

**Clinical trial results:****Estudio de fase II de la combinación de panitumumab con paclitaxel como tratamiento de primera línea de sujetos con cáncer de cabeza y cuello recurrente o metastásico. Estudio “VECTITAX”.****Summary**

EudraCT number	2010-018898-37
Trial protocol	ES
Global end of trial date	23 September 2014

**Results information**

Result version number	v1 (current)
This version publication date	08 February 2020
First version publication date	08 February 2020

**Trial information****Trial identification**

Sponsor protocol code	TTCC-2009-03
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01264328
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	TTCC Grupo Español de Tratamiento de Tumores de Cabeza y Cuello
Sponsor organisation address	C/ Velázquez, 7 - 3º , Madrid, Spain, 28001
Public contact	General Manager, Carmen Montalbán, +34 676 154 172, ttccmanager@yahoo.com
Scientific contact	Dr Ricard Mesia Nin is the scientific contact point, Ricard Mesia Nin, +34 618 179 500,

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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	02 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 September 2014
Global end of trial reached?	Yes
Global end of trial date	23 September 2014
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

To assess the effect of the combination of panitumumab and paclitaxel on objective response rate in first-line treatment of metastatic or recurrent squamous cell carcinoma of head and neck (SCCHN).

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki (Seoul 2008 version) and the local laws and regulations. The study was approved by the Institutional Review Board of the participant centers. All patients gave written informed consent. Patients could completely or partially withdraw study at any time for any reason without any disadvantage or prejudice.

The infusion was stopped in patients who experienced any serious reaction during the administration of panitumumab. Patients who experienced toxicities and needed to permanently discontinue the administration of panitumumab were withdrawn of treatment but continued a safety and survival follow-up.

Background therapy:

Not applicable.

Evidence for comparator:

Panitumumab, a fully human IgG2 anti-EGFR monoclonal antibody, has shown activity in preclinical models of SCCHN and promising activity in refractory SCCHN patients in a phase I clinical trial. Recently, our cooperative group also reported encouraging outcomes of anti-EGFR-paclitaxel combination in a phase II study. On the basis of this background, a phase II clinical trial (VECTITAX study) was designed with the objective of evaluating the activity and safety profile of panitumumab in combination with paclitaxel in patients with recurrent or metastatic SCCHN.

Actual start date of recruitment	09 March 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Spain: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

Notes:

<b>Subjects enrolled per age group</b>	
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)	29
From 65 to 84 years	11
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Between March 2011 and May 2012, 40 patients were included in 12 centers in Spain (ITT population). One patient met two exclusion criteria (second active neoplasm and B-Hepatitis) and four lacked post-baseline response assessment. Therefore, the PP population comprised 35 patients.

### Pre-assignment

Screening details:

Key inclusion criteria: adult patients with histologically/cytologically confirmed recurrent or metastatic SCCHN; ECOG performance status of 0-1; measurable disease according to RECIST 1.1 criteria; adequate hematologic, renal, hepatic and metabolic functions. Prior treatment with anti-EGFR agents was not allowed within 24 weeks prior to study.

### Period 1

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

Blinding implementation details:

Not applicable.

### Arms

<b>Arm title</b>	Panitumumab + paclitaxel
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Arm description:

Patients received paclitaxel (80 mg/m<sup>2</sup>/week) and panitumumab (6 mg/kg/2 weeks) until disease progression or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Panitumumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Panitumumab 6 mg/kg was administered every 2 weeks, in one hour the first day and in 30 min thereafter (if no infusional reaction was observed).

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel 80 mg/m<sup>2</sup> was weekly administered one hour after panitumumab in one hour infusion.

<b>Number of subjects in period 1</b>	Panitumumab + paclitaxel
Started	40
Completed	40

## Baseline characteristics

### Reporting groups

Reporting group title	Baseline
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Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	40	40	
Age categorical			
Units: Subjects			
Adults (18-64 years)	29	29	
From 65-84 years	11	11	
Age continuous			
Units: years			
median	60.8		
inter-quartile range (Q1-Q3)	56.3 to 68.3	-	
Gender categorical			
Units: Subjects			
Female	5	5	
Male	35	35	
ECOG-PS			
Eastern Cooperative Oncology Group (ECOG) performance status (PS)			
Units: Subjects			
ECOG-PS = 0	9	9	
ECOG-PS = 1	31	31	
Tumor site			
Primary tumor location			
Units: Subjects			
Larynx	14	14	
Oropharynx	12	12	
Oral cavity	10	10	
Hypopharynx	4	4	
Squamous cell carcinoma			
Grade of squamous cell carcinoma at diagnosis			
Units: Subjects			
Grade I	7	7	
Grade II	13	13	
Grade III	9	9	
Unknown	10	10	
Undifferentiated	1	1	
Laterality			
Tumor laterality at diagnosis			
Units: Subjects			
Left	10	10	
Right	25	25	
Both	3	3	
Undetermined	2	2	
Prior treatment: surgery			
Number of prior surgeries per patient			

Units: Subjects			
0 (no surgery)	11	11	
1 surgery	17	17	
2 surgeries	6	6	
3 surgeries	5	5	
4 surgeries	1	1	
Prior treatment: chemotherapy			
Number of chemotherapies per patient			
Units: Subjects			
0 (no chemotherapy)	17	17	
1 chemotherapy	9	9	
2 or more chemotherapies	14	14	
Prior treatment: radiotherapy			
Number of radiotherapies per patient			
Units: Subjects			
0 (no radiotherapy)	6	6	
1 radiotherapy	24	24	
2 radiotherapies	5	5	
3 or more radiotherapies	5	5	
Metastatic disease			
Units: Subjects			
Yes	21	21	
No	1	1	
Not available	18	18	
Locoregional recurrence			
Units: Subjects			
Yes	30	30	
No	1	1	
Not available	9	9	

## End points

### End points reporting groups

Reporting group title	Panitumumab + paclitaxel
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Reporting group description:

Patients received paclitaxel (80 mg/m<sup>2</sup>/week) and panitumumab (6 mg/kg/2 weeks) until disease progression or unacceptable toxicity.

Subject analysis set title	ITT
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

The intention-to-treat (ITT) population included all patients in the study who signed the informed consent form and received at least one dose of panitumumab.

Subject analysis set title	PP
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Subject analysis set type	Per protocol
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Subject analysis set description:

The per-protocol (PP) population is defined as the subset of patients of the ITT population who completed the study without any major protocol deviations.

### Primary: Objective response rate (ORR)

End point title	Objective response rate (ORR) <sup>[1]</sup>
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End point description:

Incidence of confirmed complete response (CR) or partial response (PR) during the treatment period according to RECIST v1.1 criteria in the intention-to-treat population (ITT).

End point type	Primary
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End point timeframe:

Tumor assessments were planned to be performed every two months. Response confirmation was to be assessed not before 4 weeks after a partial or complete response, or before 6 weeks after a stable disease.

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: Data were summarized using descriptive statistics.

End point values	ITT	PP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	35		
Units: Percentage of patients				
number (confidence interval 95%)				
Yes (CR+PR)	47.50 (32.02 to 62.98)	51.43 (34.87 to 67.99)		
No	52.50 (37.02 to 67.98)	48.57 (32.01 to 65.13)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Best response

End point title	Best response
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End point description:

End point type	Secondary
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End point timeframe:

Tumor assessments were planned to be performed every two months. Response confirmation was to be assessed not before 4 weeks after a partial or complete response, or before 6 weeks after a stable disease.

<b>End point values</b>	ITT	PP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	35		
Units: Percentage of patients				
arithmetic mean (confidence interval 95%)				
Complete response	15.00 (3.93 to 26.07)	17.14 (4.66 to 29.63)		
Partial response	32.50 (17.99 to 47.01)	34.29 (18.56 to 50.01)		
Stable disease	27.50 (13.66 to 41.34)	31.43 (16.05 to 46.81)		
Disease progression	15.00 (3.93 to 26.07)	17.14 (4.66 to 29.63)		
Non evaluable	10.00 (0.70 to 19.30)	0.00 (0.00 to 0.00)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Disease control rate

End point title	Disease control rate
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End point description:

Incidence of confirmed complete response (CR) or partial response (PR) or stable disease (SD) during the treatment period according to RECIST v1.1 criteria.

End point type	Secondary
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End point timeframe:

Tumor assessments were planned to be performed every two months. Response confirmation was to be assessed not before 4 weeks after a partial or complete response, or before 6 weeks after a stable disease.

<b>End point values</b>	ITT	PP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	35		
Units: Percentage of patients				
number (confidence interval 95%)				
Yes (CR+PR+SD)	75.00 (61.58 to 88.42)	82.86 (70.37 to 95.34)		
No	25.00 (11.58 to 38.42)	17.14 (4.66 to 29.63)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to response

End point title	Time to response
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End point description:

Time to response is defined as the number of months between the date of the first treatment administration and the date of the first objective response confirmation.

End point type	Secondary
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End point timeframe:

Until confirmed response (CR+PR). Calculated only for patients who presented objective response.

<b>End point values</b>	ITT	PP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	18		
Units: months				
median (inter-quartile range (Q1-Q3))	4.0 (3.7 to 7.2)	3.9 (3.7 to 7.2)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of response

End point title	Duration of response
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End point description:

Time from the first response until disease progression or death due to disease progression (first that occurred).

End point type	Secondary
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End point timeframe:

Until disease progression or death. Calculated only for patients who responded during the treatment period.

<b>End point values</b>	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: months				
median (confidence interval 95%)	4.30 (2.83 to 6.64)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)
End point description:	Time from the inclusion date until confirmed disease progression or death (first that occurred).
End point type	Secondary
End point timeframe:	Until disease progression or end of the study.

<b>End point values</b>	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	40			
Units: months				
median (confidence interval 95%)	7.46 (4.93 to 8.31)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival (OS)

End point title	Overall survival (OS)
End point description:	Time from the inclusion date until death due to any cause.
End point type	Secondary
End point timeframe:	Until death

<b>End point values</b>	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	40			
Units: months				
median (confidence interval 95%)	9.86 (7.95 to 16.26)			

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events were reported.

Adverse event reporting additional description:

National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	13.1
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### Reporting groups

Reporting group title	Safety population
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Reporting group description: -

<b>Serious adverse events</b>	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 40 (40.00%)		
number of deaths (all causes)	35		
number of deaths resulting from adverse events	6		
Vascular disorders			
Haemorrhage			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Lacunar infarction			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Enteritis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Haemorrhoids			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		

Respiratory insufficiency			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pneumothorax			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Disorientation			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Cervicalgia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lung abscess			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			

subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Intervertebral discitis</b>			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Respiratory tract infection</b>			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Lung infection</b>			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Pneumonia</b>			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Safety population		
<b>Total subjects affected by non-serious adverse events</b>			
subjects affected / exposed	40 / 40 (100.00%)		
<b>Vascular disorders</b>			
<b>Haemorrhage</b>			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
<b>Hypotension</b>			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
<b>General disorders and administration site conditions</b>			

Asthenia			
subjects affected / exposed	33 / 40 (82.50%)		
occurrences (all)	75		
Pain			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	6		
Facial pain			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	3		
Application site eczema			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	11		
Oedema peripheral			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	5		
Mucosal inflammation			
subjects affected / exposed	27 / 40 (67.50%)		
occurrences (all)	51		
Pyrexia			
subjects affected / exposed	8 / 40 (20.00%)		
occurrences (all)	8		
Feeling hot			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Xerosis			
subjects affected / exposed	12 / 40 (30.00%)		
occurrences (all)	29		
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Dysphonia			

subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 4		
Dyspnoea subjects affected / exposed occurrences (all)	10 / 40 (25.00%) 12		
Dyspnoea exertional subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 3		
Pulmonary embolism subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Epistaxis subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Rhinorrhoea subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Nasal dryness subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Cough subjects affected / exposed occurrences (all)	8 / 40 (20.00%) 10		
Productive cough subjects affected / exposed occurrences (all)	6 / 40 (15.00%) 8		
Psychiatric disorders			
Disorientation subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 3		
Insomnia subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3		
Investigations			
Transaminases increased			

subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 4		
Injury, poisoning and procedural complications			
Stoma site haemorrhage subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Injury subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 5		
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 3		
Dysgeusia subjects affected / exposed occurrences (all)	7 / 40 (17.50%) 7		
Dizziness subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Neuropathy peripheral subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 7		
Neurotoxicity subjects affected / exposed occurrences (all)	14 / 40 (35.00%) 37		
Paraesthesia subjects affected / exposed occurrences (all)	7 / 40 (17.50%) 14		
Somnolence subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	8 / 40 (20.00%) 11		
Leukopenia			

subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 6		
Neutropenia subjects affected / exposed occurrences (all)	5 / 40 (12.50%) 5		
Febrile neutropenia subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 3		
Eye disorders Ectropion subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Keratitis subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 4		
Gastrointestinal disorders Dry mouth subjects affected / exposed occurrences (all)	6 / 40 (15.00%) 8		
Diarrhoea subjects affected / exposed occurrences (all)	18 / 40 (45.00%) 21		
Dysphagia subjects affected / exposed occurrences (all)	8 / 40 (20.00%) 9		
Abdominal pain subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 4		
Oral pain subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 4		
Abdominal pain upper			

subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 4		
Stomatitis subjects affected / exposed occurrences (all)	6 / 40 (15.00%) 10		
Constipation subjects affected / exposed occurrences (all)	13 / 40 (32.50%) 18		
Rectal haemorrhage subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 3		
Haemorrhoids subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Salivary hypersecretion subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3		
Nausea subjects affected / exposed occurrences (all)	9 / 40 (22.50%) 14		
Odynophagia subjects affected / exposed occurrences (all)	6 / 40 (15.00%) 6		
Cheilitis subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Tongue ulceration subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Vomiting subjects affected / exposed occurrences (all)	7 / 40 (17.50%) 7		
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	6 / 40 (15.00%) 6		

Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	3		
Alopecia			
subjects affected / exposed	9 / 40 (22.50%)		
occurrences (all)	14		
Dermatitis			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	14		
Dermatitis acneiform			
subjects affected / exposed	14 / 40 (35.00%)		
occurrences (all)	67		
Nail dystrophy			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Eczema			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Erythema			
subjects affected / exposed	10 / 40 (25.00%)		
occurrences (all)	23		
Rash			
subjects affected / exposed	26 / 40 (65.00%)		
occurrences (all)	111		
Skin striae			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	8		
Skin fissures			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	20		
Skin injury			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	7		
Onycholysis			

subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 4		
Dry skin subjects affected / exposed occurrences (all)	17 / 40 (42.50%) 23		
Pruritus subjects affected / exposed occurrences (all)	15 / 40 (37.50%) 23		
Palmar-plantar erythrodysesthesia syndrome subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3		
Skin toxicity subjects affected / exposed occurrences (all)	8 / 40 (20.00%) 13		
Nail toxicity subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 5		
Nail disorder subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 5		
Skin ulcer subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 4		
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 4		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3		
Cervicalgia subjects affected / exposed occurrences (all)	5 / 40 (12.50%) 9		
Back pain			

subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 4		
Pain in jaw subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 4		
Pain in extremity subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 3		
Musculoskeletal pain subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 3		
<b>Infections and infestations</b>			
Oral candidiasis subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 4		
Cellulitis subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3		
Conjunctivitis subjects affected / exposed occurrences (all)	10 / 40 (25.00%) 12		
Folliculitis subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 4		
Respiratory tract infection subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 6		
Localised infection subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3		
Lung infection subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3		

Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 5		
Pneumonia subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 4		
Paronychia subjects affected / exposed occurrences (all)	16 / 40 (40.00%) 29		
Superinfection subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	19 / 40 (47.50%) 32		
Hypocalcaemia subjects affected / exposed occurrences (all)	7 / 40 (17.50%) 23		
Hypokalaemia subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 5		
Hypomagnesaemia subjects affected / exposed occurrences (all)	21 / 40 (52.50%) 72		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 April 2010	After reviewing the considerations of the Clinical Investigation Ethic Committees the suggested changes in the Protocol, the patient Information Sheet and the Informed Consent Form were performed, as well as in the pregnant partner data emission form, with the aim of improving the comprehension.  Moreover, the parallel optional study of molecular predictive factors (appendix L in the study protocol) as well as the patient Information Sheet and the corresponding Informed Consent (Appendix M of the study protocol) were attached, being both of new development.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27865372>