Clinical trial results:
Phase III trial of IV vinflunine versus an alkylating agent in patients with metastatic breast cancer previously treated with or resistant to an anthracycline, a taxane, an antimetabolite, and a vinca-alkaloid (study L00070 IN 308 B0)

Summary

EudraCT number	2009-011118-47
Trial protocol	FR PT IT ES BE DE AT HU GB BG
Global end of trial date	17 January 2014

Results information

Result version number	v1
This version publication date	08 January 2017
First version publication date	08 January 2017

Trial information

Trial identification

Sponsor protocol code	L00070 IN 3 08 B0

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01091168
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	PIERRE FABRE MEDICAMENT
Sponsor organisation address	45, place Abel Gance, Boulogne Billancourt, France,
Public contact	Dr Karim Keddad, INSTITUT DE RECHERCHE PIERRE FABRE, karim.keddad@pierre-fabre.com
Scientific contact	Dr Karim Keddad, Centre de Recherche et Développement clinique. 3 avenue Hubert CURIEN - 31000 TOULOUSE, karim.keddad@pierre-fabre.com
Sponsor organisation name	PIERRE FABRE MEDICAMENT
Sponsor organisation address	45, place Abel Gance, Boulogne Billancourt, France, 92654
Public contact	DR Karim Keddad, INSTITUT DE RECHERCHE PIERRE FABRE, karim.keddad@pierre-fabre.com
Scientific contact	Dr Karim KEDDAD, INSTITUT DE RECHERCHE PIERRE FABRE, karim.keddad@pierre-fabre.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	27 August 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 August 2012
Global end of trial reached?	Yes
Global end of trial date	17 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the overall survival in patients treated with i.v. vinflunine versus those receiving an alkylating agent of physician’s choice.

Protection of trial subjects:

Antiemetic (corticosteroids) in both arms
Laxatives in test drug arm
All best supportive treatment: analgesics for pain, biphosphonates for bone metastasis localized radiotheray in case of bone pain, transfusion, erythropoietin, GCSF in case of neutropenia gr 4 lasting at least 7 days or febrile neutropenia or neutropenic infection and then prophylactically in further cycles

Background therapy:

Antiemetic (corticosteroids) in both arms
Laxatives in test drug arm
All best supportive treatment: analgesics for pain, biphosphonates for bone metatstasis, localized radiotheray in case of bone pain, transfusion, erythropoietin, GCSF in case of neutropenia gr 4 lasting at least 7 days or febrile neutropenia or neutropenic infection and then prophylactically in further cycles

Evidence for comparator:

Alkylating agents (cyclophosphamide, carboplatin, cisplatine, melphalan, thiotepa, mitomycin C) are according to investigators acceptable treatment MBC in patients having exhausted the most active cytotoxics because they have shown some activity in this setting

Actual start date of recruitment	15 July 2009
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?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 15
Country: Number of subjects enrolled	Brazil: 13
Country: Number of subjects enrolled	Mexico: 13
Country: Number of subjects enrolled	South Africa: 7
Country: Number of subjects enrolled	Taiwan: 26
Country: Number of subjects enrolled	Belarus: 54
Country: Number of subjects enrolled	Russian Federation: 57
Country: Number of subjects enrolled	Serbia: 3

Country: Number of subjects enrolled	Ukraine: 10
Country: Number of subjects enrolled	Poland: 37
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Spain: 78
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	Austria: 10
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	France: 162
Country: Number of subjects enrolled	Germany: 24
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Italy: 54
Worldwide total number of subjects	594
EEA total number of subjects	396

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)	463
From 65 to 84 years	131
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was randomized on 15 July 2009 and the last patient was randomized on 11 October 2011. The recruitment period lasted 27 months. A total of 594 patients with metastatic breast cancer were randomized in the study in 130 sites over 20 countries.

Pre-assignment

Screening details:

Inclusion criteria included: women ≥ 18 years and ≤ 75 years, with histologically or cytologically confirmed breast cancer; at least two prior chemotherapy regimens for the treatment of locally recurrent and/or metastatic disease excluding chemotherapy received in the neo/adjuvant setting; prior treatment included an anthracycline (A), a taxane (T)

Pre-assignment period milestones

Number of subjects started	594
Number of subjects completed	594

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Vinflunine

Arm description:

vinflunine 280 mg/m2/day on day 1 of a 3 week cycle

Arm type	Experimental
Investigational medicinal product name	Vinflunine
Investigational medicinal product code	L0070
Other name	Javlor®
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

280 mg/m2/day on day 1 of each 3 weeks cycle, over a 20-minute intravenous (IV) infusion

Arm title	Alkylating agent

Arm description:

alkylating agent of physician choice

Arm type	Active comparator
Investigational medicinal product name	cyclophosphamide or cisplatin or carboplatin or thiotepa or melphalan or mitomycin C
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Buccal tablet, Solution for injection/infusion
Routes of administration	Buccal use, Intravenous use

Dosage and administration details:

All comparator drugs were commercially available and approved for the treatment of cancer in the country where they were used. Alkylating agents which were received as single agent every 3 weeks, included cyclophosphamide (IV or oral), melphalan (IV or oral), mitomycin C, thiotepa, cisplatin and carboplatin according to SPCs

Number of subjects in period 1	Vinflunine	Alkylating agent
Started	298	296
cut-off date	243	229
Completed	3	0
Not completed	295	296
Consent withdrawn by subject	1	3
Physician decision	15	12
Adverse event, non-fatal	21	24
progressive disease	249	234
Lost to follow-up	-	1
patient's decision	9	20
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Vinflunine
Reporting group description: vinflunine 280 mg/m2/day on day 1 of a 3 week cycle	
Reporting group title	Alkylating agent
Reporting group description: alkylating agent of physician choice	

Reporting group values	Vinflunine	Alkylating agent	Total
Number of subjects	298	296	594
Age categorical Units: Subjects			
Adults (18-64 years)	236	227	463
From 65-84 years	62	69	131
85 years and over	0	0	0
Age continuous Units: years			
geometric mean	57.2	56.5	
standard deviation	± 9.1	± 10.2	-
Gender categorical Units: Subjects			
Female	298	296	594
WHO Performance status Units: Subjects			
WHO 0	103	110	213
WHO 1	164	155	319
WHO 2	31	31	62
Menopausal status Units: Subjects			
Menopaused	237	211	448
Non Menaopaused	61	85	146
Main histopathological type Units: Subjects			
Ductal	220	220	440
Lobular	25	28	53
Carcinoma NOS	36	38	74
Others	17	10	27
Time from diagnosis to study entry Units: years			
median	1.2	1.3	
full range (min-max)	0 to 9.8	0 to 10.7	-

End points

End points reporting groups	
Reporting group title	Vinflunine
Reporting group description: vinflunine 280 mg/m2/day on day 1 of a 3 week cycle	
Reporting group title	Alkylating agent
Reporting group description: alkylating agent of physician choice	

Primary: Overall Survival (OS)	
End point title	Overall Survival (OS)
End point description: OS was defined as the time from randomisation to death.	
End point type	Primary
End point timeframe: from Baseline to cut-off date (August, 27 th 2012)	

End point values	Vinflunine	Alkylating agent		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	296		
Units: months				
median (confidence interval 95%)	9.1 (7.7 to 10.4)	9.3 (7.5 to 10.9)		

Statistical analyses

Statistical analysis title	Primary efficacy analysis
Statistical analysis description: Kaplan-Meier curves and life tables by treatment arm were provided. Confidence intervals on the median were calculated using the Brookmeyer and Crowley method. Hazard ratio and 95% confidence intervals were reported. A stratified Cox proportional model was performed to compare the two treatment arms taking into account the stratification factors (except centre) used at the time of randomisation	
Comparison groups	Alkylating agent v Vinflunine
Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.673 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.25

Notes:

[1] - As a secondary analysis of the OS, a Multivariate analysis was conducted in the ITT population using the Cox proportional hazard model to estimate the simultaneous effect of the following prognosis factors: age, number of organs involved, time from initial diagnosis to randomisation, prior hormonal therapy, prior neo/adjuvant
chemotherapy, hormone receptors and Her-2 status.
The only prognostic factor which was significant was the number of organs involved : P < 0.0001 when the number was > 2

[2] - The median OS was similar in the 2 study arms : 9.1 months in the VFL arm and 9.3 months in the aniti alkylating agents arm (HR = 1.04, 95% CI = 0.86 - 1.25, P = 0.6730)

Secondary: Progression Free Survival

End point title	Progression Free Survival

End point description:

PFS was defined as the time from randomisation to the first tumour progression or death due to any cause in the absence of previous documentation of objective tumour progression. PFS was performed in the ITT and eligible populations. For patients lost of follow up, or whithout a known record of progression or death, PFS was censored at the date of last tumour assessment or the date of last contact of a follow-up showing no progression which ever occured last

End point type	Secondary

End point timeframe:

From baseline to cut-off date

End point values	Vinflunine	Alkylating agent		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298[3]	296[4]		
Units: months				
median (confidence interval 95%)	2.5 (1.7 to 2.7)	1.9 (1.5 to 2.6)		

Notes:

[3] - 291 events-7 censored

[4] - 286 events-10 censored

Statistical analyses

Statistical analysis title	PFS secondary analysis

Statistical analysis description:

PFS was compared between the 2 treatment arms by the log-rank test procedure with the 5 % significant level, stratified on the stratification factors (except study site) as specified at the time of randomisation. Os was analysed using Kaplan-Meir ethod and summarized with median and 95% CI of the median

Comparison groups	Vinflunine v Alkylating agent

Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4927 [5]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.12

Notes:

[5] - Investigator-assessed median PFS was slightly longer in the VFL arm without statistically signicant difference : 2.5 months in the VFL arm and 1.9 months in the AA arm, p=0.4927

Secondary: Disease Control Rate

End point title	Disease Control Rate

End point description:

DCR was defined as the proportion of patients with CR, PR and stable disease (SD), relative to the total number of patients in the analysed population.

End point type	Secondary

End point timeframe:

From baseline to cut-off date

End point values	Vinflunine	Alkylating agent		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	296		
Units: percent				
median (confidence interval 95%)	43.6 (37.9 to 49.3)	35.5 (30 to 41.2)		

Statistical analyses

Statistical analysis title	DCR: Secondary efficay analysis

Statistical analysis description:

the disease control rate (DCR) were compared in the ITT population and in the population evaluable for response between the 2 arms with a cochran Mantel Haenszel, stratified on WHO performance status at baseline, number of prior chemotherapy lines for the treatement of disease and desease measurability at baseline

Comparison groups	Vinflunine v Alkylating agent
Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0424 [6]
Method	Logrank

Notes:

[6] - Disease control rates (DCRs) were significantly higher in the Vinflunine arm compared to the AA arm whatever the population considered. In the ITT population, DCRs were 43.6% in the VFL arm and 35.5% in the AA arm (P = 0.0424).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

TEAEs are reported from time of first dose of study treatment up to 30 days after last dose of study treatment at the exception of SAEs occured after discontinuation and start of a further treatment.

Adverse event reporting additional description:

The same event may appear as both an AE and SAE. However what is presented are distincts events. An event may be categorized as serious in 1 subject and as non serious in anothe. Specific AE tables were generated separately as per Eu format. we report here all "on study" SAEs and treatment related AEs by SOC and PT (PT >=1%)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	Vinflunine

Reporting group description:

vinflunine 280 mg/m2/day on day 1 of a 3-week cycle

Reporting group title	Alkylating agent

Reporting group description:

alkylating agent of physician choice

Serious adverse events	Vinflunine	Alkylating agent	
Total subjects affected by serious adverse events			
subjects affected / exposed	82 / 297 (27.61%)	66 / 290 (22.76%)	
number of deaths (all causes)	243	229	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	38 / 297 (12.79%)	43 / 290 (14.83%)	
occurrences causally related to treatment / all	0 / 38	0 / 43	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	1 / 297 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
suamous cell carninoma			

subjects affected / exposed	0 / 297 (0.00%)	1 / 290 (0.34%)	
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	2 / 297 (0.67%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	2 / 297 (0.67%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	4 / 297 (1.35%)	2 / 290 (0.69%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	6 / 297 (2.02%)	2 / 290 (0.69%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 297 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 297 (0.34%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 297 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Pneumonitis			
subjects affected / exposed	1 / 297 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 297 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
confusional state			
subjects affected / exposed	1 / 297 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	0 / 297 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Transaminases increased			
subjects affected / exposed	1 / 297 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 297 (0.34%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 297 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Allergic transfusion reaction			

subjects affected / exposed	0 / 297 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 297 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arteriospasm coronary			
subjects affected / exposed	1 / 297 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 297 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 297 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 297 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 297 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brachial plexopathy			
subjects affected / exposed	0 / 297 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			

subjects affected / exposed	0 / 297 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 297 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 297 (0.00%)	1 / 290 (0.34%)	
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			
Neutropenia			
subjects affected / exposed	6 / 297 (2.02%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	9 / 9	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	6 / 297 (2.02%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	9 / 9	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 297 (1.01%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 297 (0.34%)	2 / 290 (0.69%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis staphylococcal			
subjects affected / exposed	1 / 297 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	5 / 297 (1.68%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	6 / 297 (2.02%)	3 / 290 (1.03%)	
occurrences causally related to treatment / all	4 / 6	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	4 / 297 (1.35%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	4 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	3 / 297 (1.01%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ileus paralytic			
subjects affected / exposed	3 / 297 (1.01%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	3 / 297 (1.01%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	2 / 297 (0.67%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 297 (0.67%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			

subjects affected / exposed	1 / 297 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 297 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 297 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagial Stenosis			
subjects affected / exposed	0 / 297 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 297 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	1 / 297 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
bile duct obstruction			
subjects affected / exposed	0 / 297 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 297 (0.34%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myalgia			
subjects affected / exposed	1 / 297 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone Pain			
subjects affected / exposed	0 / 297 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Neutropenic infection			
subjects affected / exposed	4 / 297 (1.35%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoniae			
subjects affected / exposed	3 / 297 (1.01%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 297 (0.67%)	2 / 290 (0.69%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 297 (0.34%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
bronchitis			
subjects affected / exposed	1 / 297 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 297 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
influenza			

subjects affected / exposed	1 / 297 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 297 (0.34%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter related infection			
subjects affected / exposed	0 / 297 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central line infection			
subjects affected / exposed	0 / 297 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	0 / 297 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 297 (0.00%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	2 / 297 (0.67%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 297 (0.34%)	1 / 290 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			

subjects affected / exposed	0 / 297 (0.00%)	1 / 290 (0.34%)	
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: 1 %

Non-serious adverse events	Vinflunine	Alkylating agent	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	197 / 297 (66.33%)	262 / 290 (90.34%)	
Investigations			
Weight decreased			
subjects affected / exposed	26 / 297 (8.75%)	17 / 290 (5.86%)	
occurrences (all)	34	23	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	21 / 297 (7.07%)	5 / 290 (1.72%)	
occurrences (all)	48	9	
Headache			
subjects affected / exposed	7 / 297 (2.36%)	5 / 290 (1.72%)	
occurrences (all)	15	7	
Dizziness			
subjects affected / exposed	3 / 297 (1.01%)	4 / 290 (1.38%)	
occurrences (all)	4	7	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	89 / 297 (29.97%)	43 / 290 (14.83%)	
occurrences (all)	177	62	
Injection site reaction			
subjects affected / exposed	29 / 297 (9.76%)	2 / 290 (0.69%)	
occurrences (all)	58	2	
Fatigue			
subjects affected / exposed	23 / 297 (7.74%)	25 / 290 (8.62%)	
occurrences (all)	55	35	
Pain			
subjects affected / exposed	4 / 297 (1.35%)	0 / 290 (0.00%)	
occurrences (all)	4	0	

Pyrexia			
subjects affected / exposed	10 / 297 (3.37%)	3 / 290 (1.03%)	
occurrences (all)	19	5	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	37 / 297 (12.46%)	31 / 290 (10.69%)	
occurrences (all)	56	46	
Thrombocytopenia			
subjects affected / exposed	3 / 297 (1.01%)	39 / 290 (13.45%)	
occurrences (all)	3	64	
Anaemia			
subjects affected / exposed	2 / 297 (0.67%)	6 / 290 (2.07%)	
occurrences (all)	2	9	
Gastrointestinal disorders			
Constipation	Additional description: related TEAES are provided		
subjects affected / exposed	102 / 297 (34.34%)	23 / 290 (7.93%)	
occurrences (all)	181	34	
Nausea			
subjects affected / exposed	70 / 297 (23.57%)	67 / 290 (23.10%)	
occurrences (all)	131	126	
Abdominal pain			
subjects affected / exposed	66 / 297 (22.22%)	16 / 290 (5.52%)	
occurrences (all)	170	58	
Stomatitis			
subjects affected / exposed	52 / 297 (17.51%)	18 / 290 (6.21%)	
occurrences (all)	98	23	
Vomiting			
subjects affected / exposed	34 / 297 (11.45%)	33 / 290 (11.38%)	
occurrences (all)	44	45	
Diarrhoea			
subjects affected / exposed	16 / 297 (5.39%)	19 / 290 (6.55%)	
occurrences (all)	24	35	
Abdominal pain upper			
subjects affected / exposed	14 / 297 (4.71%)	4 / 290 (1.38%)	
occurrences (all)	24	5	
Abdominal distension			

subjects affected / exposed	5 / 297 (1.68%)	1 / 290 (0.34%)	
occurrences (all)	5	1	
Dyspepsia			
subjects affected / exposed	4 / 297 (1.35%)	1 / 290 (0.34%)	
occurrences (all)	4	1	
gastritis			
subjects affected / exposed	4 / 297 (1.35%)	0 / 290 (0.00%)	
occurrences (all)	4	0	
Paraesthesia			
subjects affected / exposed	4 / 297 (1.35%)	0 / 290 (0.00%)	
occurrences (all)	3	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	30 / 297 (10.10%)	9 / 290 (3.10%)	
occurrences (all)	31	12	
Pruritus			
subjects affected / exposed	7 / 297 (2.36%)	2 / 290 (0.69%)	
occurrences (all)	11	1	
Dry skin			
subjects affected / exposed	4 / 297 (1.35%)	3 / 290 (1.03%)	
occurrences (all)	4	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	10 / 297 (3.37%)	0 / 290 (0.00%)	
occurrences (all)	18	0	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	38 / 297 (12.79%)	5 / 290 (1.72%)	
occurrences (all)	78	5	
Arthralgia			
subjects affected / exposed	21 / 297 (7.07%)	3 / 290 (1.03%)	
occurrences (all)	53	3	
Pain in Jaw			
subjects affected / exposed	12 / 297 (4.04%)	0 / 290 (0.00%)	
occurrences (all)	24	0	
Muscle spasms			

subjects affected / exposed	6 / 297 (2.02%)	2 / 290 (0.69%)	
occurrences (all)	6	2	
Musculoskeletal pain			
subjects affected / exposed	4 / 297 (1.35%)	1 / 290 (0.34%)	
occurrences (all)	8	1	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	31 / 297 (10.44%)	24 / 290 (8.28%)	
occurrences (all)	62	29	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 May 2009	The extra label on the commercial packaging of the alkylating agent used as comparator drugs was deleted. The HER2 and hormonal receptors status was required to be obtained at baseline
23 September 2009	The use of GCSF had to follow local (Taiwan) guidelines and medical practice
15 December 2009	- Inclusion criterion n°4: the upper limit of number of prior chemotherapy lines (no more than 5) was deleted because approximatively 1/3 of screened patients were found ineligible - Inclusion criterion n° 9: the delay between discontinuation of anti HER2 targeted therapy was shortened from 4 to 3 weeks as far as no additional toxicity was expected - Inclusion criterion n° 10: the delay between discontinuation of radiation therapy was shortened from 4 to 3 weeks because only localised palliative radiotherapy was performed at this far advanced stage of breast cancer - Inclusion criterion n° 15: To add as prohibited treatment during the month preceding first study drug administration,transfusions except if medically indicated - Exclusion criterion n° 1: symptomatic ascites (grade ≥ 2) requiring active treatment was added To adapt the stratification factor concerning the number of prior lines for the treatment of locally recurrent/metastatic disease excluding chemotherapy given in the neo/adjuvant setting. To add complementary information to vinflunine reconstitution procedure (possibility to use G5% solution) To modify restriction of use of alkylating agents in order to stick to local practice in each countries. (Alkylating agents approved for the treatment of cancer in general in the country and not only in breast cancer were prescribed) To define the cycle for alkylating agent as a 3 week period in order to homogenize periodicity of tumour assessments between the 2 arms

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported