



Clinical trial results:

Phase IIA Exploratory Study of Oral Milciclib Maleate in Patients with Unresectable or Metastatic Hepatocellular Carcinoma

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2017-000144-18 |
| Trial protocol | GR IT |
| Global end of trial date | 20 June 2019 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 05 July 2020 |
| First version publication date | 05 July 2020 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | CDKO-125a-010 |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | ISRCTN000000000 |
| ClinicalTrials.gov id (NCT number) | NCT000000000 |
| WHO universal trial number (UTN) | U0000-0000-0000 |
| Other trial identifiers | NA: NA |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Tiziana Life Sciences Plc |
| Sponsor organisation address | 55 Park Lane, London, United Kingdom, W1k 1NA |
| Public contact | Project Management, CLIOSS S.r.l., 0039 3480840579, monica.miani@closs.com |
| Scientific contact | Project Management, CLIOSS S.r.l., 0039 3480840579, monica.miani@closs.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 20 June 2019 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 20 June 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety profile and tolerability of repeated administrations of milciclib in Child-Pugh "A" unresectable hepatocellular carcinoma (HCC) patients who failed or were not eligible for sorafenib or who actively refused it (presenting as naïve, progressing, recurrent or metastatic disease).
There was no primary efficacy endpoint in this study.

Protection of trial subjects:

The study was conducted in accordance with the the principles of the Declaration of Helsinki and Good Clinical Practice.

Patients were instructed on procedures in case of accidental opening of capsules and inhalation, skin, or eye contact with a cytotoxic product (such as milciclib).

Dose modifications required due to drug-related toxicity were detailed in the study protocol.

Evaluation of safety data was performed by an Independent Data Monitoring Committee (IDMC) as soon as the 10th treated patient had completed as per protocol the first cycle of treatment. The IDMC had the power to recommend early termination of the study in case of safety concerns.

Background therapy:

No background therapy was specified.

All patients had previously failed sorafenib treatment, were intolerant of sorafenib, or actively refused treatment with sorafenib.

Second line therapy with regorafenib discontinued for intolerance was allowed if lasting < 14 days.

Evidence for comparator:

This was a single-arm study with no comparator.

| | |
|---|-------------|
| Actual start date of recruitment | 02 May 2017 |
| 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 | Greece: 5 |
| Country: Number of subjects enrolled | Italy: 19 |
| Country: Number of subjects enrolled | Israel: 7 |
| Worldwide total number of subjects | 31 |
| EEA total number of subjects | 24 |

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) | 9 |
| From 65 to 84 years | 22 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Patients were recruited between 14 July 2017 and 29 November 2018.

Pre-assignment

Screening details:

Patients were screened prior to study entry, up to 2 weeks before study start, to ensure eligibility criteria were met.

Period 1

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

Arms

| | |
|-----------|-----------|
| Arm title | Milciclib |
|-----------|-----------|

Arm description:

This was a single-arm study. All patients started treatment on the same dose of milciclib.

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Milciclib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

100 mg/day once a day for 4-day on/3-day off every week for 4 consecutive weeks. This 4-week dosing period constituted a full treatment cycle. Each patient was to receive three full cycles (12-weeks total). Milciclib was administered on Days 1 to 4, Days 8 to 11, Days 15 to 18, Day 22 to Day 25 of each cycle.

| Number of subjects in period 1 | Milciclib |
|--------------------------------|-----------|
| Started | 31 |
| Treated | 31 |
| Completed | 13 |
| Not completed | 18 |
| Adverse event, serious fatal | 3 |
| Physician decision | 1 |
| New anticancer therapy | 5 |
| Consent withdrawn by subject | 2 |
| Lost to follow-up | 7 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Milciclib |
|-----------------------|-----------|

Reporting group description:

This was a single-arm study. All patients started treatment on the same dose of milciclib.

| Reporting group values | Milciclib | Total | |
|--|-----------|-------|--|
| Number of subjects | 31 | 31 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | | 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) | | 0 | |
| From 65-84 years | | 0 | |
| 85 years and over | | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 67.5 | | |
| standard deviation | ± 7.24 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 4 | 4 | |
| Male | 27 | 27 | |

End points

End points reporting groups

| | |
|---|--------------------|
| Reporting group title | Milciclib |
| Reporting group description: This was a single-arm study. All patients started treatment on the same dose of milciclib. | |
| Subject analysis set title | Evaluable patients |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Treated patients with evaluable tumour response data were included in the evaluable set. | |
| Subject analysis set title | Pharmacokinetics |
| Subject analysis set type | Full analysis |
| Subject analysis set description: All patients who participated in the pharmacokinetic phase of the study. | |

Primary: Objective response rate

| | |
|---|--|
| End point title | Objective response rate ^[1] |
| End point description: Objective Response Rate (ORR), i.e., confirmed complete response (CR) + confirmed partial response (PR) (based on independent central review). The objective tumor assessment was made according to the modified Response Evaluation Criteria In Solid Tumors (mRECIST) criteria for hepatocellular carcinomas (HCC). Conventional RECIST 1.1 was also assessed. ORR was assessed locally and confirmed by an Independent Central Review. | |
| End point type | Primary |
| End point timeframe: From baseline to end of participation in the trial. | |

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: Note: all efficacy endpoints were defined as secondary endpoints in this study, which had a primary objective to evaluate the safety profile of milciclib. However, for the purpose of uploading into EudraCT, one endpoint had to be defined as primary. There is no statistical analysis of this 'primary' endpoint in this single-arm study.

| End point values | Evaluable patients | | | |
|-----------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | | | | |
| Units: subjects | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical benefit rate

| | |
|---|-----------------------|
| End point title | Clinical benefit rate |
| End point description: Clinical benefit rate (CBR), calculated as the proportion of evaluable patients who have achieved (based on independent central review), as best overall response, confirmed complete response (CR), confirmed partial response (PR), or stable disease (SD) based on mRECIST tumor assessment out of the total number of evaluable patients. | |

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From baseline to end of participation in the trial. | |

| | | | | |
|-----------------------------|----------------------|--|--|--|
| End point values | Evaluable patients | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | | | | |
| Units: subjects | 17 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

| | |
|---|---------------------------|
| End point title | Progression-free survival |
| End point description: | |
| Progression-free survival (PFS) evaluated since study treatment start to progression, based on mRECIST tumor assessment, or death for any causes. | |
| End point type | Secondary |
| End point timeframe: | |
| From baseline to end of participation in the trial. | |

| | | | | |
|----------------------------------|------------------|--|--|--|
| End point values | Milciclib | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 31 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.9 (1.5 to 6.7) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression

| | |
|--|---------------------|
| End point title | Time to progression |
| End point description: | |
| Time to progression (TTP) evaluated since study treatment start to progression, based on mRECIST tumour assessment or death due to disease progression in the absence of previous documented PD. | |
| End point type | Secondary |
| End point timeframe: | |
| From baseline to end of participation in the trial. | |

| End point values | Milciclib | Evaluable patients | | |
|----------------------------------|------------------|----------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 31 | 28 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.9 (1.5 to 6.7) | 5.9 (1.5 to 6.7) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of evaluable patients known to be alive and progression free at ≥3 months

| | |
|-----------------|--|
| End point title | Proportion of evaluable patients known to be alive and progression free at ≥3 months |
|-----------------|--|

End point description:

Proportion of evaluable patients known to be alive and progression free based on mRECIST tumor assessment at ≥3 months since study treatment start out of the total number of evaluable patients (TTP-3 months).

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

End point timeframe:

From baseline to end of participation in the trial.

| End point values | Milciclib | Evaluable patients | | |
|----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 31 | 28 | | |
| Units: Percent | | | | |
| number (confidence interval 95%) | 45.2 (27.32 to 63.97) | 50.0 (30.65 to 69.35) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of evaluable patients known to be alive and progression free at ≥6 months

| | |
|-----------------|--|
| End point title | Proportion of evaluable patients known to be alive and progression free at ≥6 months |
|-----------------|--|

End point description:

Proportion of evaluable patients known to be alive and progression free based on mRECIST tumor assessment at ≥ 6 months since study treatment start out of the total number of evaluable patients

(TTP-6 months).

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From baseline to end of participation in the trial. | |

| End point values | Milciclib | Evaluable patients | | |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 31 | 28 | | |
| Units: Subjects | | | | |
| number (confidence interval 95%) | 19.4 (7.45 to 37.47) | 21.4 (8.30 to 40.95) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Milciclib Cycle-1, Day 4: Cmax

| | |
|---|--------------------------------|
| End point title | Milciclib Cycle-1, Day 4: Cmax |
| End point description: | |
| Maximum observed concentration (μM). | |
| End point type | Secondary |
| End point timeframe: | |
| Cycle-1, Day 4 | |

| End point values | Pharmacokinetics | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | | | | |
| Units: μM | | | | |
| arithmetic mean (standard deviation) | 0.527 (\pm 0.130) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Milciclib Cycle-1, Day 4: Tmax

| | |
|------------------------------|--------------------------------|
| End point title | Milciclib Cycle-1, Day 4: Tmax |
| End point description: | |
| The time take to reach Cmax. | |

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Cycle-1, Day 4 | |

| | | | | |
|---------------------------------------|----------------------|--|--|--|
| End point values | Pharmacokinetic CS | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | | | | |
| Units: hours | | | | |
| median (inter-quartile range (Q1-Q3)) | 2 (1 to 6) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Milciclib Cycle-1, Day 4: AUC24

| | |
|---|---------------------------------|
| End point title | Milciclib Cycle-1, Day 4: AUC24 |
| End point description: | |
| Area under the curve from time zero to 24 h after study drug administration (h*µM). | |
| End point type | Secondary |
| End point timeframe: | |
| Cycle-1, Day 4 | |

| | | | | |
|--------------------------------------|----------------------|--|--|--|
| End point values | Pharmacokinetic CS | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | | | | |
| Units: µM hours | | | | |
| arithmetic mean (standard deviation) | 9.31 (± 2.39) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Milciclib Cycle-1, Day 4: half-life

| | |
|---|-------------------------------------|
| End point title | Milciclib Cycle-1, Day 4: half-life |
| End point description: | |
| The time taken for the plasma concentration to fall by half its original value. | |
| End point type | Secondary |
| End point timeframe: | |
| Cycle-1, Day 4 | |

| End point values | Pharmacokinetics | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | | | | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | 34.8 (± 10.6) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Milciclib Cycle-1, Day 25: Cmax

| | |
|--------------------------------------|---------------------------------|
| End point title | Milciclib Cycle-1, Day 25: Cmax |
| End point description: | |
| Maximum observed concentration (µM). | |
| End point type | Secondary |
| End point timeframe: | |
| Cycle-1, Day 25 | |

| End point values | Pharmacokinetics | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | | | | |
| Units: µM | | | | |
| arithmetic mean (standard deviation) | 0.731 (± 0.185) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Milciclib Cycle-1, Day 25: Tmax

| | |
|------------------------------|---------------------------------|
| End point title | Milciclib Cycle-1, Day 25: Tmax |
| End point description: | |
| The time take to reach Cmax. | |
| End point type | Secondary |
| End point timeframe: | |
| Cycle-1, Day 25 | |

| End point values | Pharmacokinetics | | | |
|---------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | | | | |
| Units: hours | | | | |
| median (inter-quartile range (Q1-Q3)) | 2.42 (2 to 4) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Milciclib Cycle-1, Day 25: AUC24

| | |
|---|----------------------------------|
| End point title | Milciclib Cycle-1, Day 25: AUC24 |
| End point description: Area under the curve from time zero to 24 h after study drug administration (h*µM). | |
| End point type | Secondary |
| End point timeframe: Cycle-1, Day 25 | |

| End point values | Pharmacokinetics | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | | | | |
| Units: µM hours | | | | |
| arithmetic mean (standard deviation) | 12.4 (± 4.28) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Milciclib Cycle-1, Day 25: half-life

| | |
|---|--------------------------------------|
| End point title | Milciclib Cycle-1, Day 25: half-life |
| End point description: The time taken for the plasma concentration to fall by half its original value. | |
| End point type | Secondary |
| End point timeframe: Cycle-1, Day 25 | |

| | | | | |
|--------------------------------------|----------------------|--|--|--|
| End point values | Pharmacokinetic CS | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | | | | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | 38.1 (± 11) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: NMS-867734 Cycle-1, Day 4: Cmax

| | |
|--------------------------------------|---------------------------------|
| End point title | NMS-867734 Cycle-1, Day 4: Cmax |
| End point description: | |
| Maximum observed concentration (µM). | |
| End point type | Secondary |
| End point timeframe: | |
| Cycle-1, Day 4 | |

| | | | | |
|--------------------------------------|----------------------|--|--|--|
| End point values | Pharmacokinetic CS | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | | | | |
| Units: µM | | | | |
| arithmetic mean (standard deviation) | 0.379 (± 0.133) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: NMS-867734 Cycle-1, Day 4: Tmax

| | |
|------------------------------|---------------------------------|
| End point title | NMS-867734 Cycle-1, Day 4: Tmax |
| End point description: | |
| The time take to reach Cmax. | |
| End point type | Secondary |
| End point timeframe: | |
| Cycle-1, Day 4 | |

| | | | | |
|---------------------------------------|----------------------|--|--|--|
| End point values | Pharmacokinetic CS | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | | | | |
| Units: hours | | | | |
| median (inter-quartile range (Q1-Q3)) | 4 (3.92 to 6) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: NMS-867734 Cycle-1, Day 4: AUC24

| | |
|------------------------|---|
| End point title | NMS-867734 Cycle-1, Day 4: AUC24 |
| End point description: | Area under the curve from time zero to 24 h after study drug administration (h*µM). |
| End point type | Secondary |
| End point timeframe: | Cycle-1, Day 4 |

| | | | | |
|--------------------------------------|----------------------|--|--|--|
| End point values | Pharmacokinetic CS | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | | | | |
| Units: µM hour | | | | |
| arithmetic mean (standard deviation) | 6.25 (± 2.05) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: NMS-867734 Cycle-1, Day 4: half-life

| | |
|------------------------|---|
| End point title | NMS-867734 Cycle-1, Day 4: half-life |
| End point description: | The time taken for the plasma concentration to fall by half its original value. |
| End point type | Secondary |
| End point timeframe: | Cycle-1, Day 4 |

| | | | | |
|--------------------------------------|----------------------|--|--|--|
| End point values | Pharmacokinetic CS | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | | | | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | 29.9 (± 8.90) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: NMS-867734 Cycle-1, Day 25: Cmax

| | |
|--------------------------------------|----------------------------------|
| End point title | NMS-867734 Cycle-1, Day 25: Cmax |
| End point description: | |
| Maximum observed concentration (µM). | |
| End point type | Secondary |
| End point timeframe: | |
| Cycle-1, Day 25 | |

| | | | | |
|--------------------------------------|----------------------|--|--|--|
| End point values | Pharmacokinetic CS | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | | | | |
| Units: µM | | | | |
| arithmetic mean (standard deviation) | 0.330 (± 0.116) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: NMS-867734 Cycle-1, Day 25: Tmax

| | |
|------------------------------|----------------------------------|
| End point title | NMS-867734 Cycle-1, Day 25: Tmax |
| End point description: | |
| The time take to reach Cmax. | |
| End point type | Secondary |
| End point timeframe: | |
| Cycle-1, Day 25 | |

| | | | | |
|---------------------------------------|-----------------------|--|--|--|
| End point values | Pharmacokinetic CS | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | | | | |
| Units: hours | | | | |
| median (inter-quartile range (Q1-Q3)) | 4 (2 to 6) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: NMS-867734 Cycle-1, Day 25: AUC24

| | |
|------------------------|---|
| End point title | NMS-867734 Cycle-1, Day 25: AUC24 |
| End point description: | Area under the curve from time zero to 24 h after study drug administration (h*µM). |
| End point type | Secondary |
| End point timeframe: | Cycle-1, Day 25 |

| | | | | |
|--------------------------------------|-----------------------|--|--|--|
| End point values | Pharmacokinetic CS | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | | | | |
| Units: µM hours | | | | |
| arithmetic mean (standard deviation) | 5.79 (± 2.29) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: NMS-867734 Cycle-1, Day 25: half-life

| | |
|------------------------|---|
| End point title | NMS-867734 Cycle-1, Day 25: half-life |
| End point description: | The time taken for the plasma concentration to fall by half its original value. |
| End point type | Secondary |
| End point timeframe: | Cycle-1, Day 25 |

| | | | | |
|--------------------------------------|-----------------------|--|--|--|
| End point values | Pharmacokinetic CS | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | | | | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | 37.4 (± 7.88) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse event reporting period for this trial began upon signing of informed consent and ended 30 days after the last treatment administration.

Adverse event reporting additional description:

If the patient started a new anticancer therapy earlier than 30 days after the last dose of study drug, the adverse event reporting period ended at the time the new treatment was started.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Treated patients |
|-----------------------|------------------|

Reporting group description:

Patients treated with Milciclib during treatment period.

| Serious adverse events | Treated patients | | |
|---|------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 17 / 31 (54.84%) | | |
| number of deaths (all causes) | 3 | | |
| number of deaths resulting from adverse events | 3 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Metastases to bone | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pyrexia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Overdose | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Sciatica | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Eye disorders | | | |
| Eye haemorrhage | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Retinal haemorrhage | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Retinal tear | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Retinoschisis | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ascites | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|----------------|--|--|
| Intra-abdominal haemorrhage subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oesophageal varices haemorrhage subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic failure subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperbilirubinaemia subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Diabetic ulcer subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Cellulitis subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Treated patients | | |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 28 / 31 (90.32%) | | |
| Investigations | | | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | | |
| occurrences (all) | 2 | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | | |
| occurrences (all) | 3 | | |
| Nervous system disorders | | | |
| Dysgeusia | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | | |
| occurrences (all) | 2 | | |
| Headache | | | |
| subjects affected / exposed | 6 / 31 (19.35%) | | |
| occurrences (all) | 7 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 5 / 31 (16.13%) | | |
| occurrences (all) | 6 | | |
| Neutropenia | | | |
| subjects affected / exposed | 3 / 31 (9.68%) | | |
| occurrences (all) | 9 | | |
| General disorders and administration site conditions | | | |

| | | | |
|---|--|--|--|
| <p>Asthenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>6 / 31 (19.35%)</p> <p>8</p> | | |
| <p>Fatigue</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>4 / 31 (12.90%)</p> <p>7</p> | | |
| <p>Oedema peripheral</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 31 (9.68%)</p> <p>6</p> | | |
| <p>Pyrexia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 31 (9.68%)</p> <p>4</p> | | |
| <p>Ear and labyrinth disorders</p> <p>Vertigo</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 31 (6.45%)</p> <p>2</p> | | |
| <p>Eye disorders</p> <p>Visual acuity reduced</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 31 (6.45%)</p> <p>2</p> | | |
| <p>Gastrointestinal disorders</p> <p>Abdominal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Abdominal pain upper</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Ascites</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Constipation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Diarrhoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nausea</p> | <p>4 / 31 (12.90%)</p> <p>8</p> <p>4 / 31 (12.90%)</p> <p>5</p> <p>5 / 31 (16.13%)</p> <p>5</p> <p>3 / 31 (9.68%)</p> <p>3</p> <p>13 / 31 (41.94%)</p> <p>26</p> | | |

| | | | |
|--|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>5 / 31 (16.13%)</p> <p>10</p> <p>3 / 31 (9.68%)</p> <p>4</p> | | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Epistaxis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>4 / 31 (12.90%)</p> <p>4</p> <p>2 / 31 (6.45%)</p> <p>2</p> | | |
| <p>Skin and subcutaneous tissue disorders</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 31 (6.45%)</p> <p>2</p> | | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Myalgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Neck pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 31 (9.68%)</p> <p>3</p> <p>2 / 31 (6.45%)</p> <p>2</p> | | |
| <p>Metabolism and nutrition disorders</p> <p>Decreased appetite</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 31 (6.45%)</p> <p>2</p> | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported