



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
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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
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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)
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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
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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
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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
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	12.0
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Reporting groups

Reporting group title	Safety Paclical arm
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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
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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