



Clinical trial results:

An Open, Randomized, Multicenter Study in Patients with Recurrent Epithelial Ovarian Cancer, Primary Peritoneal Cancer or Fallopian Tube Cancer to Compare the Efficacy and Safety of paclitaxel (micellar) nanoparticles and paclitaxel(Cremophor® EL)

Summary

| | |
|--------------------------|-------------------------------|
| EudraCT number | 2008-002668-32 |
| Trial protocol | SE BE CZ HU LV SK LT DK BG FI |
| Global end of trial date | 07 November 2013 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 08 March 2017 |
| First version publication date | 08 March 2017 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | OAS-07OVA |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00989131 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Oasmia Pharmaceutical |
| Sponsor organisation address | Vallongatan 1, Uppsala, Sweden, 75228 |
| Public contact | Clinical Development, Oasmia Pharmaceutical, 46 505440, margareta.eriksson@oasmia.com |
| Scientific contact | Clinical Development, Oasmia Pharmaceutical, 46 505440, margareta.eriksson@oasmia.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 | 28 May 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 07 November 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 07 November 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

- To show non-inferiority of the experimental treatment and the control treatment in terms of progression free survival (PFS) using CT scans according to Response Criteria in Solid Tumours, RECIST ver 1.0.
- To show non-inferiority of the experimental treatment and the control treatment in terms of overall survival (OS)
- To show safety and tolerability in the two study arms

Protection of trial subjects:

- Investigators were allowed to withdraw patients at any time, other therapy may be a reason
- In case of reactions towards carboplatin patients it was possible to continue on monotherapy with paclitaxel

Background therapy:

Combination therapy was used. Carboplatin was administered 30 minutes after Paclitaxel/Taxol administration was ended.

Evidence for comparator:

Paclitaxel has been used for more than 20 years for treatment of different forms of cancer. Taxol in combination with cisplatin is authorised for the treatment of ovarian cancer, but due to safety issues with cisplatin, carboplatin is recommended standard first-line chemotherapy treatment in ovarian cancer (Gynecological Cancer Intergroup, GCIG 2005). Patients are usually re-treated with platinum and taxane therapy at their first and second relapse. Thus, paclitaxel as Taxol in combination with carboplatin was thus chosen as the comparator.

| | |
|---|-----------------|
| Actual start date of recruitment | 21 January 2009 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy |
| Long term follow-up duration | 3 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Slovakia: 12 |
| Country: Number of subjects enrolled | Sweden: 16 |
| Country: Number of subjects enrolled | Belgium: 13 |
| Country: Number of subjects enrolled | Bulgaria: 40 |
| Country: Number of subjects enrolled | Czech Republic: 11 |
| Country: Number of subjects enrolled | Denmark: 3 |
| Country: Number of subjects enrolled | Finland: 1 |
| Country: Number of subjects enrolled | Hungary: 24 |

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Latvia: 46 |
| Country: Number of subjects enrolled | Lithuania: 14 |
| Country: Number of subjects enrolled | Belarus: 107 |
| Country: Number of subjects enrolled | Croatia: 9 |
| Country: Number of subjects enrolled | Romania: 17 |
| Country: Number of subjects enrolled | Russian Federation: 348 |
| Country: Number of subjects enrolled | Serbia: 26 |
| Country: Number of subjects enrolled | Ukraine: 102 |
| Worldwide total number of subjects | 789 |
| EEA total number of subjects | 206 |

Notes:

Subjects enrolled per age group

| | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 655 |
| From 65 to 84 years | 134 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Study inclusion and exclusion criteria were assessed during the screening period, i.e. up to 6 weeks before randomisation and after patients gave their consent. Recruitment was initiated in each country/at each site after respective legal and ethical approvals. First patients were recruited in Russia in Jan 2009 and randomised in Feb 2009.

Pre-assignment

Screening details:

Platinum-sensitive patients with relapsing ovarian cancer, >6 m after end of 1st /2nd line chemotherapy, CA 125 >2xUNL at two occasions before inclusion, life expectancy >12 weeks, lab criteria to ensure safety of patients, tumours of other origin not allowed. 865 screened , 789 randomized. Most common screenfailures: CA125 <2xUNL, relapse <6 m

Pre-assignment period milestones

| | |
|--|--------------------|
| Number of subjects started | 865 ^[1] |
| Intermediate milestone: Number of subjects | Randomization: 789 |
| Number of subjects completed | 789 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|---|
| Reason: Number of subjects | Consent withdrawn by subject: 7 |
| Reason: Number of subjects | Lost of follow up: 1 |
| Reason: Number of subjects | Inclusion/Exclusion criteria failures: 60 |
| Reason: Number of subjects | Missing reason: 8 |

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same. Justification: In this reported data the pre-assignment period is equal to the enrollment period (=screening period) and number of patients enrolled worldwide are the number of patients randomized world wide. Thus, there are more patients in the beginning of the pre-assignment period (= screened) than actually randomized (= enrolled).

Period 1

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

Blinding implementation details:

Open study design when related to allocation to treatment arm. Assessments of CT Scans for PSF was made centrally and blinded. The tumour marker CA 125 was analysed in serum samples at a central lab in a blinded manner. The personnel at these labs did not have access to clinical data entered by sites or the patient's treatment.

Arms

| | |
|---|--------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Paclical |
| Arm description: | |
| Patients received the study drug under investigation, Paclical , 250 mg/m2, intravenous infusion, followed by intravenous infusion of carboplatin, 5-6 AUC. | |
| Arm type | Experimental |

| | |
|--|----------------------------------|
| Investigational medicinal product name | Paclitaxel (micellar) |
| Investigational medicinal product code | |
| Other name | Apealea |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Paclical was administered at 250mg/m² body-surface area as one hour intravenous infusion, followed by carboplatin 5-6 AUC at least 30 minutes after end of the Paclical administration. In total six treatment cycles with three weeks intervals.

Each vial contained 60 mg of lyophilized powder of Paclical for reconstitution before use. Acetate Ringer's solution or Lactated Ringer's Solution should be used for reconstitution.

60 ml of the solution for reconstitution was injected to each Paclical vial (concentration of the concentrate = 1mg/ml), after reconstitution of enough number of vials for one patient the exact dosing volume of the 1 mg/ml concentrate of Paclical required for the patient was injected into an empty sterile infusion bag. The infusion bag was protected from daylight during the infusion by using a cover.

| | |
|------------------|-------|
| Arm title | Taxol |
|------------------|-------|

Arm description:

Patients received the control drug paclitaxel, Cremophor EL (Taxol), 175 mg/m², intravenous infusion, followed by intravenous infusion of carboplatin, 5-6 AUC.

| | |
|--|---------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Taxol |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Taxol was administered at 175mg/m² body surface area as three-hour intravenous infusion, followed by carboplatin 5-6 AUC at least 30 minutes after end of the Paclical administration, in total six treatment cycles with three weeks interval.

The concentrate for solution for infusion of Taxol has a paclitaxel concentration of 6 mg/ml.

The concentrate was diluted before use according to local Summary Product Characteristics.

| Number of subjects in period 1 | Paclical | Taxol |
|--|----------|-------|
| Started | 397 | 392 |
| Completed | 292 | 311 |
| Not completed | 105 | 81 |
| Missing data of reason | 3 | - |
| Consent withdrawn by subject | 30 | 25 |
| Physician decision | 24 | 12 |
| Adverse event, non-fatal | 8 | 6 |
| Other illness that prevented further treatment wit | 2 | - |
| Other illness that prevented further treatment | - | 2 |
| Progression not confirmed in central assessment | 27 | 28 |
| Lost to follow-up | 6 | 7 |
| Protocol deviation | 5 | 1 |

Baseline characteristics

Reporting groups

| | |
|---|----------|
| Reporting group title | Paclical |
| Reporting group description: | |
| Patients received the study drug under investigation, Paclical , 250 mg/m2, intravenous infusion, followed by intravenous infusion of carboplatin, 5-6 AUC. | |
| Reporting group title | Taxol |
| Reporting group description: | |
| Patients received the control drug paclitaxel, Cremophor EL (Taxol), 175 mg/m2, intravenous infusion, followed by intravenous infusion of carboplatin, 5-6 AUC. | |

| Reporting group values | Paclical | Taxol | Total |
|--|----------|----------|-------|
| Number of subjects | 397 | 392 | 789 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 334 | 321 | 655 |
| From 65-84 years | 63 | 71 | 134 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| geometric mean | 56 | 56 | |
| full range (min-max) | 26 to 81 | 27 to 81 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 397 | 392 | 789 |
| Male | 0 | 0 | 0 |
| Tumour type | | | |
| Number of patient with either epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer. | | | |
| Units: Subjects | | | |
| Epithelial ovarian cancer | 386 | 369 | 755 |
| Primary peritoneal cancer | 4 | 10 | 14 |
| Fallopian tube cancer | 7 | 13 | 20 |
| Initial tumour stage | | | |
| Tumour stage according to FIGO classification. | | | |
| Units: Subjects | | | |
| Stage IA | 7 | 5 | 12 |
| Stage IB | 7 | 10 | 17 |
| Stage IC | 25 | 21 | 46 |
| Stage IIA | 9 | 17 | 26 |
| Stage IIB | 8 | 11 | 19 |

| | | | |
|---|-------|-------|-----|
| Stage IIC | 26 | 11 | 37 |
| Stage IIIA | 40 | 34 | 74 |
| Stage IIIB | 34 | 25 | 59 |
| Stage IIIC | 183 | 192 | 375 |
| Stage IV | 58 | 65 | 123 |
| Missing | 0 | 1 | 1 |
| Platinum-free interval | | | |
| Number of patients within platinum intervals, between last chemotherapy including platinum therapy and randomisation. | | | |
| Units: Subjects | | | |
| 6-12 months | 159 | 169 | 328 |
| 12-24 months | 121 | 132 | 253 |
| >24 months | 110 | 90 | 200 |
| Missing | 7 | 1 | 8 |
| ECOG performance score | | | |
| Units: Subjects | | | |
| Normal activity | 202 | 203 | 405 |
| Symptomatic but ambulatory self-care | 181 | 182 | 363 |
| Ambulatory >50% of the time | 14 | 7 | 21 |
| Ambulatory 50% or less of time, need nursing care | 0 | 0 | 0 |
| Bedridden, may need hospitalization | 0 | 0 | 0 |
| Body surface area (BSA) | | | |
| Calculated based on weight and height of each patient. | | | |
| Units: BSA (m2) | | | |
| geometric mean | 1.8 | 1.8 | |
| standard deviation | ± 0.2 | ± 0.2 | - |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Paclical |
| Reporting group description: Patients received the study drug under investigation, Paclical , 250 mg/m2, intravenous infusion, followed by intravenous infusion of carboplatin, 5-6 AUC. | |
| Reporting group title | Taxol |
| Reporting group description: Patients received the control drug paclitaxel, Cremophor EL (Taxol), 175 mg/m2, intravenous infusion, followed by intravenous infusion of carboplatin, 5-6 AUC. | |
| Subject analysis set title | Intention-to-treat (ITT), Paclical arm |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Same as Reporting group population. The ITT consists of all patients randomised to the Paclical arm regardless whether they received any study drug or not. This population was used to check the robustness of the efficacy data analysed on the per-protocol populations. | |
| Subject analysis set title | Intention-to-treat (ITT), Taxol arm |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Same as Reporting group population. The ITT consists of all patients randomised to the Taxol arm regardless whether they received any study drug or not. This population was used to check the robustness of the efficacy data analysed on the per-protocol populations. | |
| Subject analysis set title | Per-protocol Paclical arm |
| Subject analysis set type | Per protocol |
| Subject analysis set description: The sub-set of the intention-to-treat (ITT) Paclical arm population who received 6 treatment cycles of Paclical and had no major violation. | |
| Subject analysis set title | Per-protocol Taxol arm |
| Subject analysis set type | Per protocol |
| Subject analysis set description: The sub-set of the intention-to-treat (ITT) Taxol arm population who received 6 treatment cycles of Taxol and had no major violation. | |
| Subject analysis set title | Safety population Paclical arm |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All patients in the Paclical arm who received at least one dose of study treatment. | |
| Subject analysis set title | Safety population Taxol arm |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All patients in the Taxol arm who received at least one dose of study treatment. | |

Primary: Progression free survival

| | |
|--|---------------------------|
| End point title | Progression free survival |
| End point description: | |
| End point type | Primary |
| End point timeframe: Time in months from date of randomisation to date of progression based on CT scan assessment as confirmed by the central lab, or time to date of Death of any cause. CT scan assessment according to RECIST version 1.0. | |

| End point values | Intention-to-treat (ITT), Paclical arm | Intention-to-treat (ITT), Taxol arm | Per-protocol Paclical arm | Per-protocol Taxol arm |
|----------------------------------|---|--|------------------------------|---------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 397 | 392 | 311 | 333 |
| Units: months | | | | |
| median (confidence interval 95%) | 10.2 (10.1 to 10.6) | 10 (9.7 to 10.2) | 10.3 (10.1 to 10.7) | 10.1 (9.9 to 10.2) |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Non-inferiority testing of primary endpoint - PFS |
| Comparison groups | Per-protocol Paclical arm v Per-protocol Taxol arm |
| Number of subjects included in analysis | 644 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[1] |
| P-value | = 0.094 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.86 |
| Confidence interval | |
| level | 95 % |
| sides | 1-sided |
| upper limit | 1.03 |

Notes:

[1] - Non-inferiority margin is 1.2. Non-inferiority is established if the upper limit of the one sided 95% confidence interval of the hazard ratio of the two compared groups is lower than 1.2.

| | |
|---|--|
| Statistical analysis title | Hazard ratio of PFS in ITT |
| Statistical analysis description: | |
| To investigate the robustness of PFS results assessed in the per-protocol population. | |
| Comparison groups | Intention-to-treat (ITT), Paclical arm v Intention-to-treat (ITT), Taxol arm |
| Number of subjects included in analysis | 789 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[2] |
| P-value | = 0.055 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 1-sided |
| upper limit | 1 |

Notes:

[2] - Cox proportion hazards models was used to estimate the hazard ratio between the two groups.

Secondary: Overall survival (OS)

| | |
|-----------------|-----------------------|
| End point title | Overall survival (OS) |
|-----------------|-----------------------|

End point description:

The long term follow-up of 3 years after the date of global end of study was to collect data for the OS analysis. The statistics of OS data was received 18 Oct 2016.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Overall survival (OS) is defined as the time between randomisation and date of death of any cause.

| End point values | Intention-to-treat (ITT), Paclical arm | Intention-to-treat (ITT), Taxol arm | Per-protocol Paclical arm | Per-protocol Taxol arm |
|----------------------------------|---|--|------------------------------|---------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 397 | 392 | 311 | 333 |
| Units: months | | | | |
| median (confidence interval 95%) | 23.8 (21.5 to 26.9) | 23.5 (21.2 to 26.2) | 25.7 (22.9 to 28.1) | 24.8 (21.7 to 27.1) |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Non-inferiority testing of secondary endpoint - OS |
| Comparison groups | Per-protocol Paclical arm v Per-protocol Taxol arm |
| Number of subjects included in analysis | 644 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[3] |
| P-value | = 0.62 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.95 |
| Confidence interval | |
| level | 95 % |
| sides | 1-sided |
| upper limit | 1.16 |

Notes:

[3] - Non-inferiority margin is 1.185. Non-inferiority of OS (i.e. reject the null hypothesis for OS) is established if the upper limit of the one-sided 95% confidence interval of the hazard ratio of the two treatment groups is lower than 1.185.

| | |
|--|--|
| Statistical analysis title | Hazard ratio of OS in ITT |
| Statistical analysis description: | |
| To investigate the robustness of OS results assessed in the per-protocol population. | |
| Comparison groups | Intention-to-treat (ITT), Taxol arm v Intention-to-treat (ITT), Paclical arm |

| | |
|---|------------------------|
| Number of subjects included in analysis | 789 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.851 ^[4] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.02 |
| Confidence interval | |
| level | 95 % |
| sides | 1-sided |
| upper limit | 1.22 |

Notes:

[4] - Cox proportion hazards models was used to estimate the hazard ratio between the two groups.

Secondary: Hypersensitivity reactions (HR) during treatment

| | |
|-----------------|--|
| End point title | Hypersensitivity reactions (HR) during treatment |
|-----------------|--|

End point description:

Number of patients with at least one hypersensitivity reaction, based on British Columbia Cancer Agency.

In the Statistical analysis plan amendment dated 8 May 2014 it was clarified that the objective to show superiority of the experimental treatment over the control treatment in terms of the incidence and severity of hypersensitivity reactions was discarded for the regulatory submission in Europe. Results from the interim analysis clearly showed that due to intense pre-medication before the infusion of Taxol, it was not possible to show superiority of the experimental treatment over the control treatment. A test for superiority was thus not performed.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Assessed during infusion of Paclical/Taxol/Carboplatin and directly after the respective infusion.

| End point values | Safety population Paclical arm | Safety population Taxol arm | | |
|--|-----------------------------------|--------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 391 | 391 | | |
| Units: Number of patients with HR | | | | |
| Patients with no HR | 331 | 342 | | |
| Patients with mild HR | 32 | 28 | | |
| Patients with moderate HR | 21 | 17 | | |
| Patients with severe HR | 7 | 4 | | |
| Patients with at least 1 HR related to paclitaxel | 20 | 26 | | |
| Patients with at least 1 HR related to carboplatin | 47 | 29 | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Test of difference in HR between study arms |
|----------------------------|---|

Statistical analysis description:

The incidence of HR is counted as number of patients with at least one HR reaction.

| | |
|---|--|
| Comparison groups | Safety population Taxol arm v Safety population Paclical arm |
| Number of subjects included in analysis | 782 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.255 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|--|
| Statistical analysis title | Incidence of HR related to paclitaxel |
| Comparison groups | Safety population Taxol arm v Safety population Paclical arm |
| Number of subjects included in analysis | 782 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[5] |
| P-value | = 0.3672 |
| Method | Cochran-Mantel-Haenszel |

Notes:

[5] - Test of the difference between groups in incidence of HR related to paclitaxel, i.e. either Paclical or Taxol.

| | |
|---|--|
| Statistical analysis title | Incidence of HR related to carboplatin |
| Comparison groups | Safety population Paclical arm v Safety population Taxol arm |
| Number of subjects included in analysis | 782 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[6] |
| P-value | = 0.03 |
| Method | Cochran-Mantel-Haenszel |

Notes:

[6] - Test of the difference between groups in incidence of HR related to carboplatin.

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Adverse event reporting started Day 1 Cycle 1 and ended when patient left the study.

Adverse event reporting additional description:

In the data-output for this study AEs were categorised as All AEs (non-serious AEs+ SAEs) and SAEs. Thus, non-serious adverse events (NSAE) can not be reported here. Due to how EudraCT works the number of patients with NSAEs has to be set = 0, even if there were non-serious adverse events in the study.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 12.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Safety Paclical arm |
|-----------------------|---------------------|

Reporting group description:

The safety population consists of all patients in the Paclical arm who received at least one dose of Paclical.

Date of death, due to any cause was an end-point in the study. Therefore, only deaths related to an adverse event is reported here, not deaths as a result of disease progression.

| | |
|-----------------------|------------------|
| Reporting group title | Safety Taxol arm |
|-----------------------|------------------|

Reporting group description:

The safety population consists of all patients in the Taxol arm who received at least one dose of Taxol. Date of death, due to any cause was an end-point in the study. Therefore, only deaths related to an adverse event is reported here, not deaths as a result of disease progression.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: In the data-output for this study AEs were categorised and presented as All AEs (non-serious AEs+ SAEs) and SAEs. Thus, there are no summaries available for non-serious adverse events as per specific AE term.

| Serious adverse events | Safety Paclical arm | Safety Taxol arm | |
|---|---------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 160 / 391 (40.92%) | 106 / 391 (27.11%) | |
| number of deaths (all causes) | 10 | 5 | |
| number of deaths resulting from adverse events | 10 | 5 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Paraneoplastic syndrome | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Vascular disorders | | | |
| Circulatory collapse | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 1 / 391 (0.26%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolism | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Phlebitis | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venous thrombosis | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 391 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Multi-organ failure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 391 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 391 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Immune system disorders | | | |
| Anaphylactic shock | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 1 / 391 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypersensitivity | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Female genital tract fistula | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 391 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Genital haemorrhage | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Respiratory, thoracic and mediastinal disorders | | | |
| Allergic respiratory symptom | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 391 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleurisy | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 391 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pulmonary artery thrombosis | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 2 / 391 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory disorder | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 391 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 391 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 391 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Soft tissue injury | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 391 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 391 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 1 / 391 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 391 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 391 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (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 | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coma | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Ischaemic stroke | | | |

| | | | |
|---|--------------------|-------------------|--|
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 391 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Status epilepticus | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Neutropenia febrile | | | |
| subjects affected / exposed | 13 / 391 (3.32%) | 6 / 391 (1.53%) | |
| occurrences causally related to treatment / all | 13 / 13 | 6 / 6 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Granulocytopenia | | | |
| subjects affected / exposed | 10 / 391 (2.56%) | 5 / 391 (1.28%) | |
| occurrences causally related to treatment / all | 16 / 16 | 7 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematotoxicity | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 20 / 391 (5.12%) | 7 / 391 (1.79%) | |
| occurrences causally related to treatment / all | 23 / 23 | 7 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 110 / 391 (28.13%) | 74 / 391 (18.93%) | |
| occurrences causally related to treatment / all | 210 / 210 | 113 / 113 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 2 / 391 (0.51%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 8 / 391 (2.05%) | 8 / 391 (2.05%) | |
| occurrences causally related to treatment / all | 9 / 9 | 8 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Anaemia | | | |
| subjects affected / exposed | 16 / 391 (4.09%) | 11 / 391 (2.81%) | |
| occurrences causally related to treatment / all | 18 / 18 | 12 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal strangulated hernia | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 391 (1.02%) | 1 / 391 (0.26%) | |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enteritis | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 391 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal functional disorder | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 1 / 391 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Periproctitis | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 391 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subileus | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 391 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 1 / 391 (0.26%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 391 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Rash generalised | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin discolouration | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (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 | | | |
| Azotaemia | | | |
| subjects affected / exposed | 2 / 391 (0.51%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | |
| Hydronephrosis | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 391 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteochondrosis | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Catheter site infection | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion site cellulitis | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 2 / 391 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 1 / 391 (0.26%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 1 / 1 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 1 / 391 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycemic hyperosmolar nonketotic syndrome | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 391 (0.26%) | 0 / 391 (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: 0 %

| Non-serious adverse events | Safety Paclical arm | Safety Taxol arm | |
|---|---------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 391 (0.00%) | 0 / 391 (0.00%) | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 05 November 2008 | <p>Protocol amendment of 5 Nov 2008 was implemented before any patient was randomized in the study. This amendment was only submitted to authorities and ethics committees in Sweden, Russia and Ukraine as the original study protocol was submitted only to these countries at the time of this amendment. For the other countries the texts in amendment 1 were included in the first study protocol submitted.</p> <p>The following items were the major changes, completely or partly in the protocol amendment dated 5 Nov, 2008:</p> <ul style="list-style-type: none">• A central reading of CT scans was introduced• The study committees were reduced from four to two• Inclusion criterion 1 and 3 were modified to better agree with clinical practise and to avoid ambiguity• The procedure of assessing hypersensitivity is clarified• The Adverse Event reporting period was changed to better capture AEs related to study treatment <p>All changes were made either in order to clarify the procedures of the study or to improve its conduct.</p> |
| 02 February 2010 | <p>The background for the protocol amendment of 2 Feb, 2010 was the need to prolong the follow up period to exceed to study period of 12 months as written in the original study protocol. The prolongation was decided to achieve enough events for the statistical power in the PFS analysis.</p> |
| 14 February 2011 | <p>The protocol is aimed for submission to EMA. However, the amendment of 14 Feb 2011 was written to facilitate a future submission for a market application to FDA. The main changes were the emphasis on evaluating PFS by using CT scan and the definition of overall survival as a secondary endpoint. The frequency of CT scans was increased during the follow-up period to increase the sensitivity in the evaluation of PFS. Apart from this, the changes to the conduct of the study were minor.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------------------|--|--------------|
| 15 February 2011 | The interruption in recruiting patients was due to manufacturing problems of Paclical 60 mg vials. | 17 May 2011 |

Notes:

Limitations and caveats

None reported