Clinical trial results:
Randomised phase II trial of oral vinorelbine and cisplatin followed by maintenance with single agent oral vinorelbine (NVBO) versus gemcitabine (GEM) and cisplatin (CDDP) followed by maintenance with single agent gemcitabine in first line Locally Advanced or Metastatic Non-Small-Cell Lung Cancer patients with squamous histological type

Summary

EudraCT number	2012-003531-40
Trial protocol	ES IT AT PL FR
Global end of trial date	06 December 2016

Results information

Result version number	v1 (current)
This version publication date	10 March 2019
First version publication date	10 March 2019

Trial information

Trial identification

Sponsor protocol code	PM259CA230J1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Pierre Fabre Médicament
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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	19 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the Disease Control Rate (CR, PR, SD in both arms) on the whole study period (combination and maintenance periods).

Protection of trial subjects:

This study was performed in accordance with the principles stated in the Declaration of Helsinki and subsequent amendments and in accordance with the Good Clinical Practice Guideline (CPMP/ICH/135/95). Patient information was based on the elements set out in the Declaration of Helsinki and the ICH GCP Guideline and measures taken to safeguard subject's privacy and protection of personal data, according to European Directive 95/46 EC.

Background therapy:

NVBO+CDDP arm: A systematic anti-emetic treatment was recommended before treatment administration (at day 1 with NVBO+CDDP and day 8 with NVBO alone). NVBO dose was 60 mg/m2 in cycle 1 and was to be increased to 80 mg/m2 in the subsequent cycles (on day 1 and day 8 of each cycle). Dose escalation at cycle 2 was determined based on haematological tolerance. NVBO was recommended to be taken with food. Following NVBO intake and saline hyper-hydration, i.v. CDDP was administered at the dose of 80 mg/m² on day 1 of each cycle and according to the investigational centre routine.
GEM+CDDP arm: A systematic anti-emetic treatment was recommended before treatment administration. GEM (1250 mg/m²; i.v.) was administered on day 1 and day 8 of each cycle. Following GEM intake and saline hyperhydration, i.v. CDDP was administered at the dose of 80 mg/m² on day 1, every 3 weeks and according to the investigational centre routine. Erythropoietin was be given to patients who experienced anaemia grade 3-4. Growth factors may be given to patients who experienced febrile neutropenia (FN), grade 4 asymptomatic neutropenia lasting more than 7 days or neutropenic infection, according to institutional routine.
Patients receiving opiates were given preventive treatment for constipation and followed carefully.

Evidence for comparator:

GEM plus CDDP has been the standard doublet for squamous cell NSCLC. The importance of histological types was highlighted in a trial [Scagliotti GV, 2008], in which GEM plus CDDP combination was demonstrated to be more effective on squamous cell carcinomas than PEM plus CDDP. Therefore, this doublet was chosen as the reference treatment.

Actual start date of recruitment	01 December 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Regulatory reason, Scientific research
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 38
Country: Number of subjects enrolled	Spain: 15

Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	Brazil: 15
Worldwide total number of subjects	113
EEA total number of subjects	98

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)	65
From 65 to 84 years	48
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Twenty five centres in 6 countries screened 114 patients between the 18 of March 2013 and 19 August 2015. Of the 114 patients randomised, one patient was not treated due to forbidden radiotherapy resulting in 113 patients.

Pre-assignment

Screening details:

A 28-day screening period was planned before randomisation and screened for NSCLC stage IIIB or stage IV or relapsing after a local treatment chemo naive adult patients. All screened patients were randomised 1:1 in the 2 arms

Period 1

Period 1 title	Treatment 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	NVBO+CDDP arm:

Arm description:

o Combination period: NVBO 60 mg/m² on day 1 and day 8 (increased to 80 mg/m² at 2nd cycle according to haematological tolerance) with i.v. CDDP 80 mg/m² on day 1 every 3 weeks.
o Maintenance period (after 4 cycles for patients with OR or SD): NVBO at the last dose of cycle 4, day 1 – day 8 every 3 weeks.

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

Dosage and administration details:

During the combination period patients received 60 mg/m2 of NVBO at cycle 1 and 80 mg/m2 during subsequent cycles at days 1 and 8 of each cycle.
During the maintenance period, patient with OR or SD received the same dose as cycle 4 at days 1 and 8 of each cycle. NVBO was provided in sealed polystyrene box containing 16 blister packs of one soft capsule 20 mg or 30 mg vinorelbine each which should be used capsule per capsule for all patients according
to dosage.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	CDDP
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During the combination period patients received 80 mg/m2 of CDDP at day 1 of each cycle. CDDP was provided free of charge to each centre, in a commercial box containing one
50 mL or 100 mL vial of CDDP 1mg/mL (single use vials). CDDP was to be used vial per vial for all patients according to dosage.

Arm title	GEM + CDDP arm

Arm description:

o Combination period: GEM 1250 mg/m² on day 1 and day 8 with i.v. CDDP 75 mg/m² on day 1 every 3

weeks.
o Maintenance period (after 4 cycles for patients with OR or SD): GEM at the last dose as cycle 4, day 1 – day 8 every 3 weeks.

Arm type	Active comparator
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	CDDP
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During the combination period patients received 80 mg/m2 of CDDP at day 1 of each cycle. CDDP was provided free of charge to each centre, in a commercial box containing one
50 mL or 100 mL vial of CDDP 1mg/mL (single use vials). CDDP was to be used vial per vial for all patients according to dosage.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	GEM
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During the combination period patients received 1250 mg/m2 of GEM at day 1 and day 8 of each cycle. During the maintenance period, patients received the same dose of GEM as cycle 4 at day 1 and day 8 of each cycle.
GEM was provided in a commercial box containing one vial of 200 mg or 1 g.

Number of subjects in period 1	NVBO+CDDP arm:	GEM + CDDP arm
Started	57	56
Completed	0	0
Not completed	57	56
Progressive or recurrent disease	35	38
Death	4	1
Study drug related adverse event	6	7
Other reasons	9	2
non study drug related adverse event	2	8
Protocol deviation	1	-

Baseline characteristics

Reporting groups

Reporting group title	NVBO+CDDP arm:

Reporting group description:

o Combination period: NVBO 60 mg/m² on day 1 and day 8 (increased to 80 mg/m² at 2nd cycle according to haematological tolerance) with i.v. CDDP 80 mg/m² on day 1 every 3 weeks.
o Maintenance period (after 4 cycles for patients with OR or SD): NVBO at the last dose of cycle 4, day 1 – day 8 every 3 weeks.

Reporting group title	GEM + CDDP arm

Reporting group description:

o Combination period: GEM 1250 mg/m² on day 1 and day 8 with i.v. CDDP 75 mg/m² on day 1 every 3 weeks.
o Maintenance period (after 4 cycles for patients with OR or SD): GEM at the last dose as cycle 4, day 1 – day 8 every 3 weeks.

Reporting group values	NVBO+CDDP arm:	GEM + CDDP arm	Total
Number of subjects	57	56	113
Age categorical Units: Subjects			
Adults (18-64 years)	37	28	65
From 65-84 years	20	28	48
85 years and over	0	0	0
Age continuous Units: years			
median	60.5	63.6	
standard deviation	± 7.6	± 6.9	-
Gender categorical Units: Subjects			
Female	17	11	28
Male	40	45	85
Performance status reported in baseline clinical examination Units: Subjects			
70	2	3	5
80	22	22	44
90	23	21	44
100	10	10	20
Smoker history Units: Subjects			
Never smoked	1	0	1
Stopped smoking >=10 years ago	8	11	19
Stopped smoking <10 years ago	22	22	44
Smoker	26	23	49
Histopathological diagnosis method			
Histopathological type: squamous cell or epidermoid carcinoma (n=113)			
Units: Subjects			
Cytological	16	12	28
Histological	41	43	84

Histological/Cytological	0	1	1
TMN classification of Primary Tumor			
TMN classification at the time of first diagnosis			
Units: Subjects			
T1	1	1	2
T1B	1	2	3
T2	7	5	12
T2A	2	2	4
T2B	1	3	4
T3	17	19	36
T4	27	23	50
TX	1	1	2
TMN classification of Lymph node Units: Subjects			
N0	6	8	14
N1	2	3	5
N2	25	21	46
N3	23	23	46
NX	1	1	2
TMN classification of Distant metastasis Units: Subjects			
M0	4	7	11
M1	22	22	44
M1A	9	13	22
M1B	22	14	36
Stage at diagnosis Units: Subjects			
IA	0	1	1
IB	2	0	2
IIIA	0	1	1
IIIB	3	5	8
IV	52	49	101
Number of metastasis localizations Units: Subjects			
Zero	2	4	6
One	8	11	19
Two	25	18	43
>= Three	22	23	45
Weight Units: kg			
arithmetic mean	70.82	74.86	
standard deviation	± 14.87	± 17	-
Height Units: cm			
arithmetic mean	169.25	168.54	
standard deviation	± 9.82	± 8.08	-
Body surface area Units: m²			
arithmetic mean	1.81	1.84	
standard deviation	± 0.22	± 0.22	-
Delay between first histopathological diagnosis and study entry			

Units: months			
arithmetic mean	2.14	1.90	
standard deviation	± 4.92	± 3.20	-

End points

End points reporting groups

Reporting group title	NVBO+CDDP arm:

Reporting group description:

o Combination period: NVBO 60 mg/m² on day 1 and day 8 (increased to 80 mg/m² at 2nd cycle according to haematological tolerance) with i.v. CDDP 80 mg/m² on day 1 every 3 weeks.
o Maintenance period (after 4 cycles for patients with OR or SD): NVBO at the last dose of cycle 4, day 1 – day 8 every 3 weeks.

Reporting group title	GEM + CDDP arm

Reporting group description:

o Combination period: GEM 1250 mg/m² on day 1 and day 8 with i.v. CDDP 75 mg/m² on day 1 every 3 weeks.
o Maintenance period (after 4 cycles for patients with OR or SD): GEM at the last dose as cycle 4, day 1 – day 8 every 3 weeks.

Primary: Disease control rate (DCR)

End point title	Disease control rate (DCR)

End point description:

DCR, defined as the sum of confirmed CR, PR and SD rates, was observed in 42/57 patients (73.7%): [95% CI: 62.4%; 100%] in NVBO+CDDP arm and 42/56 patients (75.0%): [95% CI: 63.7%; 100%] in GEM+CDDP arm. Mean (SD) treatment duration was 15.21 (13.62) weeks for patients in NVBO+CDDP arm (n=57) and 16.77 (14.60) weeks for patients in GEM+CDDP arm (n=56).

End point type	Primary

End point timeframe:

DCR according to investigator was calculated among the BOCR responders (CR and PR) and stable patients in the ITT population on the whole study period (from the date of randomisation until the documentation of progression or death due to any cause).

End point values	NVBO+CDDP arm:	GEM + CDDP arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	56		
Units: pourcentage				
number (confidence interval 95%)	73.7 (62.4 to 83.0)	75.0 (63.7 to 84.2)		

Statistical analyses

Statistical analysis title	Primary efficacy analysis

Statistical analysis description:

Mean (SD) treatment duration was 15.21 (13.62) weeks for patients in NVBO+CDDP arm (n=57) and 16.77 (14.60) weeks for patients in GEM+CDDP arm (n=56). The 95% CIs are calculated using the Brookmeyer and Crowley method and computed following the exact method.

Comparison groups	NVBO+CDDP arm: v GEM + CDDP arm

Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	≤ 0.05
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided
lower limit	62.4
upper limit	100

Secondary: Objective response rate (ORR)

End point title	Objective response rate (ORR)

End point description:

Objective response rate was defined as the sum of CR and PR rate and evaluated on the whole study treatment period (combination + maintenance periods), from the date of randomisation until the end of study treatment period in the ITT population (n=113). The mean (SD) duration of follow-up was 11.52 (7.88) months for NVBO+CDDP arm and 11.09 (9.79) for the GEM+CDDP arm. ORR was observed in 31 patients (27.4%). Among them, 14 (24.6%) were from NVBO+CDDP arm and 17 (30.4%) from GEM+CDDP arm).

End point type	Secondary

End point timeframe:

Objective response rate was evaluated on the whole study treatment period (from the date of randomisation until the end of study treatment period) in the ITT population (n=113).

End point values	NVBO+CDDP arm:	GEM + CDDP arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	56		
Units: pourcentage				
number (confidence interval 95%)	24.6 (14.1 to 37.8)	30.4 (18.8 to 44.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Confirmed Response (BOCR)

End point title	Best Overall Confirmed Response (BOCR)

End point description:

The BOCR was determined once all the data for the patient were known and was categorised in 5 classes: confirmed CR, confirmed PR, SD, PD or not evaluated (NE) for the whole study treatment period in the ITT population. No patients presented with CR, 31 patients (27.4%) presented with PR while SD of ≥6 weeks was observed in
53 patients (46.9%) and PD in 20 patients (17.7%).

End point type	Secondary

End point timeframe:

Best Overall Confirmed Response was recorded from the date of randomisation until end of study treatment period. Tumour assessment was performed according to the RECIST guideline and was carried out at baseline and every 6 weeks until progressive disease.

End point values	NVBO+CDDP arm:	GEM + CDDP arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	56		
Units: patients				
PR	14	17		
SD 6 weeks	28	25		
PD	11	9		
Not evaluable	0	2		
Missing	4	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of disease control

End point title	Duration of disease control

End point description:

The duration of disease control (CR, PR and stable diasease of at least 24 weeks) was analysed in the subset of patients with disease control in ITT population for response on the whole study treatment period. In ITT population, the subset of patients with disease control rate included 42 patients in each arm. The estimated duration of disease control for these patients ranged from 1.45-22.11 months for NVBO+CDDP arm and 1.68-18.20 months for GEM+CDDP arm, respectively. The estimated median duration of disease control was 4.8 months [95% CI: 4.1; 5.7] in NVBO+CDDP arm and 5.2 months [95% CI: 4.3; 6.6] in GEM+CDDP arm. Duration of disease control was estimated using Kaplan-Meier analyses. CIs on the median were calculated using the Brookmeyer and Crowley method.

End point type	Secondary

End point timeframe:

Duration of disease control according to investigator was calculated among the BOCR stable patients from the date of randomisation until the documentation of progression or death due to any cause.

End point values	NVBO+CDDP arm:	GEM + CDDP arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	56		
Units: months				
median (confidence interval 95%)	4.8 (4.1 to 5.7)	5.2 (4.3 to 6.6)		

Attachments (see zip file)	KM curve of the duration of disease control/Kapaln Meier

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

PFS was analysed in the ITT population and estimated using Kaplan-Meier approachs. CIs on the median were calculated using the Brookmeyer and Crowley method. Patients who were lost to follow-up, or reached the time point of analysis without a known record of progression or death had the PFS censored at the date of last tumour assessment or last contact showing no progression or death, whichever occurred last. In the ITT population, the disease progressed in 36 (64.3%) from NVBO+CDDP arm and 40 patients (74.1%) during the treatment.

End point type	Secondary

End point timeframe:

PFS was calculated from the date of randomisation until the date of progression (first date where PD is assessed) or the date of death due to any cause if no progression was recorded before. The mean duration of follow-up was 11.52 vs 11.09 months.

End point values	NVBO+CDDP arm:	GEM + CDDP arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	56		
Units: months				
median (confidence interval 95%)	4.2 (2.8 to 4.9)	4.3 (3.1 to 5.5)		

Attachments (see zip file)	Progression Free Survival- Survival curves - Kapla/KM PFS.png

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS was analysed in the ITT population on the whole study period and estimated using Kaplan-Meier analyses. CIs on the median were calculated using the Brookmeyer and Crowley method. Patients who were lost to follow-up, or reached the time point of analysis without a known record of progression or death had the PFS censored at the date of last tumour assessment or last contact showing no progression or death, whichever occurred last. At the cutoff date (19-May-2017) or last contact, death was reported for 98 patients (86%) while 13 patients (11.4%) were still alive. Two patients (1.8%) were lost to follow-up and one patient remained untreated (0.9%).

End point type	Secondary

End point timeframe:

OS was the duration between the date of randomisation and the date of death (any cause). Patients lost to fup or without a known record of death were censored at the date of last contact. For alive patients, survival time was censored at date of last news

End point values	NVBO+CDDP arm:	GEM + CDDP arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	56		
Units: months				
median (confidence interval 95%)	10.2 (6.9 to 12.9)	8.4 (5.3 to 11.9)		

Attachments (see zip file)	Overall Survival time - Kaplan-M/OS-KM.png

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first response

End point title	Time to first response

End point description:

Time to first response was calculated using Kaplan-Meier cumulative incidence. In the ITT population, the estimated time to first response ranged in NVBO+CDDP arm (n=14) from 1.1-2.8 months and 1.2-4.1 months in GEM+CDDP arm (n=17). The estimated median time to first response was 1.6 months [95% CI: 1.2; 2.7] in NVBO+CDDP arm and 1.5 months [95% CI: 1.3; 2.7] in GEM+CDDP arm.

End point type	Secondary

End point timeframe:

Time to first response was calculated among responders (confirmed CR and PR) in the ITT population from the date of randomisation up to the first report of documented response. The date of first response was the first date where CR or PR was assessed.

End point values	NVBO+CDDP arm:	GEM + CDDP arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	56		
Units: months				
median (confidence interval 95%)	1.6 (1.2 to 2.7)	1.5 (1.3 to 2.7)		

Attachments (see zip file)	Time to first response/Time to first response.png

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Anti-cancer treatment during follow-up

End point title	Anti-cancer treatment during follow-up

End point description:

The number of patients with further CT and other therapy during follow-up period was presented in the ITT population. About 20% of the patients had further CT and other therapy during the follow-up period. Around 49% patients in NVBO+CDDP arm and around 27% patients in GEM+CDDP arm had at least one further CT.

End point type	Other pre-specified

End point timeframe:

The number of patients with anti-cancer treatment was measured during the follow-up period (time from 30 days after the last study treatment administration until death or decision for study closure or last contact).

End point values	NVBO+CDDP arm:	GEM + CDDP arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	56		
Units: patients				
Patients with at least one further chemotherapy	28	15		
Patients with at least one further other therapy	23	20		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any adverse or intercurrent event occurring during the study period was recorded in the CRF. All SAEs occurring after signing of the ICF and up to 30 days after the last study administration.

Adverse event reporting additional description:

At the cutoff date (19-May-17) or last contact, death was reported for 98 patients while 13 patients were still alive. 2 patients were lost to follow-up and 1 patient remained untreated. The RDI during the whole study treatment period was 86.05% for NVBO treatment in NVBO+CDDP arm and 82.16% for GEM treatment in GEM+CDDP arm.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	NVBO + CDDP arm
Reporting group description: -	
Reporting group title	GEM + CDDP arm

Reporting group description: -

Serious adverse events	NVBO + CDDP arm	GEM + CDDP arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 57 (50.88%)	31 / 56 (55.36%)	
number of deaths (all causes)	51	47	
number of deaths resulting from adverse events	3	4	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	0 / 57 (0.00%)	2 / 56 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arterial insufficiency			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Jugular vein thrombosis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 57 (1.75%)	6 / 56 (10.71%)	
occurrences causally related to treatment / all	1 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 57 (0.00%)	3 / 56 (5.36%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 57 (1.75%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	4 / 57 (7.02%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	1 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 57 (3.51%)	2 / 56 (3.57%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			

subjects affected / exposed	1 / 57 (1.75%)	2 / 56 (3.57%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 57 (1.75%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiccups			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			

subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia supraventricular			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 57 (0.00%)	2 / 56 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Altered state of consciousness			

subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peripheral motor neuropathy			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 57 (7.02%)	4 / 56 (7.14%)	
occurrences causally related to treatment / all	5 / 5	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	7 / 57 (12.28%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	8 / 8	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	6 / 57 (10.53%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 57 (1.75%)	2 / 56 (3.57%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 57 (0.00%)	3 / 56 (5.36%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			

subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal hypomotility			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 57 (1.75%)	2 / 56 (3.57%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
renal failure acute			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Bone pain			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 57 (1.75%)	5 / 56 (8.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 57 (0.00%)	3 / 56 (5.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 2	
Upper respiratory tract infection			
subjects affected / exposed	1 / 57 (1.75%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 57 (0.00%)	2 / 56 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			

subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	2 / 57 (3.51%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	NVBO + CDDP arm	GEM + CDDP arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 57 (100.00%)	56 / 56 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	5 / 57 (8.77%)	5 / 56 (8.93%)	
occurrences (all)	20	12	

Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 57 (10.53%)	4 / 56 (7.14%)	
occurrences (all)	12	4	
Hypotension			
subjects affected / exposed	5 / 57 (8.77%)	5 / 56 (8.93%)	
occurrences (all)	6	9	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	46 / 57 (80.70%)	43 / 56 (76.79%)	
occurrences (all)	132	112	
Chest pain			
subjects affected / exposed	14 / 57 (24.56%)	12 / 56 (21.43%)	
occurrences (all)	34	47	
Pyrexia			
subjects affected / exposed	7 / 57 (12.28%)	8 / 56 (14.29%)	
occurrences (all)	8	11	
Asthenia			
subjects affected / exposed	4 / 57 (7.02%)	7 / 56 (12.50%)	
occurrences (all)	6	19	
Oedema peripheral			
subjects affected / exposed	2 / 57 (3.51%)	7 / 56 (12.50%)	
occurrences (all)	3	16	
Pain			
subjects affected / exposed	4 / 57 (7.02%)	5 / 56 (8.93%)	
occurrences (all)	9	6	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	23 / 57 (40.35%)	31 / 56 (55.36%)	
occurrences (all)	75	105	
Dyspnoea			
subjects affected / exposed	20 / 57 (35.09%)	30 / 56 (53.57%)	
occurrences (all)	48	66	
Haemoptysis			
subjects affected / exposed	3 / 57 (5.26%)	9 / 56 (16.07%)	
occurrences (all)	10	10	

Dysphonia			
subjects affected / exposed	5 / 57 (8.77%)	1 / 56 (1.79%)	
occurrences (all)	14	2	
Productive cough			
subjects affected / exposed	3 / 57 (5.26%)	3 / 56 (5.36%)	
occurrences (all)	4	11	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	8 / 57 (14.04%)	7 / 56 (12.50%)	
occurrences (all)	21	20	
Insomnia			
subjects affected / exposed	8 / 57 (14.04%)	6 / 56 (10.71%)	
occurrences (all)	14	10	
Investigations			
Weight decreased			
subjects affected / exposed	19 / 57 (33.33%)	21 / 56 (37.50%)	
occurrences (all)	48	57	
Weight increased			
subjects affected / exposed	9 / 57 (15.79%)	13 / 56 (23.21%)	
occurrences (all)	18	63	
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	3 / 57 (5.26%)	3 / 56 (5.36%)	
occurrences (all)	3	4	
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	4 / 57 (7.02%)	2 / 56 (3.57%)	
occurrences (all)	7	2	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 57 (10.53%)	4 / 56 (7.14%)	
occurrences (all)	8	31	
Dysgeusia			
subjects affected / exposed	6 / 57 (10.53%)	3 / 56 (5.36%)	
occurrences (all)	9	6	
Paraesthesia			

subjects affected / exposed	4 / 57 (7.02%)	4 / 56 (7.14%)	
occurrences (all)	8	16	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	6 / 57 (10.53%)	8 / 56 (14.29%)	
occurrences (all)	11	19	
Deafness			
subjects affected / exposed	4 / 57 (7.02%)	5 / 56 (8.93%)	
occurrences (all)	12	14	
Eye disorders			
Eye disorder			
subjects affected / exposed	5 / 57 (8.77%)	5 / 56 (8.93%)	
occurrences (all)	15	13	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	30 / 57 (52.63%)	28 / 56 (50.00%)	
occurrences (all)	67	86	
Vomiting			
subjects affected / exposed	23 / 57 (40.35%)	12 / 56 (21.43%)	
occurrences (all)	33	24	
Constipation			
subjects affected / exposed	17 / 57 (29.82%)	17 / 56 (30.36%)	
occurrences (all)	33	30	
Diarrhoea			
subjects affected / exposed	18 / 57 (31.58%)	9 / 56 (16.07%)	
occurrences (all)	29	12	
Abdominal pain			
subjects affected / exposed	11 / 57 (19.30%)	7 / 56 (12.50%)	
occurrences (all)	13	13	
Stomatitis			
subjects affected / exposed	3 / 57 (5.26%)	13 / 56 (23.21%)	
occurrences (all)	5	32	
Abdominal pain upper			
subjects affected / exposed	3 / 57 (5.26%)	7 / 56 (12.50%)	
occurrences (all)	7	19	
Dyspepsia			

subjects affected / exposed	2 / 57 (3.51%)	4 / 56 (7.14%)	
occurrences (all)	3	6	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	5 / 57 (8.77%)	12 / 56 (21.43%)	
occurrences (all)	19	56	
Dry skin			
subjects affected / exposed	4 / 57 (7.02%)	3 / 56 (5.36%)	
occurrences (all)	7	4	
Pruritus			
subjects affected / exposed	4 / 57 (7.02%)	3 / 56 (5.36%)	
occurrences (all)	7	5	
Renal and urinary disorders			
renal and urinary disorders			
subjects affected / exposed	3 / 57 (5.26%)	7 / 56 (12.50%)	
occurrences (all)	5	9	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 57 (10.53%)	6 / 56 (10.71%)	
occurrences (all)	12	6	
Back pain			
subjects affected / exposed	5 / 57 (8.77%)	7 / 56 (12.50%)	
occurrences (all)	11	34	
Pain in extremity			
subjects affected / exposed	7 / 57 (12.28%)	3 / 56 (5.36%)	
occurrences (all)	8	3	
Musculoskeletal pain			
subjects affected / exposed	3 / 57 (5.26%)	6 / 56 (10.71%)	
occurrences (all)	3	17	
Bone pain			
subjects affected / exposed	4 / 57 (7.02%)	4 / 56 (7.14%)	
occurrences (all)	11	15	
Musculoskeletal chest pain			
subjects affected / exposed	7 / 57 (12.28%)	0 / 56 (0.00%)	
occurrences (all)	16	0	
Infections and infestations			

Lung infection			
subjects affected / exposed	3 / 57 (5.26%)	4 / 56 (7.14%)	
occurrences (all)	3	4	
Bronchitis			
subjects affected / exposed	3 / 57 (5.26%)	3 / 56 (5.36%)	
occurrences (all)	4	3	
Rhinitis			
subjects affected / exposed	4 / 57 (7.02%)	2 / 56 (3.57%)	
occurrences (all)	7	2	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	16 / 57 (28.07%)	20 / 56 (35.71%)	
occurrences (all)	34	58	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 November 2012	The rationale of this amendment is to extend the duration of contraception after chemotherapy with cisplatin to 6 months for patients of both sexes and with gemcitabine to 6 months for men only. In addition, typing errors regarding cisplatin and gemcitabine storage have been corrected in this amendment. These are based on the current summary of product characteristics of cisplatin and gemcitabine.
28 March 2014	The objectives of this amendment are: - to extend the recruitment period until 31 December 2014, considering that the expected accrual is not reached, - to clarify the assessments of Biochemistry tests. - to update the Sponsor's Personnel, - to update the Investigator's Brochure, - to update the World Medical Association Declaration of Helsinki (October 2013).
21 October 2014	The objective of this amendment is to extend the recruitment period until 30 June 2015, considering that the expected accrual is not reached.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported