



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/m ² 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/m ² 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/m ² 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/m ² 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) = $\geq 30\%$ 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: | |
| <p>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.</p> | |
| <p>Patients must have completed at least one course of treatment and performed at least one disease assessment to be considered evaluable for response.</p> | |
| 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)

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|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| End point title | Duration of overall response (DOR) |
| End point description: | |
| <p>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.</p> <p>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.</p> | |
| 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 patient 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: