Clinical trial results:
Neurotoxicity characterization phase II randomized study of nab-paclitaxel versus conventional paclitaxel as first-line therapy of metastatic HER2-negative breast cancer.

Summary

EudraCT number	2012-002361-36
Trial protocol	ES
Global end of trial date	29 March 2016

Results information

Result version number	v1 (current)
This version publication date	20 February 2022
First version publication date	20 February 2022

Trial information

Trial identification

Sponsor protocol code	ONCOSUR-2012-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01763710
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ONCOSUR
Sponsor organisation address	Avda. de Cordoba s.n. Hospital 12 de Octubre, Servicio de Oncología Médica, Madrid, Spain,
Public contact	Operaciones clínicas, ONCOSUR, ana.moreno@apices.es
Scientific contact	Operaciones Clínicas, ONCOSUR, ana.moreno@apices.es

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	29 March 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To characterize neurotoxicity according to Total Neuropathy Score

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 60
Worldwide total number of subjects	60
EEA total number of subjects	60

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)	45
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were included in the study between 17th January 2013 and 24th July 2014

Pre-assignment

Screening details:

65 patients were recruited initially in the study which were analyzed 60. 5 patients were screening failures

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Patients received conventional Paclitaxel 80mg/m2 at days 1, 8 and 15 in cycles of 28 days

Arm type	Standard
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

80 mg/m2 at days 1, 8 and 15 in cycles of 28 days

Arm title	Arm B

Arm description:

Patients received nab-paclitaxel 100mg/m2 at days 1, 8 and 15 in cycles of 28 days

Arm type	Experimental
Investigational medicinal product name	Nab-paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

100mg/m2 at days 1, 8 and 15 in cycles of 28 days

Arm title	Arm C

Arm description:

Patientes received Nab-paclitaxel 150mg/m2 at days 1, 8 and 15 in cycles of 28 days

Arm type	Experimental
Investigational medicinal product name	Nab-paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:
150 mg/m2 at days 1, 8 and 15 in cycles of 28 days

Arm title	Arm D

Arm description:
Patients received Nab-paclitaxel 150 mg/m2 at days 1 and 15 in cycles of 28 days

Arm type	Experimental
Investigational medicinal product name	Nab-paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:
150 mg/m2 at days 1 and 15 in cycles of 28 days

Number of subjects in period 1	Arm A	Arm B	Arm C
Started	14	16	14
Completed	14	16	14

Number of subjects in period 1	Arm D
Started	16
Completed	16

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
Patients received conventional Paclitaxel 80mg/m2 at days 1, 8 and 15 in cycles of 28 days	
Reporting group title	Arm B
Reporting group description:	
Patients received nab-paclitaxel 100mg/m2 at days 1, 8 and 15 in cycles of 28 days	
Reporting group title	Arm C
Reporting group description:	
Patientes received Nab-paclitaxel 150mg/m2 at days 1, 8 and 15 in cycles of 28 days	
Reporting group title	Arm D
Reporting group description:	
Patients received Nab-paclitaxel 150 mg/m2 at days 1 and 15 in cycles of 28 days	

Reporting group values	Arm A	Arm B	Arm C
Number of subjects	14	16	14
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	9	11	10
From 65-84 years	5	5	4
85 years and over	0	0	0
Age continuous Units: years			
median	56.8	59.8	57.3
full range (min-max)	37.4 to 80.6	40.8 to 84.6	38.8 to 78.5
Gender categorical Units: Subjects			
Female	14	16	14
Male	0	0	0
ECOG-PS Units: Subjects			
(0)	10	7	12
(1)	3	7	2
Unknown	1	2	0
Raze Units: Subjects			
Caucasian	14	14	12
Latin/hispanic	0	1	2
Arabic	0	1	0

Diagnostic stage Units: Subjects			
(I)	4	1	2
(II)	3	8	6
(III)	2	2	2
(IV)	4	5	4
ND	1	0	0
Previous radiotherapy Units: Subjects			
No	6	9	6
Yes	8	7	8
Previous surgery Units: Subjects			
No	3	4	4
Si	11	12	10
Type of surgery Units: Subjects			
mastectomy	1	2	3
modified radical mastectomy	4	4	4
radical mastectomy	3	1	1
lumpectomy	3	4	2
not available	3	5	4
Previous chemotherapy Units: Subjects			
No	7	6	5
Yes	7	10	9
weight Units: kilograms			
median	63.9	64.6	62.5
full range (min-max)	46.8 to 92.8	51.6 to 100.6	51.4 to 99
Height Units: centimeter			
median	156	158.5	159.5
full range (min-max)	148 to 169	146 to 169	144 to 174
Corporal surface Units: square meter			
median	1.6	1.7	1.7
full range (min-max)	1.4 to 2	1.5 to 1.9	1.5 to 2.0
Time since first diagnosis Units: month			
median	44.5	50.4	65.3
full range (min-max)	0.3 to 312.3	0.0 to 239.2	0.5 to 408.7
Number of cycles administered Units: cycles			
median	6.0	7.0	8.0
full range (min-max)	3 to 11	1 to 14	2 to 15
Relative dose Intensity Units: mg/m2/week			
median	0.93	0.92	0.77
full range (min-max)	0.57 to 1.00	0.33 to 1.00	0.48 to 0.89

Reporting group values	Arm D	Total	
Number of subjects	16	60	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	10	40	
From 65-84 years	6	20	
85 years and over	0	0	
Age continuous Units: years			
median	62.1		
full range (min-max)	37.8 to 79.6	-	
Gender categorical Units: Subjects			
Female	16	60	
Male	0	0	
ECOG-PS Units: Subjects			
(0)	10	39	
(1)	6	18	
Unknown	0	3	
Raze Units: Subjects			
Caucasian	15	55	
Latin/hispanic	0	3	
Arabic	1	2	
Diagnostic stage Units: Subjects			
(I)	2	9	
(II)	5	22	
(III)	4	10	
(IV)	3	16	
ND	2	3	
Previous radiotherapy Units: Subjects			
No	6	27	
Yes	10	33	
Previous surgery Units: Subjects			
No	3	14	
Si	13	46	
Type of surgery Units: Subjects			
mastectomy	0	6	
modified radical mastectomy	7	19	

radical mastectomy	0	5	
lumpectomy	6	15	
not available	3	15	
Previous chemotherapy Units: Subjects			
No	5	23	
Yes	11	37	
weight Units: kilograms			
median	63.3		
full range (min-max)	47.4 to 85.4	-	
Height Units: centimeter			
median	156		
full range (min-max)	148 to 176	-	
Corporal surface Units: square meter			
median	1.6		
full range (min-max)	1.4 to 2.0	-	
Time since first diagnosis Units: month			
median	68.5		
full range (min-max)	0.4 to 212.8	-	
Number of cycles administered Units: cycles			
median	4.5		
full range (min-max)	3 to 12	-	
Relative dose Intensity Units: mg/m2/week			
median	0.90		
full range (min-max)	0.66 to 1.00	-	

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description:	
Patients received conventional Paclitaxel 80mg/m2 at days 1, 8 and 15 in cycles of 28 days	
Reporting group title	Arm B
Reporting group description:	
Patients received nab-paclitaxel 100mg/m2 at days 1, 8 and 15 in cycles of 28 days	
Reporting group title	Arm C
Reporting group description:	
Patientes received Nab-paclitaxel 150mg/m2 at days 1, 8 and 15 in cycles of 28 days	
Reporting group title	Arm D
Reporting group description:	
Patients received Nab-paclitaxel 150 mg/m2 at days 1 and 15 in cycles of 28 days	

Primary: Total Neuropathy Score

End point title	Total Neuropathy Score[1]
End point description:	
Change from baseline in TNS score.	
End point type	Primary
End point timeframe:	
Every 12 weeks	

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: Not statistical significant differences were found (ANOVA p-value: 0.587).

End point values	Arm A	Arm B	Arm C	Arm D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	16	14	16
Units: percent				
median (full range (min-max))	3.8 (-2 to 12.0)	3.5 (-1.0 to 12.0)	3.8 (0.0 to 11.0)	2.4 (0.0 to 4.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of neuropathy

End point title	Incidence of neuropathy
End point description:	
Proportion of patients that present neuropathy (any grade) according to NCI-CTCAE.	
End point type	Secondary
End point timeframe:	
Every week	

End point values	Arm A	Arm B	Arm C	Arm D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	16	14	16
Units: percent				
number (not applicable)	50.0	81.3	78.6	62.6

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

End point title	Progression free survival

End point description:

Progression free survival is the time elapsed since the start of study treatment until the criteria for progression of the illness or the patient dies.

End point type	Secondary

End point timeframe:

Every week

End point values	Arm A	Arm B	Arm C	Arm D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	16	14	16
Units: months				
median (full range (min-max))	7.401 (3.468 to 11.334)	5.954 (0.000 to 12.588)	11.579 (11.037 to 12.121)	15.691 (12.229 to 19.153)

Statistical analyses

No statistical analyses for this end point

Secondary: Time until appearance of neurotoxicity

End point title	Time until appearance of neurotoxicity

End point description:

Time elapsed from patient entry into the study until first neurotoxicity event grade ≥ 2

Median time until appearance of neurotoxicity not reached in arms A, B and D.

End point type	Secondary

End point timeframe:

Weekly

End point values	Arm A	Arm B	Arm C	Arm D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	16	14	16
Units: month				
median (confidence interval 95%)	0 (0 to 0)	0 (0 to 0)	3.717 (2.571 to 4.863)	0 (0 to 0)

Statistical analyses

No statistical analyses for this end point

Secondary: Time until neurotoxicity recovery

End point title	Time until neurotoxicity recovery

End point description:

Time that elapses from the patient's appearance of grade 2 neurotoxicity to recovery.

End point type	Secondary

End point timeframe:

Weekly

End point values	Arm A	Arm B	Arm C	Arm D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	16	14	16
Units: months				
median (confidence interval 95%)	8.783 (0.000 to 23.262)	6.908 (5.566 to 8.250)	14.605 (9.412 to 19.798)	12.599 (0.000 to 37.742)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression

End point title	Time to progression

End point description:

Time to progression is the time from the start of study treatment until disease progression criteria are met or the patient dies due to disease progression.

End point type	Secondary

End point timeframe:

every week

End point values	Arm A	Arm B	Arm C	Arm D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	16	14	16
Units: months				
median (confidence interval 95%)	5.954 (0.000 to 12.588)	11.579 (11.037 to 12.121)	15.691 (12.229 to 19.153)	7.401 (3.468 to 11.334)

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life through the EORTC QLQC30 and EORTC QLQ-CIPN20 questionnaires.

End point title	Quality of Life through the EORTC QLQC30 and EORTC QLQ-CIPN20 questionnaires.

End point description:

Mean change in the Global Health Status EORTC QLQ-CIPN20 and in the Global Health Status EORTC QLQ-C30 scores from baseline.

End point type	Secondary

End point timeframe:

Initial visit

End point values	Arm A	Arm B	Arm C	Arm D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	16	14	16
Units: percent				
least squares mean (confidence interval 95%)				
EORTC QLQ-CPIN20	14.4 (14.4 to 14.4)	28.4 (-4.8 to 32.9)	33.4 (1.1 to 37.0)	14.0 (-17.8 to 17.1)
EORTC QLQ-C30	-12.7 (-12.7 to -12.7)	-6.6 (-21.7 to 33.9)	-24.7 (-38.1 to 14.1)	-8.9 (-21.6 to 29.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate

End point title	Objective response rate

End point description:

Proportion of patients with complete response or partial response according to RECIST 1.1 criteria.

End point type	Secondary

End point timeframe:

Every week

End point values	Arm A	Arm B	Arm C	Arm D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	16	14	16
Units: percent				
median (confidence interval 95%)	12.5 (0 to 28.7)	21.4 (0 to 42.9)	37.5 (13.8 to 61.2)	42.9 (16.9 to 68.8)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Every 15 days	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0
Reporting groups	
Reporting group title	Total
Reporting group description: -	
Reporting group title	Arm a
Reporting group description: Patients received conventional Paclitaxel 80 mg/m2 at days 1, 8 and 15 in cycles of 28 days	
Reporting group title	Arm b
Reporting group description: Patients received nab-paclitaxel 100 mg/m2 at days 1, 8 and 15 in cycles of 28 days	
Reporting group title	Arm c
Reporting group description: Patients received nab-paclitaxel 150 mg/m2 at days 1, 8 and 15 in cycles of 28 days	
Reporting group title	Arm d
Reporting group description: Patients received nab-paclitaxel 150 mg/m2 at days 1 and 15 in cycles of 28 days	

Serious adverse events	Total	Arm a	Arm b
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 60 (40.00%)	2 / 14 (14.29%)	9 / 16 (56.25%)
number of deaths (all causes)	17	8	1
number of deaths resulting from adverse events	0	0	0
Investigations			
liver biopsy			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Salpingo-oophorectomy			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingo-oophorectomy bilateral			

subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 60 (3.33%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (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
Surgical and medical procedures			
mastectomy			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
pyrexia			
subjects affected / exposed	4 / 60 (6.67%)	1 / 14 (7.14%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	1 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (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
Gastrointestinal disorders			
diarrhea			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (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
Hepatobiliary disorders			
Abnormal liver function			

subjects affected / exposed	1 / 60 (1.67%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (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
pneumothorax			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (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
Pleural effusion			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism pulmonary			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacterial peritonitis			

subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (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
Urinary tract infection			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (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

Serious adverse events	Arm c	Arm d	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 14 (64.29%)	4 / 16 (25.00%)	
number of deaths (all causes)	3	5	
number of deaths resulting from adverse events	0	0	
Investigations			
liver biopsy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Salpingo-oophorectomy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salpingo-oophorectomy bilateral			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			

subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
mastectomy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
pyrexia			
subjects affected / exposed	2 / 14 (14.29%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
diarrhea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Abnormal liver function			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			

subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumothorax			
subjects affected / exposed	0 / 14 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism pulmonary			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacterial peritonitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Total	Arm a	Arm b
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 60 (100.00%)	14 / 14 (100.00%)	16 / 16 (100.00%)
Vascular disorders			
Lymphoedema			
subjects affected / exposed	1 / 60 (1.67%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Overheating			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Hypotension			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Gait disturbance			
subjects affected / exposed	3 / 60 (5.00%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	3	1	0
Asthenia			
subjects affected / exposed	38 / 60 (63.33%)	8 / 14 (57.14%)	7 / 16 (43.75%)
occurrences (all)	38	8	7
Chest discomfort			
subjects affected / exposed	3 / 60 (5.00%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	3	1	0
Mucous dryness			
subjects affected / exposed	2 / 60 (3.33%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Peripheral edema			
subjects affected / exposed	2 / 60 (3.33%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Pyrexia			
subjects affected / exposed	2 / 60 (3.33%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Oedema			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Fatigue			

subjects affected / exposed	2 / 60 (3.33%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Mucosal inflammation			
subjects affected / exposed	4 / 60 (6.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	4	0	0
General discomfort			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Generalised oedema			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 60 (6.67%)	1 / 14 (7.14%)	2 / 16 (12.50%)
occurrences (all)	4	1	2
Nasal dryness			
subjects affected / exposed	1 / 60 (1.67%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Cold			
subjects affected / exposed	2 / 60 (3.33%)	0 / 14 (0.00%)	2 / 16 (12.50%)
occurrences (all)	2	0	2
Cough			
subjects affected / exposed	3 / 60 (5.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	3	0	1
Epistaxis			
subjects affected / exposed	2 / 60 (3.33%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Pharyngeal inflammation			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			

subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Investigations			
decreased weight			
subjects affected / exposed	1 / 60 (1.67%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Alanine aminotransferase increased			
subjects affected / exposed	4 / 60 (6.67%)	0 / 14 (0.00%)	3 / 16 (18.75%)
occurrences (all)	4	0	3
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 60 (5.00%)	0 / 14 (0.00%)	2 / 16 (12.50%)
occurrences (all)	3	0	2
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 60 (3.33%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
blood lactatodehydrogenase increased			
subjects affected / exposed	2 / 60 (3.33%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Blood albumin decreased			
subjects affected / exposed	2 / 60 (3.33%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Blood calcium decreased			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Blood alkaline phosphatase			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Blood alkaline phosphatase increased			

subjects affected / exposed	2 / 60 (3.33%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Blood glucose decreased			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Total proteins decreased			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Monocyte count elevated			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Blood urea decreased			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Blood creatinine increased			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Aphonia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Polyneuropathy			
subjects affected / exposed	41 / 60 (68.33%)	7 / 14 (50.00%)	13 / 16 (81.25%)
occurrences (all)	41	7	13
Dysgeusia			
subjects affected / exposed	2 / 60 (3.33%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Psychomotor hyperactivity			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
tingling			
subjects affected / exposed	1 / 60 (1.67%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Neurotoxicity			
subjects affected / exposed	10 / 60 (16.67%)	3 / 14 (21.43%)	1 / 16 (6.25%)
occurrences (all)	10	3	1

Paresthesia			
subjects affected / exposed	8 / 60 (13.33%)	2 / 14 (14.29%)	0 / 16 (0.00%)
occurrences (all)	8	2	0
Syncope			
subjects affected / exposed	1 / 60 (1.67%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Balance disorder			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Dizziness			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Hypoesthesia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Neuralgia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	29 / 60 (48.33%)	3 / 14 (21.43%)	8 / 16 (50.00%)
occurrences (all)	29	3	8
Leukopenia			
subjects affected / exposed	27 / 60 (45.00%)	8 / 14 (57.14%)	8 / 16 (50.00%)
occurrences (all)	27	8	8
Lymphopenia			
subjects affected / exposed	6 / 60 (10.00%)	1 / 14 (7.14%)	2 / 16 (12.50%)
occurrences (all)	6	1	2
Monocytopenia			
subjects affected / exposed	2 / 60 (3.33%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Febrile neutropenia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Thrombocytopenia			

subjects affected / exposed	4 / 60 (6.67%)	1 / 14 (7.14%)	1 / 16 (6.25%)
occurrences (all)	4	1	1
Lymphocyte count elevated			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Blindness			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	9 / 60 (15.00%)	2 / 14 (14.29%)	2 / 16 (12.50%)
occurrences (all)	9	2	2
Dyspepsia			
subjects affected / exposed	3 / 60 (5.00%)	1 / 14 (7.14%)	1 / 16 (6.25%)
occurrences (all)	3	1	1
Mouth discomfort			
subjects affected / exposed	1 / 60 (1.67%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Vomiting			
subjects affected / exposed	6 / 60 (10.00%)	1 / 14 (7.14%)	2 / 16 (12.50%)
occurrences (all)	6	1	2
Constipation			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Nausea			
subjects affected / exposed	9 / 60 (15.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	9	0	1
Abdominal pain			
subjects affected / exposed	2 / 60 (3.33%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Esophagitis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			

Hyperbilirubinaemia			
subjects affected / exposed	1 / 60 (1.67%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Hepatotoxicity			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	19 / 60 (31.67%)	6 / 14 (42.86%)	6 / 16 (37.50%)
occurrences (all)	19	6	6
Rash			
subjects affected / exposed	1 / 60 (1.67%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Onycholysis			
subjects affected / exposed	13 / 60 (21.67%)	4 / 14 (28.57%)	5 / 16 (31.25%)
occurrences (all)	13	4	5
Dry skin			
subjects affected / exposed	2 / 60 (3.33%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Nail toxicity			
subjects affected / exposed	2 / 60 (3.33%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Nail dystrophy			
subjects affected / exposed	4 / 60 (6.67%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	4	0	1
Onychoclasia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Skin toxicity			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Skin hyperpigmentation			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			

Urinary incontinence			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 60 (1.67%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Pain in an extremity			
subjects affected / exposed	3 / 60 (5.00%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	3	1	0
Musculoskeletal pain			
subjects affected / exposed	1 / 60 (1.67%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Muscle spasms			
subjects affected / exposed	4 / 60 (6.67%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	4	1	0
Myalgia			
subjects affected / exposed	4 / 60 (6.67%)	1 / 14 (7.14%)	1 / 16 (6.25%)
occurrences (all)	4	1	1
Limb discomfort			
subjects affected / exposed	2 / 60 (3.33%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Arthralgia			
subjects affected / exposed	2 / 60 (3.33%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Muscle strength loss			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	1 / 60 (1.67%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Conjunctivitis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Dental infection			

subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Cellulite			
subjects affected / exposed	2 / 60 (3.33%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Folliculitis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Herpes zoster			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 60 (10.00%)	2 / 14 (14.29%)	0 / 16 (0.00%)
occurrences (all)	6	2	0
Hyperphosphatemia			
subjects affected / exposed	1 / 60 (1.67%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Hypoproteinaemia			
subjects affected / exposed	1 / 60 (1.67%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Fluid retention			
subjects affected / exposed	11 / 60 (18.33%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Hyperglycemia			
subjects affected / exposed	4 / 60 (6.67%)	0 / 14 (0.00%)	2 / 16 (12.50%)
occurrences (all)	4	0	2
Hypoalbuminemia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Hypocalcemia			
subjects affected / exposed	3 / 60 (5.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	3	0	1
Hypophosphataemia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1

Hypoglycemia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Hypernatremia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Hypokalemia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Stomatitis			
subjects affected / exposed	2 / 60 (3.33%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Emesis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Arm c	Arm d	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 14 (100.00%)	16 / 16 (100.00%)	
Vascular disorders			
Lymphoedema			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Overheating			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Hypotension			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Gait disturbance			
subjects affected / exposed	1 / 14 (7.14%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Asthenia			
subjects affected / exposed	9 / 14 (64.29%)	14 / 16 (87.50%)	
occurrences (all)	9	14	
Chest discomfort			

subjects affected / exposed	0 / 14 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Mucous dryness			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Peripheral edema			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Oedema			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	1 / 14 (7.14%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Mucosal inflammation			
subjects affected / exposed	2 / 14 (14.29%)	2 / 16 (12.50%)	
occurrences (all)	2	2	
General discomfort			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Generalised oedema			
subjects affected / exposed	0 / 14 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 14 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Nasal dryness			

subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Cold			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Cough			
subjects affected / exposed	0 / 14 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Epistaxis			
subjects affected / exposed	2 / 14 (14.29%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Pharyngeal inflammation			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Investigations			
decreased weight			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased			

subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
blood lactatodehydrogenase increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Blood albumin decreased			
subjects affected / exposed	1 / 14 (7.14%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Blood calcium decreased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Blood alkaline phosphatase			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 14 (14.29%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Blood glucose decreased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Total proteins decreased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Monocyte count elevated			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Blood urea decreased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Nervous system disorders			
Aphonia			

subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Polyneuropathy			
subjects affected / exposed	11 / 14 (78.57%)	10 / 16 (62.50%)	
occurrences (all)	11	10	
Dysgeusia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Psychomotor hyperactivity			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
tingling			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Neurotoxicity			
subjects affected / exposed	5 / 14 (35.71%)	1 / 16 (6.25%)	
occurrences (all)	5	1	
Paresthesia			
subjects affected / exposed	3 / 14 (21.43%)	3 / 16 (18.75%)	
occurrences (all)	3	3	
Syncope			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Balance disorder			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Dizziness			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Hypoesthesia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Neuralgia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			

Anemia			
subjects affected / exposed	9 / 14 (64.29%)	9 / 16 (56.25%)	
occurrences (all)	9	9	
Leukopenia			
subjects affected / exposed	7 / 14 (50.00%)	4 / 16 (25.00%)	
occurrences (all)	7	4	
Lymphopenia			
subjects affected / exposed	1 / 14 (7.14%)	2 / 16 (12.50%)	
occurrences (all)	1	2	
Monocytopenia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Febrile neutropenia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Thrombocytopenia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Lymphocyte count elevated			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Blindness			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	3 / 14 (21.43%)	2 / 16 (12.50%)	
occurrences (all)	3	2	
Dyspepsia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Mouth discomfort			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Vomiting			

subjects affected / exposed	1 / 14 (7.14%)	2 / 16 (12.50%)	
occurrences (all)	1	2	
Constipation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	3 / 14 (21.43%)	5 / 16 (31.25%)	
occurrences (all)	3	5	
Abdominal pain			
subjects affected / exposed	1 / 14 (7.14%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Esophagitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Hepatotoxicity			
subjects affected / exposed	0 / 14 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	5 / 14 (35.71%)	2 / 16 (12.50%)	
occurrences (all)	5	2	
Rash			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Onycholysis			
subjects affected / exposed	2 / 14 (14.29%)	2 / 16 (12.50%)	
occurrences (all)	2	2	
Dry skin			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Nail toxicity			

subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Nail dystrophy			
subjects affected / exposed	2 / 14 (14.29%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Onychoclasia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Skin toxicity			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Skin hyperpigmentation			
subjects affected / exposed	0 / 14 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	1 / 14 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Pain in an extremity			
subjects affected / exposed	2 / 14 (14.29%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Muscle spasms			
subjects affected / exposed	2 / 14 (14.29%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Myalgia			
subjects affected / exposed	2 / 14 (14.29%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Limb discomfort			

subjects affected / exposed	1 / 14 (7.14%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Arthralgia			
subjects affected / exposed	0 / 14 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Muscle strength loss			
subjects affected / exposed	0 / 14 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Conjunctivitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Dental infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Cellulite			
subjects affected / exposed	2 / 14 (14.29%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Folliculitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	0 / 14 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 14 (7.14%)	3 / 16 (18.75%)	
occurrences (all)	1	3	
Hyperphosphatemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Hypoproteinaemia			

subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Fluid retention			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Hyperglycemia			
subjects affected / exposed	0 / 14 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Hypoalbuminemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Hypocalcemia			
subjects affected / exposed	0 / 14 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Hypophosphataemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Hypoglycemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Hypernatremia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Hypokalemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Stomatitis			
subjects affected / exposed	1 / 14 (7.14%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Emesis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 September 2012	Amendment 1: Protocol version 2.0
09 September 2015	Amendment 2: Protcol version 4.0

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The main limitations of this study are the small sample size and lack of blinding

Notes: