Clinical trial results:
A randomized, double-blind, placebo-controlled phase 2 study of paclitaxel in combination with reparixin compared to paclitaxel alone as front-line therapy for Metastatic Triple-Negative Breast Cancer (FRIDA).

Summary

EudraCT number	2014-004796-23
Trial protocol	BE CZ IT ES PL FR
Global end of trial date	23 March 2020

Results information

Result version number	v1 (current)
This version publication date	07 July 2022
First version publication date	07 July 2022

Trial information

Trial identification

Sponsor protocol code	REP0114

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02370238
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dompé Farmaceutici S.p.A.
Sponsor organisation address	Via Santa Lucia, 6, Milano, Italy, 20122
Public contact	Clinical Trial Transparency Manager, Dompé Farmaceutici S.p.A., 39 02 583831, clinops@pec.dompe.it
Scientific contact	Clinical Trial Transparency Manager, Dompé Farmaceutici S.p.A., 39 02 583831, clinops@pec.dompe.it

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	20 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 February 2019
Global end of trial reached?	Yes
Global end of trial date	23 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate Progression Free Survival (PFS), defined as the number of days between the date of randomization and the date of clinical disease progression (PD) according to RECIST criteria version 1.1, as assessed by Independent Radiology Review, or death for any cause, whichever occurs first, in patients with metastatic triple-negative breast cancer (TNBC) treated with the combination of paclitaxel and orally administered reparixin compared to paclitaxel alone.

Protection of trial subjects:

The study was conducted in full compliance with the principles of the "Declaration of Helsinki" and subsequent revisions, International Conference on Harmonisation (ICH) guidelines, and all of the applicable US Code of Federal Regulations (CFR), 21 CFR Part 50 & 312. In addition, this study adhered to all local regulatory requirements and requirements for data protection.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 July 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Czech Republic: 11
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Italy: 28
Country: Number of subjects enrolled	United States: 36
Worldwide total number of subjects	123
EEA total number of subjects	87

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)	90
From 65 to 84 years	33
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

195 patients were enrolled in the study; one was enrolled into the study and was a screen failure but was not counted in the analysis due to the fact that the screen failure page was not completed. Of the 194 enrolled patients, 123 were randomized and included in the ITT Population: 62 patients in Group 1 and 61 patients in Group 2.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Blinding implementation details:

Reparixin tablets and placebo tablets were packaged in white PVDC/PE//PVC/aluminum blisters in the form of patient kits and were numbered to maintain blinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1

Arm description:

Paclitaxel 80 mg/m2 intravenous (i.v.) (Days 1, 8, and 15 of 28-day cycle) + reparixin oral tablets 1200 mg three times a day (t.i.d.) continuing from Day 1 to Day 21.
Duration of Treatment: 28-day cycles of combination therapy reparixin oral tablets + paclitaxel intravenous weekly three weeks on and one week off until disease progression according to RECIST criteria version 1.1, withdrawal of consent or unacceptable toxicity, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Reparixin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1200 mg three times a day (t.i.d.) continuing from Day 1 to Day 21 of 28-day cycle.

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

Dosage and administration details:

80 mg/m2 intravenous (i.v.) (Days 1, 8, and 15 of 28-day cycle).

Arm title	Group 2

Arm description:

Paclitaxel 80 mg/m2 i.v. (Days 1, 8, and 15 of 28-day cycle) + placebo oral tablets 1200 mg t.i.d. continuing from Day 1 to Day 21.
Duration of Treatment: 28-day cycles of combination therapy placebo oral tablets + paclitaxel intravenous weekly three weeks on and one week off until PD according to RECIST criteria version 1.1, withdrawal of consent or unacceptable toxicity, whichever occurred first.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1200 mg three times a day (t.i.d.) continuing from Day 1 to Day 21 of 28-day cycle..

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

Dosage and administration details:

80 mg/m2 intravenous (i.v.) (Days 1, 8, and 15 of 28-day cycle)

Number of subjects in period 1	Group 1	Group 2
Started	62	61
Completed	15	16
Not completed	47	45
Consent withdrawn by subject	2	6
death	42	35
unknown	2	1
Lost to follow-up	1	3

Baseline characteristics

Reporting groups	
Reporting group title	Group 1
Reporting group description:	
Paclitaxel 80 mg/m2 intravenous (i.v.) (Days 1, 8, and 15 of 28-day cycle) + reparixin oral tablets 1200 mg three times a day (t.i.d.) continuing from Day 1 to Day 21. Duration of Treatment: 28-day cycles of combination therapy reparixin oral tablets + paclitaxel intravenous weekly three weeks on and one week off until disease progression according to RECIST criteria version 1.1, withdrawal of consent or unacceptable toxicity, whichever occurred first.	
Reporting group title	Group 2
Reporting group description:	
Paclitaxel 80 mg/m2 i.v. (Days 1, 8, and 15 of 28-day cycle) + placebo oral tablets 1200 mg t.i.d. continuing from Day 1 to Day 21. Duration of Treatment: 28-day cycles of combination therapy placebo oral tablets + paclitaxel intravenous weekly three weeks on and one week off until PD according to RECIST criteria version 1.1, withdrawal of consent or unacceptable toxicity, whichever occurred first.	

Reporting group values	Group 1	Group 2	Total
Number of subjects	62	61	123
Age categorical Units: Subjects			
Adults (18-64 years)	45	45	90
From 65-84 years	17	16	33
Gender categorical Units: Subjects			
Female	62	61	123

Subject analysis sets	
Subject analysis set title	Group 1 - ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The Intent-to-Treat (ITT) Population consisted of all patients who are randomized and was based upon the randomized treatment, regardless of the treatment actually received. Patients were in the ITT analysis whether or not they received study drug. The primary and secondary efficacy analyses were presented primarily for the ITT Population.	
Subject analysis set title	Group 2 - ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The Intent-to-Treat (ITT) Population consisted of all patients who are randomized and was based upon the randomized treatment, regardless of the treatment actually received. Patients were in the ITT analysis whether or not they received study drug. The primary and secondary efficacy analyses were presented primarily for the ITT Population.	
Subject analysis set title	Group 1 - Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Population consisted of all patients who had taken at least one dose of the study treatment and was based upon the treatment they actually received.	
Subject analysis set title	Group 2 - Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Population consisted of all patients who had taken at least one dose of the study treatment	

and was based upon the treatment they actually received.

Subject analysis set title	Group 1 - Response-Evaluable population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Response-Evaluable Population consisted of all patients who had completed at least one cycle of treatment and had a baseline assessment and have undergone at least one post-baseline disease assessment.

Subject analysis set title	Group 2 - Response-Evaluable population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Response-Evaluable Population consisted of all patients who had completed at least one cycle of treatment and had a baseline assessment and have undergone at least one post-baseline disease assessment.

Reporting group values	Group 1 - ITT population	Group 2 - ITT population	Group 1 - Safety population
Number of subjects	62	61	61
Age categorical Units: Subjects			
Adults (18-64 years)	45	45	44
From 65-84 years	17	16	17
Gender categorical Units: Subjects			
Female	62	61	61

Reporting group values	Group 2 - Safety population	Group 1 - Response-Evaluable population	Group 2 - Response-Evaluable population
Number of subjects	60	57	54
Age categorical Units: Subjects			
Adults (18-64 years)	44		
From 65-84 years	16		
Gender categorical Units: Subjects			
Female	60	57	54

End points

End points reporting groups

Reporting group title	Group 1

Reporting group description:

Paclitaxel 80 mg/m2 intravenous (i.v.) (Days 1, 8, and 15 of 28-day cycle) + reparixin oral tablets 1200 mg three times a day (t.i.d.) continuing from Day 1 to Day 21.
Duration of Treatment: 28-day cycles of combination therapy reparixin oral tablets + paclitaxel intravenous weekly three weeks on and one week off until disease progression according to RECIST criteria version 1.1, withdrawal of consent or unacceptable toxicity, whichever occurred first.

Reporting group title	Group 2

Reporting group description:

Paclitaxel 80 mg/m2 i.v. (Days 1, 8, and 15 of 28-day cycle) + placebo oral tablets 1200 mg t.i.d. continuing from Day 1 to Day 21.
Duration of Treatment: 28-day cycles of combination therapy placebo oral tablets + paclitaxel intravenous weekly three weeks on and one week off until PD according to RECIST criteria version 1.1, withdrawal of consent or unacceptable toxicity, whichever occurred first.

Subject analysis set title	Group 1 - ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intent-to-Treat (ITT) Population consisted of all patients who are randomized and was based upon the randomized treatment, regardless of the treatment actually received. Patients were in the ITT analysis whether or not they received study drug. The primary and secondary efficacy analyses were presented primarily for the ITT Population.

Subject analysis set title	Group 2 - ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intent-to-Treat (ITT) Population consisted of all patients who are randomized and was based upon the randomized treatment, regardless of the treatment actually received. Patients were in the ITT analysis whether or not they received study drug. The primary and secondary efficacy analyses were presented primarily for the ITT Population.

Subject analysis set title	Group 1 - Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Population consisted of all patients who had taken at least one dose of the study treatment and was based upon the treatment they actually received.

Subject analysis set title	Group 2 - Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Population consisted of all patients who had taken at least one dose of the study treatment and was based upon the treatment they actually received.

Subject analysis set title	Group 1 - Response-Evaluable population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Response-Evaluable Population consisted of all patients who had completed at least one cycle of treatment and had a baseline assessment and have undergone at least one post-baseline disease assessment.

Subject analysis set title	Group 2 - Response-Evaluable population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Response-Evaluable Population consisted of all patients who had completed at least one cycle of treatment and had a baseline assessment and have undergone at least one post-baseline disease assessment.

Primary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

PFS was defined as the time from randomization to first documentation of disease progression, according to RECIST criteria version 1.1, as assessed by Independent Radiology Review, or to death due to any cause, whichever occurred first.
Patients must have completed at least one course of treatment and performed at least one disease assessment to be considered evaluable for response.

End point type	Primary

End point timeframe:

Baseline up to every 8 weeks until disease progression or death, whichever occurs first.

End point values	Group 1 - ITT population	Group 2 - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	61		
Units: days				
median (inter-quartile range (Q1-Q3))	166 (62 to 292)	171 (105 to 393)		

Statistical analyses

Statistical analysis title	Group 1 vs Group 2
Comparison groups	Group 1 - ITT population v Group 2 - ITT population
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.589 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.81

Notes:

[1] - p-value based on a log-rank test stratified by randomized sub-populations, newly diagnosed metastatic patients and patients that had relapsed following a prior (neo)adjuvant chemotherapy regimen.

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS was defined as the time from randomization until death due to any cause.
For patients who did not die, time of death was censored at the date of last contact.
Patients must have completed at least one course of treatment and performed at least one disease assessment to be considered evaluable for response.

End point type	Secondary

End point timeframe:

Baseline until death due to any cause.

End point values	Group 1 - ITT population	Group 2 - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	61		
Units: days				
median (inter-quartile range (Q1-Q3))	483 (272 to 812)	531 (334 to 787)		

Statistical analyses

Statistical analysis title	Group 1 vs Group 2
Comparison groups	Group 1 - ITT population v Group 2 - ITT population
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.897 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.65

Notes:

[2] - Overall survival was summarized in the ITT Population using Kaplan-Meier curves and compared between treatment groups using a stratified log-rank test.
[3] - p-value based on a log-rank test stratified by randomized sub-populations, newly diagnosed metastatic patients and patients that had relapsed following a prior (neo)adjuvant chemotherapy regimen.

Secondary: Objective response rate (ORR)

End point title	Objective response rate (ORR)

End point description:

The ORR was defined as the percentage of patients achieving CR or PR in the Evaluable Population. The response rate was calculated from the independently reviewed assessment best response. In case of PR or CR, only confirmed cases were considered to be responses.
Complete Response (CR) = Disappearance of all target lesions;
Partial Response (PR) = >=30% decrease in the sum of the longest diameter of target lesions;
Overall Response (OR) = CR + PR.
Patients with unknown or missing response, including response of “not all evaluated” or “unable to determine”, were treated as non-responders; i.e., they were included in the denominator when calculating the percentages.
Patients must have completed at least one course of treatment and performed at least one disease assessment to be considered evaluable for response.

End point type	Secondary

End point timeframe:

Baseline up to every 8 weeks until documented disease progression.

End point values	Group 1 - Response-Evaluable population	Group 2 - Response-Evaluable population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	57	54		
Units: percent				
number (confidence interval 95%)	28.1 (17.0 to 41.5)	25.9 (15.0 to 39.7)		

Statistical analyses

Statistical analysis title	Group 1 vs Group 2
Comparison groups	Group 2 - Response-Evaluable population v Group 1 - Response-Evaluable population
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.667 [4]
Method	Zelen's test
Parameter estimate	Odds ratio (OR)
Point estimate	1.262
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4909
upper limit	3.963

Notes:

[4] - P-value is based on Zelen’s test for homogeneity of the odds ratios.

Secondary: Median progression-free survival (mPFS)

End point title	Median progression-free survival (mPFS)

End point description:

PFS was defined as the time from randomization to first documentation of disease progression, according to RECIST criteria version 1.1, as assessed by Independent Radiology Review, or to death due to any cause, whichever occurred first. For each treatment group, the Kaplan-Meier estimates for the median PFS time, the first and third quartiles were presented, along with approximate 95% confidence intervals if there were a sufficient number of progressions or deaths.

Patients must have completed at least one course of treatment and performed at least one disease assessment to be considered evaluable for response.

End point type	Secondary

End point timeframe:

At screening and every 8 weeks

End point values	Group 1 - ITT population	Group 2 - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	61		
Units: days				
median (confidence interval 95%)	166 (109 to 218)	171 (117 to 226)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of overall response (DOR)

End point title	Duration of overall response (DOR)

End point description:

Duration of overall response (DOR) in days for the investigator assessments is measured from the time response criteria are first met for CR or PR (whichever is first recorded on the "Disease Response" page on the CRF) until either death or the first date that recurrent or PD is objectively documented (on the "Disease Response" page on the CRF or the Follow-Up Disease Evaluation page indicates disease progression and there is supporting information in the Disease Status pages) per RECIST version 1.1.
If a patient is lost to follow-up with no documentation of PD, DOR was censored at the last evaluable tumor assessment. DOR was calculated only for responding patients (PR or CR) as recorded on the CRF page "Disease Response" based upon the RECIST version 1.1.
Duration of overall response was calculated only for patients with confirmed CR or PR.
Patients must have completed at least 1 cycle and performed at least 1 disease assessment to be considered evaluable for response.

End point type	Secondary

End point timeframe:

Baseline up to every 8 weeks until documented disease progression.

End point values	Group 1 - Response-Evaluable population	Group 2 - Response-Evaluable population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	57	54		
Units: days				
median (inter-quartile range (Q1-Q3))	293.0 (119.0 to 505.0)	172.0 (115.0 to 443.0)		

Statistical analyses

Statistical analysis title	Group 1 vs Group 2
Comparison groups	Group 1 - Response-Evaluable population v Group 2 - Response-Evaluable population

Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.767 [5]
Method	Logrank

Notes:

[5] - For the All Patients group, p-value was based on a log-rank test stratified by actual sub-populations, newly diagnosed metastatic patients and patients that had relapsed following a prior (neo) adjuvant chemotherapy regimen.

Secondary: Number of TEAEs, overall and by grade

End point title	Number of TEAEs, overall and by grade

End point description:

Treatment-emergent adverse events (TEAEs) are those which first occur or increase in severity or relationship to study drug after the first dose of study drug and before 30 days after the last dose of study treatment, reparixin/placebo. In the case of missing or partial dates, any AE that could have started on or after first dose date was assumed to be treatment-emergent. In the case of missing or partial dates, imputed dates (see section 10.1 AE date imputation) were used.

End point type	Secondary

End point timeframe:

Throughout the study, until off-treatment visit (performed 14 to 28 days following the last dose of study drug), up to 985 days.

End point values	Group 1 - Safety population	Group 2 - Safety population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61	60		
Units: number of events				
Overall	865	730		
Grade 1 (Mild)	563	478		
Grade 2 (Moderate)	230	194		
Grade 3 (Severe)	67	50		
Grade 4 (Life-threatening or disabling)	2	4		
Grade 5 (Death)	3	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Serious AEs and fatal AEs

End point title	Serious AEs and fatal AEs

End point description:

A serious adverse event (SAE) in human drug trials is defined as any untoward medical occurrence that at any dose
1 - results in death, (fatal)
2 - is life-threatening
3 - requires inpatient hospitalization or causes prolongation of existing hospitalization
4 - results in persistent or significant disability/incapacity,
5 - may have caused a congenital anomaly/birth defect, or

6 - requires intervention to prevent permanent impairment or damage.

End point type	Secondary

End point timeframe:

Throughout the study, until off-treatment visit.

End point values	Group 1 - Safety population	Group 2 - Safety population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61	60		
Units: number of events				
serious AE	31	25		
fatal AE	3	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Best overall response (BOR)

End point title	Best overall response (BOR)

End point description:

BOR is defined as the best response among all overall responses (in the order complete response [CR], partial response [PR], stable disease [SD], and progressive disease [PD]) recorded as an independent review response from the start of reparixin or placebo until disease progression/recurrence or end of treatment, or death, whichever comes first. The status of BOR of PR or CR needs to be confirmed by repeat tumor assessment within no less than 4 weeks according to RECIST
version 1.1. If the status of CR or PR cannot be confirmed by repeat tumor assessment, the best overall response of unconfirmed CR and PR will be PR and SD, respectively.
Patients must have completed at least 1 cycle and performed at least 1 disease assessment to be considered evaluable for response.

End point type	Secondary

End point timeframe:

From the start of treatment, every 8 weeks.

End point values	Group 1 - Response-Evaluable population	Group 2 - Response-Evaluable population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	57[6]	54		
Units: participants				
CR	1	0		
PR	15	14		
SD	16	23		
PD	22	14		
NE	3	3		
Unable to determine	0	0		

Unknown/not done	0	0		

Notes:

[6] - 1 patinet wasn't assessed

Statistical analyses

Statistical analysis title	Group 1 vs group 2
Comparison groups	Group 2 - Response-Evaluable population v Group 1 - Response-Evaluable population
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.667 [7]
Method	Zelen's test
Parameter estimate	Odds ratio (OR)
Point estimate	1.101
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.437
upper limit	2.79

Notes:

[7] - P-value was based on Zelen’s test for homogeneity of the odds ratios

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout the study, until off-treatment visit (performed 14 to 28 days following the last dose of study drug), up to 985 days.

Adverse event reporting additional description:

Incidence and profile of the TEAEs during the study are typical and expected for patients on chemotherapy, and was similar in both groups.
The most common TEAEs in group 1 were nausea, alopecia, anemia, asthenia, and diarrhea. The most common TEAEs in group 2 were fatigue, nausea, alopecia, diarrhea, and asthenia. Here only these are reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Group 1 - Safety population

Reporting group description:

The Safety Population consisted of all patients who had taken at least one dose of the study treatment and was based upon the treatment they actually received.

Reporting group title	Group 2- Safety population

Reporting group description:

The Safety Population consisted of all patients who had taken at least one dose of the study treatment and was based upon the treatment they actually received.

Serious adverse events	Group 1 - Safety population	Group 2- Safety population	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 61 (21.31%)	12 / 60 (20.00%)	
number of deaths (all causes)	42	35	
number of deaths resulting from adverse events	3	4	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to central nervous system			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Deep vein thrombosis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (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	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	2 / 61 (3.28%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Condition aggravated			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 61 (1.64%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Pyrexia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Disease progression			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 61 (3.28%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
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	0 / 61 (0.00%)	3 / 60 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (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			
Ankle fracture			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Myelopathy			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haedache			

subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 61 (1.64%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Erysipelas			

subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (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	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Group 1 - Safety population	Group 2- Safety population	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 61 (98.36%)	57 / 60 (95.00%)	
Blood and lymphatic system disorders			
Anaemia	Additional description: For each system organ class and preferred term, patients are counted only once, even if they experienced multiple events in that system organ class or preferred term.		
subjects affected / exposed	18 / 61 (29.51%)	8 / 60 (13.33%)	
occurrences (all)	18	8	
General disorders and administration site conditions			
Asthenia	Additional description: For each system organ class and preferred term, patients are counted only once, even if they experienced multiple events in that system organ class or preferred term.		
subjects affected / exposed	16 / 61 (26.23%)	13 / 60 (21.67%)	
occurrences (all)	16	13	
Fatigue	Additional description: For each system organ class and preferred term, patients are counted only once, even if they experienced multiple events in that system organ class or preferred term.		
subjects affected / exposed	11 / 61 (18.03%)	26 / 60 (43.33%)	
occurrences (all)	11	26	
Gastrointestinal disorders			
Diarrhoea	Additional description: For each system organ class and preferred term, patients are counted only once, even if they experienced multiple events in that system organ class or preferred term.		
subjects affected / exposed	16 / 61 (26.23%)	15 / 60 (25.00%)	
occurrences (all)	16	15	
Nausea	Additional description: For each system organ class and preferred term, patients are counted only once, even if they experienced multiple events in that system organ class or preferred term.		
subjects affected / exposed	23 / 61 (37.70%)	22 / 60 (36.67%)	
occurrences (all)	23	22	
Skin and subcutaneous tissue disorders			

Alopecia	Additional description: For each system organ class and preferred term, patients are counted only once, even if they experienced multiple events in that system organ class or preferred term.		
subjects affected / exposed	21 / 61 (34.43%)	21 / 60 (35.00%)	
occurrences (all)	21	21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 July 2015	Primary endpoint, ECG at pre-study, concomitant therapies, methods of birth control, paclitaxel dose modifications and delays
16 September 2016	Primary endpoint and inclusion of newly diagnosed metastatic patients.
01 December 2017	Patients' follow up.
09 April 2019	Patients' follow up.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No limitations or caveats are applicable to this summary of the results.

Notes: