



## 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                                                                    |
| Sponsor organisation address | 45 place Abel Gance, Boulogne, France, 92100                                               |
| Public contact               | Marcello RIGGI, Pierre Fabre Medicament, +33 149 10 81 77, marcello.riggi@pierre-fabre.com |
| Scientific contact           | Marcello RIGGI, Pierre Fabre Medicament, +33 149 10 81 77, marcello.riggi@pierre-fabre.com |

Notes:

### Paediatric regulatory details

|                                                                      |    |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|                                                      |                  |
|------------------------------------------------------|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 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/m<sup>2</sup> in cycle 1 and was to be increased to 80 mg/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup>; 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/m<sup>2</sup> 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:

| <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)                      | 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/m<sup>2</sup> on day 1 and day 8 (increased to 80 mg/m<sup>2</sup> at 2nd cycle according to haematological tolerance) with i.v. CDDP 80 mg/m<sup>2</sup> 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/m<sup>2</sup> of NVBO at cycle 1 and 80 mg/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> on day 1 and day 8 with i.v. CDDP 75 mg/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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.

| <b>Number of subjects in period 1</b> | 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              |
| Protocol deviation                    | 1              | -              |
| non study drug related adverse event  | 2              | 8              |

## Baseline characteristics

### Reporting groups

|                       |                |
|-----------------------|----------------|
| Reporting group title | NVBO+CDDP arm: |
|-----------------------|----------------|

Reporting group description:

- o Combination period: NVBO 60 mg/m<sup>2</sup> on day 1 and day 8 (increased to 80 mg/m<sup>2</sup> at 2nd cycle according to haematological tolerance) with i.v. CDDP 80 mg/m<sup>2</sup> 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/m<sup>2</sup> on day 1 and day 8 with i.v. CDDP 75 mg/m<sup>2</sup> 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: m <sup>2</sup>                                           |         |        |     |
| 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/m<sup>2</sup> on day 1 and day 8 (increased to 80 mg/m<sup>2</sup> at 2nd cycle according to haematological tolerance) with i.v. CDDP 80 mg/m<sup>2</sup> 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/m<sup>2</sup> on day 1 and day 8 with i.v. CDDP 75 mg/m<sup>2</sup> 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 disease 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) |  |  |

|                                   |                                                          |
|-----------------------------------|----------------------------------------------------------|
| <b>Attachments (see zip file)</b> | KM curve of the duration of disease control/Kaplan 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 approaches. 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) |  |  |

|                                   |                                                               |
|-----------------------------------|---------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | 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) |  |  |

|                                   |                                            |
|-----------------------------------|--------------------------------------------|
| <b>Attachments (see zip file)</b> | 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) |  |  |

|                                   |                                                   |
|-----------------------------------|---------------------------------------------------|
| <b>Attachments (see zip file)</b> | 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).

---

| <b>End point values</b>                          | 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              |  |  |

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**Statistical analyses**

No statistical analyses for this end point

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## 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<br>subjects affected / exposed               | 1 / 57 (1.75%) | 0 / 56 (0.00%)  |  |
| occurrences causally related to<br>treatment / all                   | 0 / 1          | 0 / 0           |  |
| deaths causally related to<br>treatment / all                        | 0 / 0          | 0 / 0           |  |
| General disorders and administration<br>site conditions              |                |                 |  |
| General physical health deterioration<br>subjects affected / exposed | 1 / 57 (1.75%) | 6 / 56 (10.71%) |  |
| occurrences causally related to<br>treatment / all                   | 1 / 1          | 0 / 6           |  |
| deaths causally related to<br>treatment / all                        | 0 / 0          | 0 / 0           |  |
| Fatigue<br>subjects affected / exposed                               | 0 / 57 (0.00%) | 3 / 56 (5.36%)  |  |
| occurrences causally related to<br>treatment / all                   | 0 / 0          | 2 / 3           |  |
| deaths causally related to<br>treatment / all                        | 0 / 0          | 0 / 0           |  |
| Pyrexia<br>subjects affected / exposed                               | 1 / 57 (1.75%) | 1 / 56 (1.79%)  |  |
| occurrences causally related to<br>treatment / all                   | 1 / 1          | 0 / 1           |  |
| deaths causally related to<br>treatment / all                        | 0 / 0          | 0 / 0           |  |
| Death<br>subjects affected / exposed                                 | 1 / 57 (1.75%) | 0 / 56 (0.00%)  |  |
| occurrences causally related to<br>treatment / all                   | 0 / 1          | 0 / 0           |  |
| deaths causally related to<br>treatment / all                        | 0 / 1          | 0 / 0           |  |
| Respiratory, thoracic and mediastinal<br>disorders                   |                |                 |  |
| Pulmonary embolism<br>subjects affected / exposed                    | 4 / 57 (7.02%) | 1 / 56 (1.79%)  |  |
| occurrences causally related to<br>treatment / all                   | 1 / 4          | 2 / 2           |  |
| deaths causally related to<br>treatment / all                        | 0 / 0          | 0 / 0           |  |
| Dyspnoea<br>subjects affected / exposed                              | 2 / 57 (3.51%) | 2 / 56 (3.57%)  |  |
| occurrences causally related to<br>treatment / all                   | 0 / 3          | 0 / 2           |  |
| deaths causally related to<br>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          |  |
| <b>Pulmonary sepsis</b>                         |                |                |  |
| 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          |  |
| <b>Sepsis</b>                                   |                |                |  |
| 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          |  |
| <b>Staphylococcal infection</b>                 |                |                |  |
| 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          |  |
| <b>Metabolism and nutrition disorders</b>       |                |                |  |
| <b>Hyperglycaemia</b>                           |                |                |  |
| 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          |  |
| <b>Hyponatraemia</b>                            |                |                |  |
| 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 %

| <b>Non-serious adverse events</b>                                          | NVBO + CDDP arm   | GEM + CDDP arm    |  |
|----------------------------------------------------------------------------|-------------------|-------------------|--|
| <b>Total subjects affected by non-serious adverse events</b>               |                   |                   |  |
| subjects affected / exposed                                                | 57 / 57 (100.00%) | 56 / 56 (100.00%) |  |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |                   |                   |  |
| <b>Tumour pain</b>                                                         |                   |                   |  |
| 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<br>subjects affected / exposed<br>occurrences (all)                                                | 5 / 57 (8.77%)<br>14   | 1 / 56 (1.79%)<br>2    |  |
| Productive cough<br>subjects affected / exposed<br>occurrences (all)                                         | 3 / 57 (5.26%)<br>4    | 3 / 56 (5.36%)<br>11   |  |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)                         | 8 / 57 (14.04%)<br>21  | 7 / 56 (12.50%)<br>20  |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                                                 | 8 / 57 (14.04%)<br>14  | 6 / 56 (10.71%)<br>10  |  |
| Investigations<br>Weight decreased<br>subjects affected / exposed<br>occurrences (all)                       | 19 / 57 (33.33%)<br>48 | 21 / 56 (37.50%)<br>57 |  |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)                                         | 9 / 57 (15.79%)<br>18  | 13 / 56 (23.21%)<br>63 |  |
| Injury, poisoning and procedural complications<br>Injury<br>subjects affected / exposed<br>occurrences (all) | 3 / 57 (5.26%)<br>3    | 3 / 56 (5.36%)<br>4    |  |
| Cardiac disorders<br>Cardiac disorder<br>subjects affected / exposed<br>occurrences (all)                    | 4 / 57 (7.02%)<br>7    | 2 / 56 (3.57%)<br>2    |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)                     | 6 / 57 (10.53%)<br>8   | 4 / 56 (7.14%)<br>31   |  |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)                                                | 6 / 57 (10.53%)<br>9   | 3 / 56 (5.36%)<br>6    |  |
| Paraesthesia                                                                                                 |                        |                        |  |

|                                                  |                     |                      |  |
|--------------------------------------------------|---------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all) | 4 / 57 (7.02%)<br>8 | 4 / 56 (7.14%)<br>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<br>occurrences (all) | 2 / 57 (3.51%)<br>3 | 4 / 56 (7.14%)<br>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<br>subjects affected / exposed<br>occurrences (all)                                           | 3 / 57 (5.26%)<br>3    | 4 / 56 (7.14%)<br>4    |  |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                                               | 3 / 57 (5.26%)<br>4    | 3 / 56 (5.36%)<br>3    |  |
| Rhinitis<br>subjects affected / exposed<br>occurrences (all)                                                 | 4 / 57 (7.02%)<br>7    | 2 / 56 (3.57%)<br>2    |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 16 / 57 (28.07%)<br>34 | 20 / 56 (35.71%)<br>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.<br>In addition, typing errors regarding cisplatin and gemcitabine storage have been corrected in this amendment.<br>These are based on the current summary of product characteristics of cisplatin and gemcitabine.                                     |
| 28 March 2014    | The objectives of this amendment are: <ul style="list-style-type: none"><li>- to extend the recruitment period until 31 December 2014, considering that the expected accrual is not reached,</li><li>- to clarify the assessments of Biochemistry tests.</li><li>- to update the Sponsor's Personnel,</li><li>- to update the Investigator's Brochure,</li><li>- to update the World Medical Association Declaration of Helsinki (October 2013).</li></ul> |
| 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:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported