Clinical trial results:
Phase II trial of oral vinorelbine in combination with capecitabine and trastuzumab as first line therapy in women with previously untreated HER2 positive metastatic breast cancer.

Summary

EudraCT number	2004-000748-26
Trial protocol	ES
Global end of trial date	21 May 2019

Results information

Result version number	v1 (current)
This version publication date	19 June 2022
First version publication date	19 June 2022

Trial information

Trial identification

Sponsor protocol code	PM0259CA215B0

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Pierre Fabre Medicament
Sponsor organisation address	Les Cauquillous, Lavaur, France, 81500
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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	17 December 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the Overall Response Rate (ORR) of oral vinorelbine (Navelbine Oral) in combination with capecitabine (Xeloda) and i.v. trastuzumab (Herceptin) for HER2 positive patients.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and was consistent with International Conference on Harmonization Good Clinical Practice (ICH GCP) and applicable regulatory requirements. The study was conducted in compliance with the protocol. The protocol, amendments, the subject information leaflet and the subject informed consent were approved by the appropriate independent Ethics Committee(s) in the involved countries prior to implementation.

Background therapy:

Patients had to receive full supportive care including antibiotics, anti-diarrhoeals, analgesics, transfusion of blood products, when appropriate. The use of drugs with laxative properties had to be avoided.
Use of vitamin B6 pyridoxine (50-150 mg/BID) was permitted for symptomatic or secondary prophylactic treatment of hand-foot syndrome.
Primary prophylactic use of Granulocyte Colony Stimulating Factors (G-CSF) was not allowed during the study treatment. G-CSF use was allowed as secondary prophylaxis in case of occurrence of febrile neutropenia, grade 4 asymptomatic neutropenia or neutropenic infection according to institutional rules. The use of G-CSF to treat neutropenia had to be correctly documented in patient’s medical file and in the CRF.
Patients receiving opiates could receive treatment for constipation but had to be followed carefully.
Patients receiving bisphosphonates were eligible for this study but had to have bone scans (and X-rays of areas of enhanced uptake indicative of bone metastasis) at baseline. Those starting bisphosphonates during the study but without other clear evidence of disease progression were not to be diagnosed as having progressive disease on that evidence alone.

Evidence for comparator:

The study is a non-comparative, single-arm study. No control arm was planned as the study aimed at evaluating the triple combination regimen for the first time in this population of patients.

Actual start date of recruitment	08 March 2004
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	Australia: 20
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Czechia: 4
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Italy: 6

Country: Number of subjects enrolled	South Africa: 2
Country: Number of subjects enrolled	Spain: 3
Worldwide total number of subjects	50
EEA total number of subjects	28

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)	41
From 65 to 84 years	8
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 13 centres in 7 countries enrolled a total of 50 women with previously untreated HER2 positive metastatic breast cancer between March 2004 and December 2010.

Pre-assignment

Screening details:

A 21-day screening period was planned before randomisation and screened previously untreated women with HER2 positive metastatic breast cancer. Once the screening period was successufully completed, patients who fulfilled the eligibility critera and gave their written consent, were included in the treatment period of the study.

Period 1

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

Blinding implementation details:

The study was an open-label study.

Arms

Arm title	Vinorelbine + Capecitabine + Trastuzumab

Arm description:

This experimental arm consisted of all registered and treated patients (ITT population, N=50).

Arm type	Experimental
Investigational medicinal product name	Oral Vinorelbine (OV)
Investigational medicinal product code	
Other name	Navelbine
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Patients received OV at the dose of 60 mg/m² on day 1 and day 8 every 3 weeks for cycle 1, and then 80 mg/m² on day 1 and day 8, every 3 weeks for subsequent cycles.
The dosage was calculated according to BSA.
Patients received at least 2 cycles of OV and treatment was administered until progressive disease, unacceptable toxicty or patient refusal.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	Xeloda
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patient < 65 years old at the time of inclusion received capecitabine at the dose of 1000 mg/m² twice a day (2000 mg/m² daily) from day 1 to day 14, every 3 weeks.
Patient ≥ 65 years old at the time of inclusion received capecitabine at the dose of 750 mg/m² twice a day (1500 mg/m²) from day 1 to day 14, every 3 weeks.
The dosage was calculated according to BSA.
Patients received at least 2 cycles of capecitabine.
Treatment was administered until disease progression, unacceptable toxicity, patient’s refusal or investigator’s decision.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	Herceptin
Pharmaceutical forms	Solution for injection/infusion

Routes of administration	Intravenous use

Dosage and administration details:

Patients received trastuzumab at the dose of 4 mg/kg on day 1 (loading dose) infused over a 90 minute period and then 2 mg/kg infused over a 30 minute period weekly starting on day 8 and continuing weekly for subsequent cycles.
Patients received at least 2 cycles of trastuzumab. The amount of trastuzumab administered was calculated according to the patient’s body weight.
Treatment was administered until disease progression, unacceptable toxicity, patient’s refusal or investigator’s decision.
Patients were observed for at least six hours after the start of the first dose of trastuzumab (i.e. 4.5 hours from the end of the infusion). If no adverse events occured during the first infusion, the observation period for the second infusion was decreased to 2 hours after the start of the infusion (i.e. an hour and a half from the end of the infusion).

Number of subjects in period 1	Vinorelbine + Capecitabine + Trastuzumab
Started	50
Completed	3
Not completed	47
Adverse event, serious fatal	1
Consent withdrawn by subject	6
Physician decision	8
Adverse event, non-fatal	12
Patient's convenience	1
Progressive disease	18
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Treatment period (overall trial)

Reporting group description: -

Reporting group values	Treatment period (overall trial)	Total	
Number of subjects	50	50	
Age categorical Units: Subjects			
Adults (18-64 years)	41	41	
From 65-84 years	8	8	
85 years and over	1	1	
Age continuous Units: years			
arithmetic mean	55.6		
standard deviation	± 12.1	-	
Gender categorical Units: Subjects			
Female	50	50	
Male	0	0	
Karnofsky Performance Status (KPS) Units: Subjects			
70	3	3	

Time from initial diagnosis to first relapse/progression Units: year arithmetic mean standard deviation	 2.7 ± 2.5	 -	
Number of organs involved at study entry Units: number arithmetic mean standard deviation	 2.4 ± 1.3	 -	

End points

End points reporting groups

Reporting group title	Vinorelbine + Capecitabine + Trastuzumab

Reporting group description:

This experimental arm consisted of all registered and treated patients (ITT population, N=50).

Primary: Overall response rate (ORR)

End point title	Overall response rate (ORR)[1]

End point description:

Overall response rate (ORR) was defined as the percentage of responses (complete and partial) in the ITT population according to investigator assessment based on the Response Evaluation Criteria in Solid Tumours (RECIST).

End point type	Primary

End point timeframe:

ORR was calculated from the date of randomisation until the documentation of progression or death. Tumour evaluations were performed every 6 weeks until disease progression.

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: If overall response (complete or partial) was observed in 20 or more patients, the study was considered to have met its primary endpoint.

End point values	Vinorelbine + Capecitabine + Trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: percentage of patients				
number (confidence interval 95%)	69.4 (54.6 to 81.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first response

End point title	Time to first response

End point description:

The time to first response was defined as the time from the registration date to the date of first documented response (complete or partial) and was measured from the registration until the documentation of progression or death from any cause, whichever occurred first.

End point type	Secondary

End point timeframe:

Time to first response was measured during the study period.

End point values	Vinorelbine + Capecitabine + Trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: month				
median (confidence interval 95%)	3.2 (3.0 to 4.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR)

End point title	Duration of response (DOR)

End point description:

Duration of response was defined as the time from the date of first documented response (complete or partial) until the date of progression, death due to any cause or the date of start of a new anti-tumoural treatment.

End point type	Secondary

End point timeframe:

DOR was measured among the responders during the study period.

End point values	Vinorelbine + Capecitabine + Trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: month				
median (confidence interval 95%)	6.8 (3.0 to 10.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

Progression-free survival (PFS) was defined as the time from the registration date until the date of progression or death due to any cause.

End point type	Secondary

End point timeframe:

PFS was measured during the study period.

End point values	Vinorelbine + Capecitabine + Trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: month				
median (confidence interval 95%)	12.8 (10.5 to 16.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

Overall survival (OS) was defined as the duration between the date of registration and the date of death due to any cause.

End point type	Secondary

End point timeframe:

OS was measured during the study period.

End point values	Vinorelbine + Capecitabine + Trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: month				
median (confidence interval 95%)	47.0 (30.5 to 64.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to treatment failure (TTF)

End point title	Time to treatment failure (TTF)

End point description:

Time to treatment failure (TTF) was defined as the time from the registration date up to the date of failure. Failure was defined as disease progression, death adverse event leading to withdrawal, patient's refusal, protocol deviation, lost to follow-up or start of a new anti-tumoural treatment.

End point type	Secondary

End point timeframe:

TTF was measured during the study period.

End point values	Vinorelbine + Capecitabine + Trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: month				
median (confidence interval 95%)	7.8 (5.6 to 9.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any adverse event (AE) that first occurred during the treatment period (i.e. from first study treatment administration date up to last administration date + 30 days) was recorded in the CRF and included in the analysis of AEs (on-study AE).

Adverse event reporting additional description:

At the cut-off date (17-DEC-2010), 3 patients were still on treatment. A total of 17 patients were being followed for survival, 3 were lost to follow-up and 30 died.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	7.1

Reporting groups

Reporting group title	ITT population

Reporting group description:

The population evaluable for safety consisted of all treated patients unless patient was lost to follow-up immediately after the start of the treatment (no follow-up visit).

Serious adverse events	ITT population		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 50 (28.00%)		
number of deaths (all causes)	30		
number of deaths resulting from adverse events	1		
Vascular disorders			
Phlebitis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Left ventricular failure			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Myocarditis			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Neutropenic infection			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Catheter site infection			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	ITT population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 50 (100.00%)		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	17		
Hot flush			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	18		
Hypertension			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	4		
Hypotension			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	8		
Lymphoedema			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	12		
Phlebitis			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	3		
General disorders and administration site conditions			

Chest pain subjects affected / exposed occurrences (all)	 7 / 50 (14.00%) 30		
Chills subjects affected / exposed occurrences (all)	 6 / 50 (12.00%) 10		
Fatigue subjects affected / exposed occurrences (all)	 46 / 50 (92.00%) 550		
Influenza like illness subjects affected / exposed occurrences (all)	 17 / 50 (34.00%) 41		
Injection site reaction subjects affected / exposed occurrences (all)	 2 / 50 (4.00%) 2		
Oedema subjects affected / exposed occurrences (all)	 3 / 50 (6.00%) 4		
Oedema peripheral subjects affected / exposed occurrences (all)	 4 / 50 (8.00%) 9		
Pain subjects affected / exposed occurrences (all)	 4 / 50 (8.00%) 11		
Pyrexia subjects affected / exposed occurrences (all)	 37 / 50 (74.00%) 436		
Unevaluable event subjects affected / exposed occurrences (all)	 34 / 50 (68.00%) 868		
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	 3 / 50 (6.00%) 3		
Reproductive system and breast disorders			

Menstruation irregular			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 50 (24.00%)		
occurrences (all)	23		
Dyspnoea			
subjects affected / exposed	37 / 50 (74.00%)		
occurrences (all)	443		
Epistaxis			
subjects affected / exposed	10 / 50 (20.00%)		
occurrences (all)	16		
hoarseness			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Pharyngolaryngeal abscess			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	11		
Postnasal drip			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	13		
Rhinitis allergic			
subjects affected / exposed	7 / 50 (14.00%)		
occurrences (all)	52		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	10 / 50 (20.00%)		
occurrences (all)	15		
Depression			
subjects affected / exposed	11 / 50 (22.00%)		
occurrences (all)	24		
Insomnia			
subjects affected / exposed	13 / 50 (26.00%)		
occurrences (all)	37		
Investigations			

Ejection fraction decreased			
subjects affected / exposed	17 / 50 (34.00%)		
occurrences (all)	126		
Weight decreased			
subjects affected / exposed	27 / 50 (54.00%)		
occurrences (all)	183		
Weight increased			
subjects affected / exposed	15 / 50 (30.00%)		
occurrences (all)	197		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	4		
Cardiac disorders			
Palpitations			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	12		
Ventricular dysfunction			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	10		
Nervous system disorders			
Amnesia			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Dizziness			
subjects affected / exposed	8 / 50 (16.00%)		
occurrences (all)	39		
Dysgeusia			
subjects affected / exposed	9 / 50 (18.00%)		
occurrences (all)	56		
Headache			
subjects affected / exposed	19 / 50 (38.00%)		
occurrences (all)	107		

Peripheral motor neuropathy			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Peripheral sensory neuropathy			
subjects affected / exposed	21 / 50 (42.00%)		
occurrences (all)	164		
Syncope			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	5		
Vertigo			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	4		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	4		
Dry eye			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	66		
Lacrimation increased			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	97		
Vision blurred			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	6		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	12		
Abdominal pain			
subjects affected / exposed	22 / 50 (44.00%)		
occurrences (all)	44		
Abdominal pain upper			

subjects affected / exposed	8 / 50 (16.00%)		
occurrences (all)	16		
Constipation			
subjects affected / exposed	23 / 50 (46.00%)		
occurrences (all)	78		
Diarrhoea			
subjects affected / exposed	45 / 50 (90.00%)		
occurrences (all)	597		
Dry mouth			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	10		
Dyspepsia			
subjects affected / exposed	11 / 50 (22.00%)		
occurrences (all)	32		
Dysphagia			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	11		
Flatulence			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	8		
Gastritis			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	3		
Haemorrhoids			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	9		
Ileus			
subjects affected / exposed	34 / 50 (68.00%)		
occurrences (all)	431		
Nausea			
subjects affected / exposed	46 / 50 (92.00%)		
occurrences (all)	571		
Rectal haemorrhage			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	7		
Stomatitis			

subjects affected / exposed	40 / 50 (80.00%)		
occurrences (all)	496		
Toothache			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	6		
Vomiting			
subjects affected / exposed	44 / 50 (88.00%)		
occurrences (all)	465		
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	38 / 50 (76.00%)		
occurrences (all)	468		
Dry skin			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	19		
Erythema			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	3		
Hyperhidrosis			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	3		
Nail disorder			
subjects affected / exposed	11 / 50 (22.00%)		
occurrences (all)	90		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	36 / 50 (72.00%)		
occurrences (all)	560		
Photosensitivity reaction			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	3		
Pigmentation disorder			

subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	9		
Pruritus			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	23		
Rash			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	13		
Skin lesion			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	16 / 50 (32.00%)		
occurrences (all)	76		
Arthritis			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	16		
Bone pain			
subjects affected / exposed	19 / 50 (38.00%)		
occurrences (all)	99		
Chest wall pain			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	5		
Muscle cramp			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	12		
Muscular weakness			

subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	8		
Myalgia			
subjects affected / exposed	13 / 50 (26.00%)		
occurrences (all)	52		
Neck pain			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	10 / 50 (20.00%)		
occurrences (all)	12		
Tendonitis			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	15		
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Cystitis			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	3		
Eye infection			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	10		
Gastroenteritis			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Herpes simplex			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	8		
Influenza			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Localised infection			
subjects affected / exposed	8 / 50 (16.00%)		
occurrences (all)	15		

Lower respiratory tract infection subjects affected / exposed occurrences (all)	4 / 50 (8.00%) 5		
Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 4		
Oral candidiasis subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 3		
Pharyngitis subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 4		
Rhinitis subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 4		
Sinusitis subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 2		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	9 / 50 (18.00%) 17		
Urinary tract infection subjects affected / exposed occurrences (all)	5 / 50 (10.00%) 7		
Viral infection subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 2		
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	36 / 50 (72.00%) 441		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 June 2005	Duration of study recruitment period modification: From Q3 2005 in the initial version of the protocol to Q3 2006.
07 April 2014	XELODA new information added ICF modified and updated NVB AEs reporting IB version updated Declaration of Helsinki updated Sponsor's personnel list updated

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported