1143 200 mg, oral solution, once daily for 14 days in each 21-day cycle for 3 cycles, i.e., on Days 1-14, 22-35 and 43-56 along with concomitant CRT [cisplatin, 100 mg/m^2, 1-hour IV infusion, once on Day 2 in a 21-day cycle for 3 cycles i.e., on Days 2, 23 and 44 and standard fraction RT of 2 Gy, daily for 5 days per week, up to 7 weeks].	
Reporting group title	Part A: Debio 1143 300mg + CRT
Reporting group description:	
Subjects were assigned Debio 1143 300 mg, oral solution, once daily for 14 days in each 21-day cycle for 3 cycles, i.e., on Days 1-14, 22-35 and 43-56 along with concomitant CRT [cisplatin, 100 mg/m^2, 1-hour IV infusion, once on Day 2 in a 21-day cycle for 3 cycles i.e., on Days 2, 23 and 44 and standard fraction RT of 2 Gy, daily for 5 days per week, up to 7 weeks].	
Reporting group title	Part B: Debio 1143 200mg + CRT
Reporting group description:	
Subjects were assigned Debio 1143 200 mg, oral solution, once daily for 14 days in each 21-day cycle for 3 cycles, i.e., on Days 1-14, 22-35 and 43-56 along with concomitant CRT [cisplatin, 100 mg/m^2, 1-hour IV infusion once on Day 2 in a 21-day cycle for 3 cycles i.e., on Days 2, 23 and 44 and standard fraction RT of 2 Gy, daily for 5 days per week, up to 7 weeks].	
Reporting group title	Part B: Placebo + CRT
Reporting group description:	
Subjects were assigned Debio 1143 matching placebo, oral solution, once daily for 14 days in each 21-day cycle for 3 cycles, i.e., on Days 1-14, 22-35 and 43-56 along with concomitant CRT [cisplatin, 100 mg/m^2, 1-hour IV infusion once on Day 2 in a 21-day cycle for 3 cycles i.e., on Days 2, 23 and 44 and standard fraction RT of 2 Gy, daily for 5 days per week, up to 7 weeks].	

Reporting group values	Part A: Debio 1143 100 mg + CRT	Part A: Debio 1143 200mg + CRT	Part A: Debio 1143 300mg + CRT
Number of subjects	5	6	3
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	58.20	64.17	63.67
standard deviation	± 11.10	± 3.19	± 5.86
Gender categorical Units: Subjects			
Female	1	1	0
Male	4	5	3
Race Units: Subjects			
White	5	6	3
Asian	0	0	0
Not Reported	0	0	0
Ethnicity			

Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	5	6	3
Missing	0	0	0

Reporting group values	Part B: Debio 1143 200mg + CRT	Part B: Placebo + CRT	Total
Number of subjects	48	48	110
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	56.4	59.1	
standard deviation	± 7.06	± 6.28	-
Gender categorical Units: Subjects			
Female	11	7	20
Male	37	41	90
Race Units: Subjects			
White	48	44	106
Asian	0	1	1
Not Reported	0	3	3
Ethnicity Units: Subjects			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	47	44	105
Missing	0	4	4

End points

End points reporting groups

Reporting group title	Part A: Debio 1143 100 mg + CRT

Reporting group description:

Subjects were assigned Debio 1143 100 milligram (mg), oral solution, once daily for 14 days in each 21-day cycle for 3 cycles, i.e., on Days 1-14, 22-35 and 43-56 along with concomitant CRT [cisplatin, 100 mg/m^2, 1-hour IV infusion, once on Day 2 in a 21-day cycle for 3 cycles i.e., on Days 2, 23 and 44 and standard fraction RT of 2 Gy, daily for 5 days per week, up to 7 weeks].

Reporting group title	Part A: Debio 1143 200mg + CRT

Reporting group description:

Subjects were assigned Debio 1143 200 mg, oral solution, once daily for 14 days in each 21-day cycle for 3 cycles, i.e., on Days 1-14, 22-35 and 43-56 along with concomitant CRT [cisplatin, 100 mg/m^2, 1-hour IV infusion, once on Day 2 in a 21-day cycle for 3 cycles i.e., on Days 2, 23 and 44 and standard fraction RT of 2 Gy, daily for 5 days per week, up to 7 weeks].

Reporting group title	Part A: Debio 1143 300mg + CRT

Reporting group description:

Subjects were assigned Debio 1143 300 mg, oral solution, once daily for 14 days in each 21-day cycle for 3 cycles, i.e., on Days 1-14, 22-35 and 43-56 along with concomitant CRT [cisplatin, 100 mg/m^2, 1-hour IV infusion, once on Day 2 in a 21-day cycle for 3 cycles i.e., on Days 2, 23 and 44 and standard fraction RT of 2 Gy, daily for 5 days per week, up to 7 weeks].

Reporting group title	Part B: Debio 1143 200mg + CRT

Reporting group description:

Subjects were assigned Debio 1143 200 mg, oral solution, once daily for 14 days in each 21-day cycle for 3 cycles, i.e., on Days 1-14, 22-35 and 43-56 along with concomitant CRT [cisplatin, 100 mg/m^2, 1-hour IV infusion once on Day 2 in a 21-day cycle for 3 cycles i.e., on Days 2, 23 and 44 and standard fraction RT of 2 Gy, daily for 5 days per week, up to 7 weeks].

Reporting group title	Part B: Placebo + CRT

Reporting group description:

Subjects were assigned Debio 1143 matching placebo, oral solution, once daily for 14 days in each 21-day cycle for 3 cycles, i.e., on Days 1-14, 22-35 and 43-56 along with concomitant CRT [cisplatin, 100 mg/m^2, 1-hour IV infusion once on Day 2 in a 21-day cycle for 3 cycles i.e., on Days 2, 23 and 44 and standard fraction RT of 2 Gy, daily for 5 days per week, up to 7 weeks].

Primary: Part A: Percentage of Subjects Experiencing Dose-Limiting Toxicities (DLTs)

End point title	Part A: Percentage of Subjects Experiencing Dose-Limiting Toxicities (DLTs)[1][2]

End point description:

DLT was defined as the occurrence of life-threatening toxicities and/or specific severe laboratory abnormalities or treatment related adverse events (AEs). It is defined by any of the following: Common Terminology Criteria (CTC) Grade 4 neutropenia that is uncomplicated (not associated with fever >38.5°C lasting ≥ 7 days; CTC Grade 3 or 4 neutropenia concomitant with fever >38.5ºC or Grade ≥3 infection; thrombocytopenia <25,000/µL lasting ≥ 5 days or <50,000/µL with bleeding or requiring platelets transfusion; CTC Grade ≥3 non-haematologic toxicity (except untreated nausea, untreated vomiting, or untreated diarrhoea); CTC grade 2/higher ototoxicity, worsening of renal function, grade 3 or higher decrease in cardiac left ventricular function, grade 4 skin or mucosal reactions; Cisplatin and/or Debio 1143 treatment delay >2 weeks for related adverse event (AE) occurring during the DLT period. Safety population included all subjects who received any dose of Debio 1143 or cisplatin or RT.

End point type	Primary

End point timeframe:

From first dose of study drug up to Week 9

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.

[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: This endpoint was the primary endpoint only for part A.

End point values	Part A: Debio 1143 100 mg + CRT	Part A: Debio 1143 200mg + CRT	Part A: Debio 1143 300mg + CRT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	6	3	
Units: percentage of subjects				
number (not applicable)	20.0	33.3	66.7	

Statistical analyses

No statistical analyses for this end point

Primary: Part B: Percentage of Subjects Achieving Locoregional Control (LRC) at 18 Months From the End of Chemo-Radiation Therapy (CRT)

End point title	Part B: Percentage of Subjects Achieving Locoregional Control (LRC) at 18 Months From the End of Chemo-Radiation Therapy (CRT)[3]

End point description:

LRC at a time point is defined as absence of locoregional relapse up to and including that time point, where locoregional relapse is defined as progressive disease at the site of the primary tumour or the locoregional lymph nodes. Intention-to-treat (ITT) population included all subjects who were randomised to treatment.

End point type	Primary

End point timeframe:

From the end of CRT (Week 9) up to 18 months

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: This endpoint was the primary endpoint only for part B.

End point values	Part B: Debio 1143 200mg + CRT	Part B: Placebo + CRT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	48		
Units: percentage of subjects				
number (confidence interval 95%)	54.2 (39.2 to 68.6)	33.3 (20.4 to 48.4)		

Statistical analyses

Statistical analysis title	Part B: Debio 1143 200 mg vs Placebo
Comparison groups	Part B: Debio 1143 200mg + CRT v Part B: Placebo + CRT

Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0232 [4]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.15
upper limit	6.53

Notes:

[4] - P-value was calculated using logistic regression stratified for the randomization factors of nodal involvement, cancer localization and human papillomavirus (HPV)-16 status.

Secondary: Part A: Number of Subjects Experiencing at Least One Treatment Emergent Adverse Event (TEAE), Grade 3 or Above TEAE, and Serious Adverse Event (SAE)

End point title	Part A: Number of Subjects Experiencing at Least One Treatment Emergent Adverse Event (TEAE), Grade 3 or Above TEAE, and Serious Adverse Event (SAE)[5]

End point description:

An adverse event (AE) is any untoward medical occurrence in a clinical trial subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. A TEAE is any new, undesirable medical occurrence or change of an existing condition in a subject that occurs during or after first investigational medicinal product administration (Debio 1143/cisplatin/RT), whether or not considered to be drug-related. A SAE is any untoward medical occurrence that, at any dose, results in death; is life threatening (i.e., puts subject at immediate risk of death); requires inpatient hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect. TEAEs were graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4. Safety population=All subjects who received any dose of Debio 1143/cisplatin/RT.

End point type	Secondary

End point timeframe:

Up to 30 days after EOT (approximately 13 weeks for subjects who completed the 9-week treatment period)

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: This endpoint was the key secondary endpoint only for part A.

End point values	Part A: Debio 1143 100 mg + CRT	Part A: Debio 1143 200mg + CRT	Part A: Debio 1143 300mg + CRT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	6	3	
Units: subjects				
TEAE	5	6	3	
Grade 3 or Above TEAE	5	5	3	
SAE	3	2	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Number of Subjects With Treatment Discontinuations and Treatment Modifications due to AEs

End point title	Part A: Number of Subjects With Treatment Discontinuations and Treatment Modifications due to AEs[6]

End point description:

Safety population included all subjects who received any dose of Debio 1143 or cisplatin or RT.

End point type	Secondary

End point timeframe:

Up to 30 days after EOT (approximately 13 weeks for subjects who completed the 9-week treatment period)

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: This endpoint was the key secondary endpoint only for part A.

End point values	Part A: Debio 1143 100 mg + CRT	Part A: Debio 1143 200mg + CRT	Part A: Debio 1143 300mg + CRT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	6	3	
Units: subjects				
Treatment Discontinuations	1	1	1	
Treatment Modifications	1	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Percentage of Subjects With Tumour Response: Best Overall Response

End point title	Part A: Percentage of Subjects With Tumour Response: Best Overall Response[7]

End point description:

Best overall response was defined as best response recorded from start of study treatment until disease progression (PD)/recurrence was documented, a new systemic therapy was started or analysis cut-off, whichever occurred first. PD criteria for target lesions: At least 20% increase in sum of diameters of lesions, referring smallest sum on study, in addition to relative increase of 20%, sum should be an increase of at least 5 mm. Appearance of one/more new lesions is also considered progression. Per protocol (PP) population=all subjects who had measurable disease, according to Response Evaluation Criteria in Solid Tumours (RECIST) and underwent a baseline disease assessment and at least one post-baseline assessment, but excluded those who fulfilled any of following conditions: Violation of clinically relevant criteria; Administration of non-permitted concomitant treatments; Did not receive at least 70% of planned Debio 1143/RT dose; Did not receive at least 100 mg/m^2 of cisplatin.

End point type	Secondary

End point timeframe:

Up to the disease progression or recurrence or end of study for Part A (up to 24.9 months)

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: This endpoint was the key secondary endpoint only for part A.

End point values	Part A: Debio 1143 100 mg + CRT	Part A: Debio 1143 200mg + CRT	Part A: Debio 1143 300mg + CRT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	3	
Units: percentage of subjects				
number (not applicable)				
Complete response	40	80	100	
Partial response	40	0	0	
Progressive disease	20	20	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Maximum Observed Plasma Concentration (Cmax) for Debio 1143 and D-1143-MET1

End point title	Part A: Maximum Observed Plasma Concentration (Cmax) for Debio 1143 and D-1143-MET1[8]

End point description:

Geometric coefficient of variation (CV) reported in this endpoint is geometric CV%. Pharmacokinetic (PK) population included all subjects who underwent the specific PK assessments who did not have a major protocol deviation that may have had an impact on the PK outcome. Number analysed 'n' indicates the number of subjects with data available for analyses at the specified time point.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 1, 1.5 (only for Days 1, 2), 2, 3, 4, 6, 8 and 24 hours post dose on Days 1,2 and 9 of Cycle 1 (1 Cycle = 21 days)

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: This endpoint was the key secondary endpoint only for part A.

End point values	Part A: Debio 1143 100 mg + CRT	Part A: Debio 1143 200mg + CRT	Part A: Debio 1143 300mg + CRT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	6	3	
Units: nanograms/millilitre (ng/ml)				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1: Debio 1143 (n= 5,5,2)	1029.18 (± 32.48)	2519.12 (± 42.84)	4000.15 (± 104.38)	
Cycle 1 Day 1: D-1143-MET-1 (n=5,5,2)	735.55 (± 22.39)	1416.11 (± 30.76)	1238.62 (± 35.47)	
Cycle 1 Day 2: Debio 1143 (n= 5,5,2)	914.25 (± 88.32)	2938.54 (± 38.45)	4704.93 (± 0.75)	
Cycle 1 Day 2: D-1143-MET-1 (n=5,5,2)	892.59 (± 86.01)	1557.80 (± 43.67)	1910.24 (± 10.01)	
Cycle 1 Day 9: Debio 1143 (n= 4,4,3)	1646.92 (± 34.17)	1548.99 (± 30.02)	3998.26 (± 71.13)	
Cycle 1 Day 9: D-1143-MET-1 (n=4,4,3)	1139.68 (± 33.42)	2202.85 (± 51.24)	1674.55 (± 59.87)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Area Under the Plasma Concentration-time Curve From Administration up to the Last Quantifiable Concentration (AUC0-t) for Debio 1143 and D-1143-MET1

End point title	Part A: Area Under the Plasma Concentration-time Curve From Administration up to the Last Quantifiable Concentration (AUC0-t) for Debio 1143 and D-1143-MET1[9]

End point description:

Geometric CV reported in this endpoint is geometric CV%. PK population included all subjects who underwent the specific PK assessments, who did not have a major protocol deviation that may have had an impact on the PK outcome. Number analysed 'n' indicates the number of subjects with data available for analyses at the specified time point. 99999= not reported due to no available data, standard deviation (SD) cannot be calculated for 1 subject.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 1, 1.5 (only for Days 1, 2), 2, 3, 4, 6, 8 and 24 hours post dose on Days 1,2 and 9 of Cycle 1 (1 Cycle = 21 days)

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: This endpoint was the key secondary endpoint only for part A.

End point values	Part A: Debio 1143 100 mg + CRT	Part A: Debio 1143 200mg + CRT	Part A: Debio 1143 300mg + CRT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	6	3	
Units: hour×nanograms/millilitre (h×ng/ml)				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1: Debio-1143 (n=5,5,2)	5297.53 (± 39.89)	10399.11 (± 39.10)	17983.33 (± 12.22)	
Cycle 1 Day 1: Debio-1143-MET-1 (n=2,4,2)	8324.46 (± 1.61)	15346.86 (± 37.27)	15674.82 (± 31.63)	
Cycle 1 Day 2: Debio-1143 (n=5,5,2)	4974.63 (± 82.85)	14911.070 (± 46.03)	22492.67 (± 13.88)	
Cycle 1 Day 2: Debio-1143-MET-1 (n=0,3,2)	99999 (± 99999)	21576.38 (± 18.03)	26061.66 (± 26.34)	
Cycle 1 Day 9: Debio-1143 (n=4,5,3)	7723.25 (± 15.91)	6693.57 (± 45.50)	21283.34 (± 20.23)	
Cycle 1 Day 9: Debio-1143-MET-1 (n=3,3,1)	12509.81 (± 43.66)	27287.56 (± 79.05)	31200.00 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Area Under the Plasma Concentration-time Curve From Administration up to Infinity (AUC∞) for Debio 1143 and D-1143-MET1

End point title	Part A: Area Under the Plasma Concentration-time Curve From Administration up to Infinity (AUC∞) for Debio 1143 and D-1143-MET1[10]

End point description:

Geometric CV reported in this endpoint is geometric CV%. PK population included all subjects who underwent the specific PK assessments, who did not have a major protocol deviation that may have had an impact on the PK outcome. Number of subjects analysed indicates the number of subjects with data available for analysis for this endpoint. 99999= SD cannot be calculated for 1 subject or not reported due to no available data.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 24 hours post dose on Day 1 of Cycle 1 (1 Cycle = 21 days)

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: This endpoint was the key secondary endpoint only for part A.

End point values	Part A: Debio 1143 100 mg + CRT	Part A: Debio 1143 200mg + CRT	Part A: Debio 1143 300mg + CRT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	6	3	
Units: h×ng/ml				
geometric mean (geometric coefficient of variation)				
Debio-1143 (n=5,5,2)	5551.59 (± 40.13)	11084.39 (± 38.97)	19002.11 (± 10.06)	
D-1143-MET-1 (n=1,2,0)	9110.00 (± 99999)	14129.76 (± 22.20)	99999 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Progression-Free Survival (PFS)

End point title	Part B: Progression-Free Survival (PFS)[11]

End point description:

PFS is defined as the time elapsed between treatment initiation and tumour progression or death from any cause, whichever occurs first. Progression for target lesions: At least 20% increase in sum of diameters of lesions, referring the smallest sum on study, in addition to relative increase of 20%, sum should be an increase of at least 5 mm. Appearance of one/more new lesions is also considered progression. 99999= The median PFS and upper limit was not reached due to insufficient number of events. ITT population included all subjects who were randomised to treatment.

End point type	Secondary

End point timeframe:

Up to the tumour progression or death or end of study for Part B (up to 52.1 months)

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: This endpoint was the key secondary endpoint only for part B.

End point values	Part B: Debio 1143 200mg + CRT	Part B: Placebo + CRT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	48		
Units: months				
median (confidence interval 95%)	99999 (37.4 to 99999)	16.9 (7.5 to 36.1)		

Statistical analyses

Statistical analysis title	Part B: Debio 1143 200 mg vs Placebo
Comparison groups	Part B: Debio 1143 200mg + CRT v Part B: Placebo + CRT
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0019 [12]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	0.67

Notes:

[12] - P-value was calculated using cox model stratified for the randomization factors of nodal involvement, tumor localization and HPV-16 status.

Secondary: Part B: Duration of Locoregional Control (LRC)

End point title	Part B: Duration of Locoregional Control (LRC)[13]

End point description:

Locoregional control is defined as the absence of PD or recurrence at the site of the primary tumour or locoregional lymph nodes. Duration of LRC is defined as the as the time from treatment initiation to the occurrence of locoregional relapse. PD criteria for target lesions: At least 20% increase in sum of diameters of lesions, referring the smallest sum on study, in addition to relative increase of 20%, sum should be an increase of at least 5 mm. Appearance of one/more new lesions is also considered progression. 99999=The median duration of LRC was not reached due to insufficient number of events. ITT population included all subjects randomised to treatment.

End point type	Secondary

End point timeframe:

From end of CRT up to the disease progression or recurrence or end of study for Part B (up to 50 months)

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: This endpoint was the key secondary endpoint only for part B.

End point values	Part B: Debio 1143 200mg + CRT	Part B: Placebo + CRT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	48		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (14.9 to 99999)		

Statistical analyses

Statistical analysis title	Part B: Debio 1143 200 mg vs Placebo
Comparison groups	Part B: Debio 1143 200mg + CRT v Part B: Placebo + CRT
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0893 [14]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	1.13

Notes:

[14] - P-value was calculated using cox model stratified for the randomization factors of node involvement, tumor localization and HPV-16 status.

Secondary: Part B: Time to Distant Relapse

End point title	Part B: Time to Distant Relapse[15]

End point description:

Time to distant relapse duration is defined as the time elapsed between treatment initiation and the distant relapse. Distant relapse at a time point is defined as PD in a location other than the site of the primary tumour or locoregional lymph nodes at any assessment up to and including that time point. PD criteria for target lesions: At least 20% increase in sum of diameters of lesions, referring the smallest sum on study, in addition to relative increase of 20%, sum should be an increase of at least 5 mm. Appearance of one/more new lesions is also considered progression. 99999=The median duration was not reached due to insufficient number of events. ITT population included all subjects randomised to treatment.

End point type	Secondary

End point timeframe:

Up to the disease progression or end of study for Part B (up to 50 months)

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: This endpoint was the key secondary endpoint only for part B.

End point values	Part B: Debio 1143 200mg + CRT	Part B: Placebo + CRT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	48		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Part B: Debio 1143 200 mg vs Placebo
Comparison groups	Part B: Debio 1143 200mg + CRT v Part B: Placebo + CRT
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2858 [16]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	1.58

Notes:

[16] - P-value was calculated using cox model stratified for the randomization factors of node involvement, tumor localization and HPV-16 status.

Secondary: Part B: Overall Survival (OS)

End point title	Part B: Overall Survival (OS)[17]

End point description:

Overall survival is defined as the duration between the first dose date of Debio 1143 and the date of death due to any cause. ITT population included all subjects randomised to treatment. 99999=The Median duration was not reached due to insufficient number of events.

End point type	Secondary

End point timeframe:

Up to the death or end of study for Part B (up to 71.3 months)

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: This endpoint was the key secondary endpoint only for part B.

End point values	Part B: Debio 1143 200mg + CRT	Part B: Placebo + CRT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	48		
Units: months				
median (confidence interval 95%)	99999 (40.3 to 99999)	36.1 (21.8 to 46.7)		

Statistical analyses

Statistical analysis title	Part B: Debio 1143 200 mg vs Placebo
Comparison groups	Part B: Placebo + CRT v Part B: Debio 1143 200mg + CRT
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0101 [18]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	0.84

Notes:

[18] - P-value was calculated using cox model stratified for the randomization factors of node involvement, tumor localization and HPV-16 status.

Secondary: Part B: Number of Subjects Experiencing at Least One TEAE and Grade 3 or Above TEAE

End point title	Part B: Number of Subjects Experiencing at Least One TEAE and Grade 3 or Above TEAE[19]

End point description:

An AE is any untoward medical occurrence in a clinical trial subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. A TEAE is any new, undesirable medical occurrence or change of an existing condition in a subject that occurs during or after the first investigational medicinal product administration (Debio 1143, cisplatin or RT), whether or not considered to be drug-related. TEAEs were graded according to NCI-CTCAE version 4. Safety population included all subjects who received any dose of Debio 1143 or placebo or cisplatin or RT.

End point type	Secondary

End point timeframe:

Up to 30 days after EOT (approximately 13 weeks for subjects who completed the 9-week treatment period)

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: This endpoint was the key secondary endpoint only for part B.

End point values	Part B: Debio 1143 200mg + CRT	Part B: Placebo + CRT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: subjects				
TEAE	48	47		

Garde 3 or Above TEAE	42	40		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Number of Subjects Experiencing Any Late Toxicity

End point title	Part B: Number of Subjects Experiencing Any Late Toxicity[20]

End point description:

Safety population included all subjects who received any dose of Debio 1143 or placebo or cisplatin or RT.

End point type	Secondary

End point timeframe:

From 30 days after EOT until EOS (up to 52 months)

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: This endpoint was the key secondary endpoint only for part B.

End point values	Part B: Debio 1143 200mg + CRT	Part B: Placebo + CRT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: subjects	39	33		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Part A: Up to 30 days after EOT (approximately 13 weeks for subjects who completed the 9-week treatment period); Part B: Up to 30 days after EOT (approximately 13 weeks for subjects who completed the 9-week treatment period)

Adverse event reporting additional description:

Safety population included all subjects who received any dose of Debio 1143 or placebo or cisplatin or RT.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Part A: Debio 1143 100 mg + CRT

Reporting group description:

Subjects were assigned Debio 1143 100 mg, oral solution, once daily for 14 days in each 21-day cycle for 3 cycles, i.e., on Days 1-14, 22-35 and 43-56 along with concomitant CRT [cisplatin, 100 mg/m^2, 1-hour IV infusion, once on Day 2 in a 21-day cycle for 3 cycles i.e., on Days 2, 23 and 44 and standard fraction RT of 2 Gy, daily for 5 days per week, up to 7 weeks].

Reporting group title	Part A: Debio 1143 200mg + CRT

Reporting group description:

Subjects were assigned Debio 1143 200 mg, oral solution, once daily for 14 days in each 21-day cycle for 3 cycles, i.e., on Days 1-14, 22-35 and 43-56 along with concomitant CRT [cisplatin, 100 mg/m^2, 1-hour IV infusion, once on Day 2 in a 21-day cycle for 3 cycles i.e., on Days 2, 23 and 44 and standard fraction RT of 2 Gy, daily for 5 days per week, up to 7 weeks].

Reporting group title	Part A: Debio 1143 300mg + CRT

Reporting group description:

Subjects were assigned Debio 1143 300 mg, oral solution, once daily for 14 days in each 21-day cycle for 3 cycles, i.e., on Days 1-14, 22-35 and 43-56 along with concomitant CRT [cisplatin, 100 mg/m^2, 1-hour IV infusion, once on Day 2 in a 21-day cycle for 3 cycles i.e., on Days 2, 23 and 44 and standard fraction RT of 2 Gy, daily for 5 days per week, up to 7 weeks].

Reporting group title	Part B: Debio 1143 200mg + CRT

Reporting group description:

Subjects were assigned Debio 1143 200 mg, oral solution, once daily for 14 days in each 21-day cycle for 3 cycles, i.e., on Days 1-14, 22-35 and 43-56 along with concomitant CRT [cisplatin, 100 mg/m^2, 1-hour IV infusion once on Day 2 in a 21-day cycle for 3 cycles i.e., on Days 2, 23 and 44 and standard fraction RT of 2 Gy, daily for 5 days per week, up to 7 weeks].

Reporting group title	Part B: Placebo + CRT

Reporting group description:

Subjects were assigned Debio 1143 matching placebo, oral solution, once daily for 14 days in each 21-day cycle for 3 cycles, i.e., on Days 1-14, 22-35 and 43-56 along with concomitant CRT [cisplatin, 100 mg/m^2, 1-hour IV infusion once on Day 2 in a 21-day cycle for 3 cycles i.e., on Days 2, 23 and 44 and standard fraction RT of 2 Gy, daily for 5 days per week, up to 7 weeks].

Serious adverse events	Part A: Debio 1143 100 mg + CRT	Part A: Debio 1143 200mg + CRT	Part A: Debio 1143 300mg + CRT
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 5 (60.00%)	2 / 6 (33.33%)	3 / 3 (100.00%)
number of deaths (all causes)	2	0	1
number of deaths resulting from adverse events	0	0	0

Surgical and medical procedures			
Parenteral nutrition			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	2 / 3 (66.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal inflammation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthermia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (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
Pulmonary embolism			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (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
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asphyxia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Lipase increased			

subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amylase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nutritional condition abnormal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oxygen saturation decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Gastrostomy tube site complication			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Cerebrovascular accident			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (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
Neutropenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone marrow failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Ulcerative keratitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral pain			

subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tongue haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal tubular necrosis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (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

Acute kidney injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oliguria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteonecrosis of jaw			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacterial sepsis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (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
Device related infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumococcal infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Staphylococcal infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part B: Debio 1143 200mg + CRT	Part B: Placebo + CRT	
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 48 (62.50%)	28 / 47 (59.57%)	
number of deaths (all causes)	21	29	
number of deaths resulting from adverse events	1	3	
Surgical and medical procedures			
Parenteral nutrition			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 48 (6.25%)	4 / 47 (8.51%)	
occurrences causally related to treatment / all	1 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	4 / 48 (8.33%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 48 (4.17%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial pain			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			

subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 48 (4.17%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 48 (2.08%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asphyxia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Lipase increased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 48 (2.08%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amylase increased			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nutritional condition abnormal			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Gastrostomy tube site complication			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			

subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 48 (2.08%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 48 (4.17%)	2 / 47 (4.26%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 48 (4.17%)	3 / 47 (6.38%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			

subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Ulcerative keratitis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	0 / 48 (0.00%)	2 / 47 (4.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 48 (4.17%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 48 (4.17%)	2 / 47 (4.26%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral pain			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue haemorrhage			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Renal failure			
subjects affected / exposed	2 / 48 (4.17%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular necrosis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	1 / 48 (2.08%)	4 / 47 (8.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oliguria			
subjects affected / exposed	2 / 48 (4.17%)	3 / 47 (6.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteonecrosis of jaw			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacterial sepsis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 48 (2.08%)	2 / 47 (4.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumococcal infection			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 16	2 / 25	
Staphylococcal infection			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 48 (4.17%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 2	
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	3 / 48 (6.25%)	3 / 47 (6.38%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 48 (2.08%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 48 (2.08%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			

subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Part A: Debio 1143 100 mg + CRT	Part A: Debio 1143 200mg + CRT	Part A: Debio 1143 300mg + CRT
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	6 / 6 (100.00%)	3 / 3 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Hypotension			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Orthostatic hypotension			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Application site pruritus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Asthenia			
subjects affected / exposed	4 / 5 (80.00%)	5 / 6 (83.33%)	1 / 3 (33.33%)
occurrences (all)	4	6	1
Chest pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Fatigue			

subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
General physical health deterioration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Hyperthermia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Mucosal inflammation			
subjects affected / exposed	3 / 5 (60.00%)	4 / 6 (66.67%)	3 / 3 (100.00%)
occurrences (all)	3	4	4
Oedema peripheral			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	1 / 3 (33.33%)
occurrences (all)	2	1	1
Xerosis			
subjects affected / exposed	0 / 5 (0.00%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 5 (60.00%)	2 / 6 (33.33%)	2 / 3 (66.67%)
occurrences (all)	3	2	2
Dysphonia			
subjects affected / exposed	2 / 5 (40.00%)	1 / 6 (16.67%)	1 / 3 (33.33%)
occurrences (all)	2	1	1
Dyspnoea			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Epistaxis			

subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Hiccups			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Lung disorder			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Respiratory disorder			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Confusional state			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Depressed mood			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	0 / 5 (0.00%)	2 / 6 (33.33%)	2 / 3 (66.67%)
occurrences (all)	0	2	2
Amylase increased			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	1 / 3 (33.33%)
occurrences (all)	1	2	2
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Blood creatinine increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Blood urea increased			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Blood potassium decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Ejection fraction decreased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Lipase increased			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
Protein total decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Troponin I increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Weight decreased			

subjects affected / exposed	3 / 5 (60.00%)	6 / 6 (100.00%)	2 / 3 (66.67%)
occurrences (all)	3	6	2
White blood cell count decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	3 / 5 (60.00%)	6 / 6 (100.00%)	3 / 3 (100.00%)
occurrences (all)	3	7	3
Cardiac disorders			
Bundle branch block left			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Sinus tachycardia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Ventricular extrasystoles			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	3 / 5 (60.00%)	6 / 6 (100.00%)	1 / 3 (33.33%)
occurrences (all)	3	7	1
Headache			
subjects affected / exposed	1 / 5 (20.00%)	2 / 6 (33.33%)	1 / 3 (33.33%)
occurrences (all)	1	2	2
Neuropathy peripheral			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Neuralgia			

subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 5 (80.00%)	3 / 6 (50.00%)	2 / 3 (66.67%)
occurrences (all)	6	3	3
Antiphospholipid syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Leukopenia			
subjects affected / exposed	3 / 5 (60.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	4	0	1
Lymphopenia			
subjects affected / exposed	1 / 5 (20.00%)	2 / 6 (33.33%)	3 / 3 (100.00%)
occurrences (all)	1	2	5
Neutropenia			
subjects affected / exposed	5 / 5 (100.00%)	3 / 6 (50.00%)	0 / 3 (0.00%)
occurrences (all)	5	3	0
Thrombocytopenia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Ear pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypoacusis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Ototoxicity			

subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Tinnitus			
subjects affected / exposed	3 / 5 (60.00%)	2 / 6 (33.33%)	1 / 3 (33.33%)
occurrences (all)	3	3	1
Vertigo			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Abdominal pain upper			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Aptyalism			
subjects affected / exposed	2 / 5 (40.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Cheilitis			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Constipation			
subjects affected / exposed	3 / 5 (60.00%)	2 / 6 (33.33%)	3 / 3 (100.00%)
occurrences (all)	3	2	3
Diarrhoea			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	2 / 3 (66.67%)
occurrences (all)	1	1	2
Dry mouth			
subjects affected / exposed	1 / 5 (20.00%)	3 / 6 (50.00%)	1 / 3 (33.33%)
occurrences (all)	1	3	1
Dyspepsia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dysphagia			
subjects affected / exposed	4 / 5 (80.00%)	2 / 6 (33.33%)	2 / 3 (66.67%)
occurrences (all)	5	2	3

Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Glossitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Glossodynia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Melaena			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Mouth ulceration			
subjects affected / exposed	0 / 5 (0.00%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Nausea			
subjects affected / exposed	1 / 5 (20.00%)	6 / 6 (100.00%)	1 / 3 (33.33%)
occurrences (all)	3	7	1
Odynophagia			
subjects affected / exposed	3 / 5 (60.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	3	1	0
Oesophagitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Oral pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Salivary hypersecretion			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Stomatitis			
subjects affected / exposed	0 / 5 (0.00%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Vomiting			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	1 / 3 (33.33%)
occurrences (all)	1	1	2

Hepatobiliary disorders			
Renal failure acute			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 5 (20.00%)	2 / 6 (33.33%)	1 / 3 (33.33%)
occurrences (all)	1	2	1
Dermatitis			
subjects affected / exposed	2 / 5 (40.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Dermatitis bullous			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Dry skin			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Erythema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hair growth abnormal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Pain of skin			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Pigmentation disorder			
subjects affected / exposed	2 / 5 (40.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Pruritus			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Urticaria			

subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Renal failure			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	1 / 3 (33.33%)
occurrences (all)	0	1	2
Acute kidney injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Neck pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Trismus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Bronchopneumonia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Folliculitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Fungal infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gingivitis			

subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Haemophilus infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Herpes zoster			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Impetigo			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Localised infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Mucosal infection			
subjects affected / exposed	2 / 5 (40.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Oral fungal infection			
subjects affected / exposed	0 / 5 (0.00%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Oral candidiasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Skin infection			
subjects affected / exposed	2 / 5 (40.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Staphylococcal skin infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Tooth infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			

subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 5 (20.00%)	3 / 6 (50.00%)	2 / 3 (66.67%)
occurrences (all)	1	3	2
Hyperkalaemia			
subjects affected / exposed	2 / 5 (40.00%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	2	3	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Hypomagnesaemia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	1 / 3 (33.33%)
occurrences (all)	1	2	1
Hyponatraemia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	1 / 3 (33.33%)
occurrences (all)	1	1	4
Hypophosphataemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Hyperglycaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Malnutrition			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part B: Debio 1143 200mg + CRT	Part B: Placebo + CRT	
Total subjects affected by non-serious adverse events			

subjects affected / exposed	48 / 48 (100.00%)	46 / 47 (97.87%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 48 (6.25%)	4 / 47 (8.51%)	
occurrences (all)	7	7	
Hypotension			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Orthostatic hypotension			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Application site pruritus			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Asthenia			
subjects affected / exposed	16 / 48 (33.33%)	19 / 47 (40.43%)	
occurrences (all)	16	20	
Chest pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	9 / 48 (18.75%)	6 / 47 (12.77%)	
occurrences (all)	10	7	
General physical health deterioration			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Hyperthermia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Mucosal inflammation			
subjects affected / exposed	36 / 48 (75.00%)	31 / 47 (65.96%)	
occurrences (all)	39	33	
Oedema peripheral			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	

Pain			
subjects affected / exposed	3 / 48 (6.25%)	5 / 47 (10.64%)	
occurrences (all)	3	6	
Pyrexia			
subjects affected / exposed	9 / 48 (18.75%)	6 / 47 (12.77%)	
occurrences (all)	11	6	
Xerosis			
subjects affected / exposed	4 / 48 (8.33%)	2 / 47 (4.26%)	
occurrences (all)	4	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 48 (10.42%)	6 / 47 (12.77%)	
occurrences (all)	5	7	
Dysphonia			
subjects affected / exposed	5 / 48 (10.42%)	7 / 47 (14.89%)	
occurrences (all)	5	7	
Dyspnoea			
subjects affected / exposed	1 / 48 (2.08%)	4 / 47 (8.51%)	
occurrences (all)	1	5	
Epistaxis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Hiccups			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Lung disorder			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Oropharyngeal pain			
subjects affected / exposed	7 / 48 (14.58%)	4 / 47 (8.51%)	
occurrences (all)	7	4	
Productive cough			
subjects affected / exposed	4 / 48 (8.33%)	1 / 47 (2.13%)	
occurrences (all)	5	1	
Respiratory disorder			

subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Rhinorrhoea			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	7 / 48 (14.58%)	3 / 47 (6.38%)	
occurrences (all)	7	3	
Confusional state			
subjects affected / exposed	3 / 48 (6.25%)	0 / 47 (0.00%)	
occurrences (all)	3	0	
Depressed mood			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Insomnia			
subjects affected / exposed	5 / 48 (10.42%)	4 / 47 (8.51%)	
occurrences (all)	5	4	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	13 / 48 (27.08%)	8 / 47 (17.02%)	
occurrences (all)	20	11	
Amylase increased			
subjects affected / exposed	2 / 48 (4.17%)	4 / 47 (8.51%)	
occurrences (all)	2	4	
Aspartate aminotransferase increased			
subjects affected / exposed	9 / 48 (18.75%)	3 / 47 (6.38%)	
occurrences (all)	13	5	
Blood creatinine increased			
subjects affected / exposed	3 / 48 (6.25%)	5 / 47 (10.64%)	
occurrences (all)	3	6	
Blood urea increased			
subjects affected / exposed	4 / 48 (8.33%)	5 / 47 (10.64%)	
occurrences (all)	5	6	
Blood potassium decreased			

subjects affected / exposed	0 / 48 (0.00%)	3 / 47 (6.38%)	
occurrences (all)	0	3	
Ejection fraction decreased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	7 / 48 (14.58%)	5 / 47 (10.64%)	
occurrences (all)	10	6	
Lipase increased			
subjects affected / exposed	4 / 48 (8.33%)	1 / 47 (2.13%)	
occurrences (all)	4	1	
Protein total decreased			
subjects affected / exposed	0 / 48 (0.00%)	3 / 47 (6.38%)	
occurrences (all)	0	3	
Troponin I increased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Weight decreased			
subjects affected / exposed	28 / 48 (58.33%)	21 / 47 (44.68%)	
occurrences (all)	30	27	
White blood cell count decreased			
subjects affected / exposed	4 / 48 (8.33%)	3 / 47 (6.38%)	
occurrences (all)	6	4	
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	25 / 48 (52.08%)	20 / 47 (42.55%)	
occurrences (all)	25	20	
Cardiac disorders			
Bundle branch block left			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Sinus tachycardia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Tachycardia			

subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Ventricular extrasystoles			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 48 (2.08%)	3 / 47 (6.38%)	
occurrences (all)	1	3	
Dysgeusia			
subjects affected / exposed	12 / 48 (25.00%)	15 / 47 (31.91%)	
occurrences (all)	13	15	
Headache			
subjects affected / exposed	4 / 48 (8.33%)	6 / 47 (12.77%)	
occurrences (all)	4	6	
Neuropathy peripheral			
subjects affected / exposed	4 / 48 (8.33%)	1 / 47 (2.13%)	
occurrences (all)	4	1	
Neuralgia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Paraesthesia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	30 / 48 (62.50%)	26 / 47 (55.32%)	
occurrences (all)	38	37	
Antiphospholipid syndrome			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Leukopenia			
subjects affected / exposed	7 / 48 (14.58%)	8 / 47 (17.02%)	
occurrences (all)	9	11	
Lymphopenia			

subjects affected / exposed	3 / 48 (6.25%)	0 / 47 (0.00%)	
occurrences (all)	3	0	
Neutropenia			
subjects affected / exposed	12 / 48 (25.00%)	17 / 47 (36.17%)	
occurrences (all)	16	24	
Thrombocytopenia			
subjects affected / exposed	7 / 48 (14.58%)	7 / 47 (14.89%)	
occurrences (all)	8	10	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Ear pain			
subjects affected / exposed	4 / 48 (8.33%)	0 / 47 (0.00%)	
occurrences (all)	4	0	
Hypoacusis			
subjects affected / exposed	4 / 48 (8.33%)	3 / 47 (6.38%)	
occurrences (all)	4	3	
Ototoxicity			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Tinnitus			
subjects affected / exposed	15 / 48 (31.25%)	10 / 47 (21.28%)	
occurrences (all)	17	11	
Vertigo			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Abdominal pain upper			
subjects affected / exposed	3 / 48 (6.25%)	2 / 47 (4.26%)	
occurrences (all)	4	2	
Aptyalism			

subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Cheilitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Constipation			
subjects affected / exposed	16 / 48 (33.33%)	16 / 47 (34.04%)	
occurrences (all)	21	18	
Diarrhoea			
subjects affected / exposed	7 / 48 (14.58%)	6 / 47 (12.77%)	
occurrences (all)	8	6	
Dry mouth			
subjects affected / exposed	20 / 48 (41.67%)	19 / 47 (40.43%)	
occurrences (all)	21	20	
Dyspepsia			
subjects affected / exposed	3 / 48 (6.25%)	2 / 47 (4.26%)	
occurrences (all)	3	2	
Dysphagia			
subjects affected / exposed	36 / 48 (75.00%)	29 / 47 (61.70%)	
occurrences (all)	38	30	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 48 (2.08%)	3 / 47 (6.38%)	
occurrences (all)	1	3	
Glossitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Glossodynia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Melaena			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Mouth ulceration			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Nausea			

subjects affected / exposed	20 / 48 (41.67%)	17 / 47 (36.17%)	
occurrences (all)	30	24	
Odynophagia			
subjects affected / exposed	10 / 48 (20.83%)	10 / 47 (21.28%)	
occurrences (all)	11	10	
Oesophagitis			
subjects affected / exposed	4 / 48 (8.33%)	4 / 47 (8.51%)	
occurrences (all)	4	4	
Oral pain			
subjects affected / exposed	7 / 48 (14.58%)	1 / 47 (2.13%)	
occurrences (all)	7	1	
Salivary hypersecretion			
subjects affected / exposed	4 / 48 (8.33%)	5 / 47 (10.64%)	
occurrences (all)	4	5	
Stomatitis			
subjects affected / exposed	8 / 48 (16.67%)	9 / 47 (19.15%)	
occurrences (all)	8	9	
Vomiting			
subjects affected / exposed	13 / 48 (27.08%)	11 / 47 (23.40%)	
occurrences (all)	20	13	
Hepatobiliary disorders			
Renal failure acute			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	4 / 48 (8.33%)	7 / 47 (14.89%)	
occurrences (all)	4	7	
Dermatitis			
subjects affected / exposed	20 / 48 (41.67%)	19 / 47 (40.43%)	
occurrences (all)	22	20	
Dermatitis bullous			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Dry skin			

subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Erythema			
subjects affected / exposed	1 / 48 (2.08%)	4 / 47 (8.51%)	
occurrences (all)	1	4	
Hair growth abnormal			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Pain of skin			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Pigmentation disorder			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Pruritus			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Rash			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Urticaria			
subjects affected / exposed	3 / 48 (6.25%)	0 / 47 (0.00%)	
occurrences (all)	3	0	
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Renal failure			
subjects affected / exposed	2 / 48 (4.17%)	5 / 47 (10.64%)	
occurrences (all)	2	5	
Acute kidney injury			
subjects affected / exposed	11 / 48 (22.92%)	4 / 47 (8.51%)	
occurrences (all)	16	5	
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Neck pain			
subjects affected / exposed	9 / 48 (18.75%)	7 / 47 (14.89%)	
occurrences (all)	10	8	
Trismus			
subjects affected / exposed	5 / 48 (10.42%)	1 / 47 (2.13%)	
occurrences (all)	5	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 48 (6.25%)	1 / 47 (2.13%)	
occurrences (all)	3	1	
Bronchopneumonia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Folliculitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Fungal infection			
subjects affected / exposed	6 / 48 (12.50%)	4 / 47 (8.51%)	
occurrences (all)	6	4	
Gingivitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Haemophilus infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Herpes zoster			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Impetigo			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Localised infection			

subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Mucosal infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Oral fungal infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Oral candidiasis			
subjects affected / exposed	4 / 48 (8.33%)	5 / 47 (10.64%)	
occurrences (all)	4	5	
Pharyngitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Skin infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Staphylococcal skin infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Tooth infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Urinary tract infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	12 / 48 (25.00%)	12 / 47 (25.53%)	
occurrences (all)	13	12	
Hyperkalaemia			
subjects affected / exposed	3 / 48 (6.25%)	2 / 47 (4.26%)	
occurrences (all)	4	3	
Hypoalbuminaemia			
subjects affected / exposed	5 / 48 (10.42%)	6 / 47 (12.77%)	
occurrences (all)	6	7	

Hypokalaemia			
subjects affected / exposed	6 / 48 (12.50%)	5 / 47 (10.64%)	
occurrences (all)	6	7	
Hypomagnesaemia			
subjects affected / exposed	3 / 48 (6.25%)	8 / 47 (17.02%)	
occurrences (all)	3	9	
Hyponatraemia			
subjects affected / exposed	1 / 48 (2.08%)	5 / 47 (10.64%)	
occurrences (all)	1	7	
Hypophosphataemia			
subjects affected / exposed	0 / 48 (0.00%)	4 / 47 (8.51%)	
occurrences (all)	0	5	
Hyperglycaemia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Hypocalcaemia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Malnutrition			
subjects affected / exposed	0 / 48 (0.00%)	4 / 47 (8.51%)	
occurrences (all)	0	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 July 2015	This protocol amendment was aimed at correcting, clarifying and improving the contents and structure of Part B prior to its initiation.
24 August 2016	The main change introduced by this amendment was the inclusion of HPV-16-positive subjects.
07 November 2018	This amendment for study Part B was issued following the decision to: • Add an extra follow up period (extended follow up) and revise statistical sections including establishing an Internal Steering Committee. • Modify secondary endpoints.
05 March 2020	• Extension of the survival follow up period by 2 years until 5 years after CRT initiation for the last participant to start treatment. • Collection of subsequent antineoplastic therapy information: Early stopping rules were added for the survival follow-up in case insufficient OS and subsequent antineoplastic therapy information could be collected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported