



Clinical trial results:

Efficacy of Gemcitabine With Pazopanib as Second Line Treatment in Patient With Metastatic or Relapsed Uterine (LMS03)

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2011-001308-36 |
| Trial protocol | FR |
| Global end of trial date | 30 March 2018 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 23 April 2021 |
| First version publication date | 23 April 2021 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | SARCOME 11 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01442662 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | UNICANCER |
| Sponsor organisation address | 101 RUE DE TOLBIAC, PARIS, France, 75013 |
| Public contact | N. AIT RAHMOUNE, UNICANCER, 33 (0) 1 71 93 674 04, n.ait-rahmoune@unicancer.fr |
| Scientific contact | N. AIT RAHMOUNE, UNICANCER, 33 (0) 1 71 93 6740, n.ait-rahmoune@unicancer.fr |

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 | 31 July 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 March 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 March 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of the combination of gemcitabine and pazopanib for treating patients with leiomyosarcoma (uterine or soft tissue) either metastatic and/or inoperable at relapse after first-line anthracycline-based therapy, according to the 9-month PFS rate.

Protection of trial subjects:

In order to ensure the protection of the rights, safety and well-being of trial subjects, this clinical trial was performed in compliance with the principles laid down in the declaration of Helsinki, good Clinical Practice and European regulation.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 20 October 2011 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy |
| Long term follow-up duration | 3 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | France: 106 |
| Worldwide total number of subjects | 106 |
| EEA total number of subjects | 106 |

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) | 72 |
| From 65 to 84 years | 34 |

| | |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

Subject disposition

Recruitment

Recruitment details:

Study Initiation Date: 20-Oct-2011

Last patient included: 12-May-2016

Pre-assignment

Screening details:

Patients with histologically confirmed leiomyosarcoma (uterine or soft tissue) either metastatic and/or inoperable at relapse after first-line anthracycline-based therapy.

Patients having received adjuvant therapy less than one year before relapse are considered as having received first-line therapy. Furthermore, if the maximum anthracycline do

Period 1

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

Arms

| | |
|-----------|---------------|
| Arm title | Treatment arm |
|-----------|---------------|

Arm description:

Patients received:

- Gemcitabine (1000 mg/m²/day) was to be administered intravenously on D1 and D8 of a 21-day cycle. The gemcitabine solution was perfused at a rate of 10 mg/m²/min. Gemcitabine treatment was planned for a maximum of 8 cycles.

- Oral pazopanib was taken daily at a dose of 800 mg/day (4 x 200-mg tablets). If after 6-8 weeks of being treated with pazopanib plus gemcitabine, the tumour response was stable disease (SD), partial (PR) or complete response (CR). The patients could have been treated with pazopanib monotherapy until disease progression, limiting toxicity, or patient's refusal to continue treatment.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | GEMCITABIN |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Gemcitabine (1000 mg/m²/day) was to be administered intravenously on D1 and D8 of a 21-day cycle. The gemcitabine solution was perfused at a rate of 10 mg/m²/min. Gemcitabine treatment was planned for a maximum of 8 cycles.

| | |
|--|-----------|
| Investigational medicinal product name | PAZOPANIB |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Oral pazopanib was taken daily at a dose of 800 mg/day (4 x 200-mg tablets). If after 6-8 weeks of being treated with pazopanib plus gemcitabine, the tumour response was stable disease (SD), partial (PR) or complete response (CR). The patients could have been treated with pazopanib monotherapy until disease progression, limiting toxicity, or patient's refusal to continue treatment.

| Number of subjects in period 1 ^[1] | Treatment arm |
|--|---------------|
| | |
| Started | 105 |
| Completed | 105 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 105 patients were included and treated in this study

Baseline characteristics

Reporting groups

Reporting group title

Overall trial

Reporting group description: -

| Reporting group values | Overall trial | Total | |
|---|---------------|-------|--|
| Number of subjects | 105 | 105 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 71 | 71 | |
| From 65-84 years | 34 | 34 | |
| 85 years and over | 0 | 0 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 90 | 90 | |
| Male | 15 | 15 | |

End points

End points reporting groups

| Reporting group title | Treatment arm |
|--|---------------|
| Reporting group description: | |
| Patients received: | |
| - Gemcitabine (1000 mg/m ² /day) was to be administered intravenously on D1 and D8 of a 21-day cycle. The gemcitabine solution was perfused at a rate of 10 mg/m ² /min. Gemcitabine treatment was planned for a maximum of 8 cycles. | |
| - Oral pazopanib was taken daily at a dose of 800 mg/day (4 x 200-mg tablets). If after 6-8 weeks of being treated with pazopanib plus gemcitabine, the tumour response was stable disease (SD), partial (PR) or complete response (CR). The patients could have been treated with pazopanib monotherapy until disease progression, limiting toxicity, or patient's refusal to continue treatment. | |

Primary: Primary endpoint (9month PFS)

| End point title | Primary endpoint (9month PFS) ^[1] |
|--|--|
| End point description: | |
| To assess the efficacy of the combination of gemcitabine and pazopanib for treating patients with leiomyosarcoma (uterine or soft tissue) either metastatic and/or inoperable at relapse after firstline anthracycline-based therapy, according to the 9-month PFS rate. | |
| End point type | Primary |
| End point timeframe: | |
| 9 month | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Efficacy endpoints were reported as rates with 95% CIs. Kaplan-Meier analyses were used for the time-to-event outcomes and Kaplan-Meier plots were

| End point values | Treatment arm | | | |
|--|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 105 | | | |
| Units: percent | | | | |
| arithmetic mean (confidence interval 5%) | 32.1 (23.1 to 41.4) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety data were collected for each cycle of the gemcitabine-pazopanib combination and every 6 weeks for pazopanib monotherapy.

Serious adverse events were collected since patient's consent until 30 days after last study treatment administration

Adverse event reporting additional description:

For non serious adverse events only name of event must be take into account.

The number of subjects affected and the number of occurrence are not available and will be always noted "1"

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 15 |

Reporting groups

| | |
|-----------------------|----------------------|
| Reporting group title | All patients treated |
|-----------------------|----------------------|

Reporting group description: -

| Serious adverse events | All patients treated | | |
|---|----------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 71 / 105 (67.62%) | | |
| number of deaths (all causes) | 105 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumor pain | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Ischemic stroke | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient ischemic attacks | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Metastasectomy | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Fever | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oedema lower limb | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thorax pain | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnea | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnea exacerbated | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Interstitial pneumonitis | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 8 / 105 (7.62%) | | |
| occurrences causally related to treatment / all | 8 / 9 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SGPT increased | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transaminases increased | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiomyopathy secondary | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Left ventricular dysfunction | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocarditis | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Diplopia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Headache | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anemia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bicytopenia | | | |
| subjects affected / exposed | 5 / 105 (4.76%) | | |
| occurrences causally related to treatment / all | 5 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile aplasia | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lymphopenia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 33 / 105 (31.43%) | | |
| occurrences causally related to treatment / all | 44 / 44 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytosis | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombopenia | | | |
| subjects affected / exposed | 15 / 105 (14.29%) | | |
| occurrences causally related to treatment / all | 15 / 15 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ascites | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sigmoiditis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholangiolitis | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic enzymes increased | | | |
| subjects affected / exposed | 5 / 105 (4.76%) | | |
| occurrences causally related to treatment / all | 5 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic insufficiency | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Skin eruption | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Acute renal insufficiency | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Neutropenic infection | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| | | | |
|---|----------------------|--|--|
| Non-serious adverse events | All patients treated | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 34 / 105 (32.38%) | | |
| Vascular disorders | | | |
| Transient ischemic attack | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Haemorrhage | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Other vascular toxicities | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |

| | | | |
|---|-----------------|--|--|
| Anorexia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Weight loss | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Fatigue/asthenia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Fever | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Oedema | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Thyroid gland perturbation | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Other general toxicities | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchospasms | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Interstitial pneumopathy | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Other pulmonary and upper air tract toxicities | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Investigations | | | |

| | | | |
|---|-----------------|--|--|
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Proteinuria | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Hyperuricemia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Hyponatremia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Other biological investigation toxicities | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Cardiac disorders | | | |
| Decrease in LVEF | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Cardiac ischemia/heart attack/angina | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Temporary ECG modifications | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| QTc prolongation | | | |

| | | | |
|--------------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Torsade de pointes | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Other cardiac toxicities | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Anxiety/depression | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Neurosensory problems | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Neuromotor problems | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Other neurological toxicities | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Blood and lymphatic system disorders | | | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Neutrophil count decreased | | | |

| | | | |
|---------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Constipation | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Other haematological toxicities | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Ear and labyrinth disorders | | | |
| Loss of hearing | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Other auditive toxicities | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Eye disorders | | | |
| Visual problems | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Other ocular toxicities | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Dyspepsia | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Mucositis/stomatitis | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Other digestive toxicities | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Hepatobiliary disorders | | | |
| Elevated ASAT/ALAT | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Elevated bilirubin | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Elevated phosphatase alkaline | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Other hepatobiliary toxicities | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Depigmentation of the hair/skin | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences (all) | 1 | | |
| Skin eruptions/rash | | | |

| | | | |
|---|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 105 (0.95%) 1 | | |
| Hand and foot syndrome subjects affected / exposed occurrences (all) | 1 / 105 (0.95%) 1 | | |
| Other skin/hair toxicities subjects affected / exposed occurrences (all) | 1 / 105 (0.95%) 1 | | |
| Renal and urinary disorders Kidney failure subjects affected / exposed occurrences (all) | 1 / 105 (0.95%) 1 | | |
| Elevation of creatinine level subjects affected / exposed occurrences (all) | 1 / 105 (0.95%) 1 | | |
| Other renal toxicities subjects affected / exposed occurrences (all) | 1 / 105 (0.95%) 1 | | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 1 / 105 (0.95%) 1 | | |
| Myalgia subjects affected / exposed occurrences (all) | 1 / 105 (0.95%) 1 | | |
| Other musculo-skeletal toxicities subjects affected / exposed occurrences (all) | 1 / 105 (0.95%) 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 25 October 2011 | Precision concerning one inclusion criteria, information concerning dose adptation and precision concerning exams required by the protocol |
| 12 December 2011 | New name of the sponsor |
| 12 July 2012 | Submission of the new investigator brochure |
| 26 March 2013 | Modification of protocol in order to take in account new requirement concerning liver tests |
| 04 July 2014 | Protocole updated |
| 14 January 2015 | Protocol updated |
| 02 February 2016 | Submission of the new investigator's brichure and protocole was updated |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------------------|---|--------------|
| 19 December 2013 | After information of safety concerning severe liver toxicity observed in another clinical trial with the same study products, it was decided to interrupt inclusion. After evaluation of this event, the relation with the study treatment was not confirmed. It was decided to continue inclusion. | - |

Notes:

Limitations and caveats

None reported