



## Clinical trial results:

### A phase 1/2a, dose escalation study of CHR-3996 in combination with tosedostat in subjects with relapsed, refractory multiple myeloma

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2011-001914-33  |
| Trial protocol           | GB              |
| Global end of trial date | 30 October 2017 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 08 November 2018 |
| First version publication date | 08 November 2018 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | HM11/9825 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |                |
|------------------------------------|----------------|
| ISRCTN number                      | ISRCTN24989786 |
| ClinicalTrials.gov id (NCT number) | -              |
| WHO universal trial number (UTN)   | -              |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | University of Leeds   |
| Sponsor organisation address | CTRU, Leeds, United Kingdom, LS2 9JT  |
| Public contact               | Louise Flanagan, CTRU, University of Leeds , 44 1133431477, medctco@leeds.ac.uk |
| Scientific contact           | Sarah Brown, CTRU, University of Leeds , 44 1133431477, medctco@leeds.ac.uk     |

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                       | 11 May 2016     |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 11 May 2016     |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 30 October 2017 |
| Was the trial ended prematurely?                     | Yes             |

Notes:

---

**General information about the trial**

---

Main objective of the trial:

During the dose escalation phase, the purpose of the study is to determine the maximum tolerated dose (MTD) of CHR-3996 and tosedostat administered in combination in subjects with relapsed or refractory multiple myeloma.

In the dose expansion phase the purpose of the study is to determine the safety profile of CHR-3996 and tosedostat administered in combination and to estimate the response rate.

---

Protection of trial subjects:

N/A

Background therapy:

There are no comparators for this trial all participants received the trial drug.

Evidence for comparator:

N/A

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 01 August 2011 |
| 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 | United Kingdom: 27 |
| Worldwide total number of subjects   | 27                 |
| EEA total number of subjects         | 27                 |

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) | 14 |
| From 65 to 84 years  | 13 |
| 85 years and over    | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Participants were recruited from NHS Hospitals in the UK with ethical and regulatory approval. Participants were approached during their usual clinic visits by a doctor and consented if they were willing to take part. They were registered to the trial and eligibility checked. The recruitment period was July 2012 - December 2015.

### Pre-assignment

Screening details:

Participants were screened for eligibility once consented and registered to the trial to ensure they met all criteria.

### 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 | Safety analysis population |
|-----------|----------------------------|

Arm description:

The safety analysis population includes all participants who received at least one dose of trial treatment. Only participants, for whom written informed consent has not been received, are not included in this population.

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | CHR-3996      |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

20mg/20mg/40mg/40mg once daily for 28 day cycle

|  |               |
|--|---------------|
| Investigational medicinal product name | tosedostat    |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

60mg/0mg/0mg/60mg once daily for 28 day cycle

| Number of subjects in period 1 <sup>[1]</sup> | Safety analysis population |
|---|----------------------------|
| Started                                       | 22                         |
| Completed                                     | 22                         |

---

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: There were 27 patients recruited to the trial, but only 22 went on to receive treatment. This is why the number of patients in the safety analysis population (baseline period) does not match the number enrolled in the trial. This was agreed with the Scientific Lead.

## Baseline characteristics

### Reporting groups

| Reporting group title          | Overall Trial |
|--------------------------------|---------------|
| Reporting group description: - |               |

| Reporting group values                                | Overall Trial | Total |  |
|---|---------------|-------|--|
| Number of subjects                                    | 22            | 22    |  |
| Age categorical                                       |               |       |  |
| Units: Subjects                                       |               |       |  |
| In utero  | 0             | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0             | 0     |  |
| Newborns (0-27 days)                                  | 0             | 0     |  |
| Infants and toddlers (28 days-23<br>months)           | 0             | 0     |  |
| Children (2-11 years)                                 | 0             | 0     |  |
| Adolescents (12-17 years)                             | 0             | 0     |  |
| Adults (18-64 years)                                  | 11            | 11    |  |
| From 65-84 years                                      | 11            | 11    |  |
| 85 years and over                                     | 0             | 0     |  |
| Age continuous  |               |       |  |
| Age at registration                                   |               |       |  |
| Units: years  |               |       |  |
| arithmetic mean                                       | 62.9          |       |  |
| standard deviation                                    | ± 8.7         | -     |  |
| Gender categorical                                    |               |       |  |
| Units: Subjects                                       |               |       |  |
| Female  | 9             | 9     |  |
| Male  | 12            | 12    |  |
| Missing   | 1             | 1     |  |
| ECOG status   |               |       |  |
| Units: Subjects                                       |               |       |  |
| Zero  | 4             | 4     |  |
| One   | 18            | 18    |  |
| Previous treatment lines                              |               |       |  |
| Units: Subjects                                       |               |       |  |
| Two   | 1             | 1     |  |
| Three   | 3             | 3     |  |
| Four  | 7             | 7     |  |
| Five  | 4             | 4     |  |
| Six   | 1             | 1     |  |
| Seven   | 2             | 2     |  |
| Eight   | 2             | 2     |  |
| Nine  | 1             | 1     |  |
| Missing   | 1             | 1     |  |
| Tumour Stage  |               |       |  |
| Units: Subjects                                       |               |       |  |
| One   | 5             | 5     |  |

|  |         |    |  |
|--|---------|----|--|
| Two  | 11      | 11 |  |
| Three  | 5       | 5  |  |
| Missing  | 1       | 1  |  |
| Paraprotein type<br>Units: Subjects                                    |         |    |  |
| IgG  | 15      | 15 |  |
| IgA  | 4       | 4  |  |
| Light chain only   | 3       | 3  |  |
| Light chain type<br>Units: Subjects                                    |         |    |  |
| Kappa  | 13      | 13 |  |
| Lambda   | 9       | 9  |  |
| Systolic BP<br>Units: mmHg   |         |    |  |
| arithmetic mean  | 127.0   |    |  |
| standard deviation   | ± 17.21 | -  |  |
| Diastolic BP<br>Units: mmHg  |         |    |  |
| arithmetic mean  | 76.8    |    |  |
| standard deviation   | ± 7.58  | -  |  |
| Pulse rate<br>Units: bpm   |         |    |  |
| arithmetic mean  | 80.8    |    |  |
| standard deviation   | ± 11.22 | -  |  |
| Temperature<br>Units: degrees celcius                                  |         |    |  |
| arithmetic mean  | 36.5    |    |  |
| standard deviation   | ± 0.37  | -  |  |
| QTcF interval<br>Units: msec   |         |    |  |
| arithmetic mean  | 393.1   |    |  |
| standard deviation   | ± 82.03 | -  |  |
| Time from most recent relapse to registration                          |         |    |  |
| Time from most recent relapse to registration date                     |         |    |  |
| Units: Months  |         |    |  |
| arithmetic mean  | 1.3     |    |  |
| standard deviation   | ± 1.2   | -  |  |
| Time from last dose of systemic anti-myeloma treatment to registration |         |    |  |
| Units: Months  |         |    |  |
| arithmetic mean  | 1.5     |    |  |
| standard deviation   | ± 1.81  | -  |  |

### Subject analysis sets

|  |                                   |
|--|-----------------------------------|
| Subject analysis set title   | Primary analysis set              |
| Subject analysis set type  | Intention-to-treat                |
| Subject analysis set description:  |                                   |
| The ITT population is defined by all participants registered to receive the recommended dose (20mg CHR-3996 and 60mg tosedostat), and who received at least one dose of trial treatment. |                                   |
| Subject analysis set title   | Non-recommended dose analysis set |

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

The ITT population is defined by all participants who were not registered to receive the recommended dose (20mg CHR-3996 and 60mg tosedostat), and who received at least one dose of trial treatment.

| Reporting group values                             | Primary analysis set | Non-recommended dose analysis set |  |
|--|----------------------|-----------------------------------|--|
| Number of subjects                                 | 10                   | 12                                |  |
| 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)                               | 6                    | 5                                 |  |
| From 65-84 years                                   | 4                    | 7                                 |  |
| 85 years and over                                  | 0                    | 0                                 |  |
| Age continuous                                     |                      |                                   |  |
| Age at registration                                |                      |                                   |  |
| Units: years                                       |                      |                                   |  |
| arithmetic mean                                    | 61.2                 | 64.2                              |  |
| standard deviation                                 | ± 9.34               | ± 8.38                            |  |
| Gender categorical                                 |                      |                                   |  |
| Units: Subjects                                    |                      |                                   |  |
| Female   | 4                    | 5                                 |  |
| Male   | 5                    | 7                                 |  |
| Missing  | 1                    | 0                                 |  |
| ECOG status  |                      |                                   |  |
| Units: Subjects                                    |                      |                                   |  |
| Zero   | 2                    | 2                                 |  |
| One  | 8                    | 10                                |  |
| Previous treatment lines                           |                      |                                   |  |
| Units: Subjects                                    |                      |                                   |  |
| Two  | 1                    | 0                                 |  |
| Three  | 0                    | 3                                 |  |
| Four   | 6                    | 1                                 |  |
| Five   | 0                    | 4                                 |  |
| Six  | 0                    | 1                                 |  |
| Seven  | 1                    | 1                                 |  |
| Eight  | 0                    | 2                                 |  |
| Nine   | 1                    | 0                                 |  |
| Missing  | 1                    | 0                                 |  |
| Tumour Stage                                       |                      |                                   |  |
| Units: Subjects                                    |                      |                                   |  |
| One  | 2                    | 3                                 |  |
| Two  | 5                    | 6                                 |  |
| Three  | 3                    | 2                                 |  |
| Missing  | 0                    | 1                                 |  |
| Paraprotein type                                   |                      |                                   |  |



|  |         |          |  |
|--|---------|----------|--|
| Units: Subjects  |         |          |  |
| IgG  | 7       | 8        |  |
| IgA  | 2       | 2        |  |
| Light chain only   | 1       | 2        |  |
| Light chain type   |         |          |  |
| Units: Subjects  |         |          |  |
| Kappa  | 6       | 7        |  |
| Lambda   | 4       | 5        |  |
| Systolic BP  |         |          |  |
| Units: mmHg  |         |          |  |
| arithmetic mean  | 117.5   | 134.8    |  |
| standard deviation   | ± 13.71 | ± 16.21  |  |
| Diastolic BP   |         |          |  |
| Units: mmHg  |         |          |  |
| arithmetic mean  | 75.4    | 77.9     |  |
| standard deviation   | ± 9.18  | ± 6.13   |  |
| Pulse rate   |         |          |  |
| Units: bpm   |         |          |  |
| arithmetic mean  | 84.6    | 77.6     |  |
| standard deviation   | ± 9.50  | ± 11.91  |  |
| Temperature  |         |          |  |
| Units: degrees celcius   |         |          |  |
| arithmetic mean  | 36.6    | 36.5     |  |
| standard deviation   | ± 0.20  | ± 0.47   |  |
| QTcF interval  |         |          |  |
| Units: msec  |         |          |  |
| arithmetic mean  | 409.4   | 379.6    |  |
| standard deviation   | ± 18.15 | ± 110.16 |  |
| Time from most recent relapse to registration                          |         |          |  |
| Time from most recent relapse to registration date                     |         |          |  |
| Units: Months  |         |          |  |
| arithmetic mean  | 0.7     | 1.7      |  |
| standard deviation   | ± 0.46  | ± 1.38   |  |
| Time from last dose of systemic anti-myeloma treatment to registration |         |          |  |
| Units: Months  |         |          |  |
| arithmetic mean  | 0.5     | 2.3      |  |
| standard deviation   | ± 0.24  | ± 2.17   |  |

## End points

### End points reporting groups

|  |                                   |
|--|-----------------------------------|
| Reporting group title  | Safety analysis population        |
| Reporting group description:<br>The safety analysis population includes all participants who received at least one dose of trial treatment. Only participants, for whom written informed consent has not been received, are not included in this population. |                                   |
| Subject analysis set title   | Primary analysis set              |
| Subject analysis set type  | Intention-to-treat                |
| Subject analysis set description:<br>The ITT population is defined by all participants registered to receive the recommended dose (20mg CHR-3996 and 60mg tosedostat), and who received at least one dose of trial treatment.                                |                                   |
| Subject analysis set title   | Non-recommended dose analysis set |
| Subject analysis set type  | Intention-to-treat                |
| Subject analysis set description:<br>The ITT population is defined by all participants who were not registered to receive the recommended dose (20mg CHR-3996 and 60mg tosedostat), and who received at least one dose of trial treatment.                   |                                   |

### Primary: Dose escalation phase: Dose limiting toxicity (DLT)

|  |  |
|--|--|
| End point title  | Dose escalation phase: Dose limiting toxicity (DLT) <sup>[1]</sup> |
| End point description:<br>The number of participants recruited to the dose escalation phase of the study, experiencing DLTs within the first 28-day cycle of CHR-3996 and tosedostat.<br><br>DLT was defined by any of the following events: <ul style="list-style-type: none"><li>- Any non haematological toxicity <math>\geq</math> Grade 3 according to NCI CTCAE Version 4 which fails to return to <math>\leq</math> Grade 1 or baseline after 7 days. Nausea, vomiting, diarrhoea and electrolyte imbalances will be considered DLTs only if they reach <math>\geq</math> Grade 3 severity despite adequate supportive care measures.</li><li>- Grade 4 neutropenia with sepsis or Grade 4 neutropenia lasting <math>&gt;7</math> days despite adequate supportive care measures.</li><li>- Any grade 4 thrombocytopenia which fails to return to baseline after 7 days with platelet support</li><li>- Omission of <math>&gt; 7</math> days for resumption of treatment due to toxicity (i.e an inability to commence cycle 2 until after day 8)</li><li>- Treatment related death</li></ul> |  |
| End point type   | Primary  |
| End point timeframe:<br>DLTs were assessed during the first cycle of treatment, up to the administration of cycle 2 day 1 of dose escalation patients.   |  |
| Notes:<br>[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.<br>Justification: As this is a phase I study, the primary endpoint related to data summaries only.   |  |

| End point values                       | Safety analysis population |  |  |  |
|--|----------------------------|--|--|--|
| Subject group type                     | Reporting group            |  |  |  |
| Number of subjects analysed            | 15 <sup>[2]</sup>          |  |  |  |
| Units: Number of DLTs                  |                            |  |  |  |
| 20mg CHR-3996, 0mg Tosedostat - DLT    | 0                          |  |  |  |
| 20mg CHR-3996, 0mg Tosedostat - no DLT | 3                          |  |  |  |
| 40mg CHR-3996, 0mg Tosedostat - DLT    | 0                          |  |  |  |
| 40mg CHR-3996, 0mg Tosedostat - no DLT | 3                          |  |  |  |
| 40mg CHR-3996, 60mg Tosedostat - DLT   | 1                          |  |  |  |

|   |   |  |  |  |
|---|---|--|--|--|
| 40mg CHR-3996, 60mg Tosedostat - no DLT | 2 |  |  |  |
| 20mg CHR-3996, 60mg Tosedostat - DLT    | 0 |  |  |  |
| 20mg CHR-3996, 60mg Tosedostat - no DLT | 6 |  |  |  |

Notes:

[2] - 15 participants were recruited to the dose escalation phase and were evaluable for DLTs

## Statistical analyses

No statistical analyses for this end point

### Primary: Expansion phase: Stable disease

|                 |  |
|-----------------|--|
| End point title | Expansion phase: Stable disease <sup>[3]</sup> |
|-----------------|--|

End point description:

The proportion of participants achieving at least stable disease (SD) after 4 cycles of CHR-3996 and tosedostat.

Response to treatment is assessed after a participant has received 4 cycles of treatment. If a participant stops treatment within 4 months of registration for reasons other than disease progression, response will be assessed every 4 weeks until 4 months post-registration or disease progression, whichever is earlier. If a participant progresses within 4 cycles of treatment, the participant will be classed as not achieving at least stable disease after 4 cycles of treatment.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

after 4 cycles of CHR-3996 and tosedostat

Notes:

[3] - 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: As this is a phase I study, the primary endpoint related to data summaries only.

| End point values                 | Primary analysis set | Non-recommended dose analysis set |  |  |
|----------------------------------|----------------------|-----------------------------------|--|--|
| Subject group type               | Subject analysis set | Subject analysis set              |  |  |
| Number of subjects analysed      | 10                   | 12                                |  |  |
| Units: Proportion                |                      |                                   |  |  |
| number (confidence interval 95%) | 30 (6.7 to 65.2)     | 16.7 (2.1 to 48.4)                |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Maximum response (6 cycles)

|                 |                             |
|-----------------|-----------------------------|
| End point title | Maximum response (6 cycles) |
|-----------------|-----------------------------|

End point description:

The proportion of participants with each maximum response category within 6 cycles of therapy.

Maximum response is defined as the maximum response category achieved within the corresponding assessment period, for each participant. The response categories are: stringent complete response (sCR); complete response (CR); very good partial response (VGPR); partial response (PR); minimal

response (MR); stable disease (SD)/no change (NC).

|   |           |
|---|-----------|
| End point type                          | Secondary |
| End point timeframe:<br>within 6 cycles |           |

| End point values                                 | Primary analysis set | Non-recommended dose analysis set |  |  |
|--|----------------------|-----------------------------------|--|--|
| Subject group type                               | Subject analysis set | Subject analysis set              |  |  |
| Number of subjects analysed                      | 10                   | 12                                |  |  |
| Units: Subjects                                  |                      |                                   |  |  |
| PR   | 1                    | 0                                 |  |  |
| SD or NC   | 4                    | 9                                 |  |  |
| PD   | 4                    | 3                                 |  |  |
| Participant died within first cycle of treatment | 1                    | 0                                 |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Maximum response (overall)

|  |                            |
|--|----------------------------|
| End point title  | Maximum response (overall) |
| End point description:<br>The proportion of participants with each maximum response category to therapy overall.<br><br>Maximum response is defined as the maximum response category achieved within the corresponding assessment period, for each participant. The response categories are: stringent complete response (sCR); complete response (CR); very good partial response (VGPR); partial response (PR); minimal response (MR); stable disease (SD)/no change (NC). |                            |
| End point type   | Secondary                  |
| End point timeframe:<br>over the whole trial   |                            |

| End point values            | Primary analysis set | Non-recommended dose analysis set |  |  |
|-----------------------------|----------------------|-----------------------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set              |  |  |
| Number of subjects analysed | 10                   | 12                                |  |  |
| Units: Subjects             |                      |                                   |  |  |
| PR                          | 1                    | 0                                 |  |  |
| MR                          | 1                    | 0                                 |  |  |
| SD or NC                    | 3                    | 9                                 |  |  |

|  |   |   |  |  |
|--|---|---|--|--|
| PD   | 4 | 3 |  |  |
| Participant died within first cycle of treatment | 1 | 0 |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to maximum response

|                 |                          |
|-----------------|--------------------------|
| End point title | Time to maximum response |
|-----------------|--------------------------|

End point description:

Time to maximum response was defined as the time from registration until the patient achieved their maximum response. Those who did not achieve maximum response, are censored at the date of disease progression.

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

End point timeframe:

registration until patient achieved their maximum response

| End point values                 | Primary analysis set | Non-recommended dose analysis set |  |  |
|----------------------------------|----------------------|-----------------------------------|--|--|
| Subject group type               | Subject analysis set | Subject analysis set              |  |  |
| Number of subjects analysed      | 5 <sup>[4]</sup>     | 9 <sup>[5]</sup>                  |  |  |
| Units: Months                    |                      |                                   |  |  |
| median (confidence interval 95%) | 1.84 (1.09 to 8.65)  | 1.45 (1.22 to 1.81)               |  |  |

Notes:

[4] - Of the 10 participants in the primary analysis set, only 5 achieved a maximum response.

[5] - Of the 12 participants in the non-RD analysis set, only 9 achieved a maximum response.

## 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 is defined as the time from registration to first documented evidence of disease progression or death. Participants who, at the time of analysis, have not progressed will be censored at the last date they were known to be alive and progression free.

Calculated using the Kaplan-Meier method.

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

End point timeframe:

registration until first documented evidence of disease progression or death.

| End point values                 | Primary analysis set |  |  |  |
|----------------------------------|----------------------|--|--|--|
| Subject group type               | Subject analysis set |  |  |  |
| Number of subjects analysed      | 10                   |  |  |  |
| Units: Month                     |                      |  |  |  |
| median (confidence interval 95%) | 1.8 (0.92 to 4.61)   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: CHR-3996 dose reduction (toxicity)

|  |                                    |
|--|------------------------------------|
| End point title  | CHR-3996 dose reduction (toxicity) |
| End point description:<br>Number of dose reductions, is defined as the number of participants experiencing at least 1 CHR-3996 dose reduction due to toxicity. |                                    |
| End point type   | Secondary                          |
| End point timeframe:<br>whilst receiving trial treatment   |                                    |

| End point values            | Primary analysis set | Non-recommended dose analysis set |  |  |
|-----------------------------|----------------------|-----------------------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set              |  |  |
| Number of subjects analysed | 10                   | 12                                |  |  |
| Units: Subjects             |                      |                                   |  |  |
| No reduction                | 8                    | 10                                |  |  |
| Reduction                   | 2                    | 2                                 |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Tosedostat dose reduction (toxicity)

|  |                                      |
|--|--------------------------------------|
| End point title  | Tosedostat dose reduction (toxicity) |
| End point description:<br>Number of dose reductions, is defined as the number of participants experiencing at least 1 tosedostat dose reduction due to toxicity. |                                      |
| End point type   | Secondary                            |

End point timeframe:  
whilst receiving trial treatment

| End point values            | Primary analysis set | Non-recommended dose analysis set |  |  |
|-----------------------------|----------------------|-----------------------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set              |  |  |
| Number of subjects analysed | 10                   | 12                                |  |  |
| Units: Subject              |                      |                                   |  |  |
| No reduction                | 9                    | 12                                |  |  |
| Reduction                   | 1                    | 0                                 |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Treatment compliance

|                 |                      |
|-----------------|----------------------|
| End point title | Treatment compliance |
|-----------------|----------------------|

End point description:

Participants will be regarded as compliant to treatment where treatment is received as per protocol until withdrawal from trial treatment, without missing >5 days of either CHR-3996 or tosedostat in the first cycle for reasons other than toxicity, or >5 days of either treatment in any subsequent cycle.

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

End point timeframe:

until withdrawal from trial treatment

| End point values                     | Primary analysis set | Non-recommended dose analysis set |  |  |
|--------------------------------------|----------------------|-----------------------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set              |  |  |
| Number of subjects analysed          | 10                   | 12                                |  |  |
| Units: Subjects                      |                      |                                   |  |  |
| Missed more than 5 days dosing       | 6                    | 8                                 |  |  |
| Did not miss more than 5 days dosing | 4                    | 4                                 |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Safety: number of patients with 1 or more SAEs

|   |  |
|---|--|
| End point title   | Safety: number of patients with 1 or more SAEs |
| End point description:<br>The number of patients with one or more serious adverse reaction (SAR)/serious adverse event (SAE). |  |
| End point type  | Secondary                                      |
| End point timeframe:<br>time of written informed consent until 30 days post cessation of trial therapy.                       |  |

| End point values            | Primary analysis set | Non-recommended dose analysis set |  |  |
|-----------------------------|----------------------|-----------------------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set              |  |  |
| Number of subjects analysed | 10                   | 12                                |  |  |
| Units: Subjects             |                      |                                   |  |  |
| Yes: SAR                    | 2                    | 3                                 |  |  |
| Yes: SAE                    | 7                    | 4                                 |  |  |
| No                          | 1                    | 5                                 |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Safety: SAEs

|   |              |
|---|--------------|
| End point title   | Safety: SAEs |
| End point description:<br>Summary statistics of the number of serious adverse events (SAEs) reported    |              |
| End point type  | Secondary    |
| End point timeframe:<br>time of written informed consent until 30 days post cessation of trial therapy. |              |

| End point values                        | Primary analysis set | Non-recommended dose analysis set |  |  |
|---|----------------------|-----------------------------------|--|--|
| Subject group type                      | Subject analysis set | Subject analysis set              |  |  |
| Number of subjects analysed             | 10                   | 12                                |  |  |
| Units: Subjects/SAEs                    |                      |                                   |  |  |
| Number of patients with one of more SAE | 9                    | 7                                 |  |  |
| Number of SAEs reported                 | 14                   | 8                                 |  |  |

### Statistical analyses



No statistical analyses for this end point

### Secondary: Safety: number of SAEs per patient

|                 |                                    |
|-----------------|------------------------------------|
| End point title | Safety: number of SAEs per patient |
|-----------------|------------------------------------|

End point description:

Summary statistics of the number of serious adverse events (SAEs) per patient.

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

End point timeframe:

time of written informed consent until 30 days post cessation of trial therapy.

| End point values                     | Primary analysis set | Non-recommended dose analysis set |  |  |
|--------------------------------------|----------------------|-----------------------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set              |  |  |
| Number of subjects analysed          | 9 <sup>[6]</sup>     | 7 <sup>[7]</sup>                  |  |  |
| Units: SAEs                          |                      |                                   |  |  |
| arithmetic mean (standard deviation) |                      |                                   |  |  |
| Number of SAEs per patient           | 1.6 (± 0.88)         | 1.1 (± 0.38)                      |  |  |

Notes:

[6] - 9 out of the 10 participants in the primary population experienced an SAE

[7] - 7 out of the 12 participants in the non-RD population experienced an SAE

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival

|                 |                  |
|-----------------|------------------|
| End point title | Overall survival |
|-----------------|------------------|

End point description:

Overall survival is defined as the time from registration to date of death from any cause. Participants who were still alive at the time of analysis were censored at the last date they were known to be alive.

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

End point timeframe:

registration until date of death or final analysis, which was sooner.

| End point values            | Primary analysis set | Non-recommended dose analysis set |  |  |
|-----------------------------|----------------------|-----------------------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set              |  |  |
| Number of subjects analysed | 10                   | 12                                |  |  |
| Units: Deaths               |                      |                                   |  |  |
| Died                        | 5                    | 2                                 |  |  |
| Not died                    | 5                    | 12                                |  |  |

## **Statistical analyses**

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All AEs occurring for all participants from the time of written informed consent until 30 days post cessation of trial therapy.

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

### Dictionary used

|                 |       |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

|                    |     |
|--------------------|-----|
| Dictionary version | 4.0 |
|--------------------|-----|

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Safety population |
|-----------------------|-------------------|

Reporting group description:

The safety population includes all participants who have received at least one dose of any trial treatment. Only patients for whom written informed consent was not received are excluded.

| Serious adverse events                               | Safety population |  |  |
|--|-------------------|--|--|
| Total subjects affected by serious adverse events    |                   |  |  |
| subjects affected / exposed                          | 16 / 22 (72.73%)  |  |  |
| number of deaths (all causes)                        | 7                 |  |  |
| number of deaths resulting from adverse events       | 1                 |  |  |
| Injury, poisoning and procedural complications       |                   |  |  |
| Fall   |                   |  |  |
| subjects affected / exposed                          | 2 / 22 (9.09%)    |  |  |
| occurrences causally related to treatment / all      | 0 / 2             |  |  |
| deaths causally related to treatment / all           | 1 / 7             |  |  |
| Blood and lymphatic system disorders                 |                   |  |  |
| Thrombocytopenia                                     |                   |  |  |
| subjects affected / exposed                          | 1 / 22 (4.55%)    |  |  |
| occurrences causally related to treatment / all      | 1 / 1             |  |  |
| deaths causally related to treatment / all           | 0 / 7             |  |  |
| Epistaxis  |                   |  |  |
| subjects affected / exposed                          | 1 / 22 (4.55%)    |  |  |
| occurrences causally related to treatment / all      | 0 / 1             |  |  |
| deaths causally related to treatment / all           | 0 / 7             |  |  |
| General disorders and administration site conditions |                   |  |  |
| Fatigue  |                   |  |  |

|  |                |  |  |
|--|----------------|--|--|
| subjects affected / exposed                            | 1 / 22 (4.55%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1          |  |  |
| deaths causally related to treatment / all             | 0 / 7          |  |  |
| <b>Gastrointestinal disorders</b>                      |                |  |  |
| Diarrhoea, vomiting and C-difficile                    |                |  |  |
| subjects affected / exposed                            | 1 / 22 (4.55%) |  |  |
| occurrences causally related to treatment / all        | 1 / 1          |  |  |
| deaths causally related to treatment / all             | 0 / 7          |  |  |
| Dehydration, vomiting and nausea                       |                |  |  |
| subjects affected / exposed                            | 1 / 22 (4.55%) |  |  |
| occurrences causally related to treatment / all        | 1 / 1          |  |  |
| deaths causally related to treatment / all             | 0 / 7          |  |  |
| Nausea and diarrhoea                                   |                |  |  |
| subjects affected / exposed                            | 1 / 22 (4.55%) |  |  |
| occurrences causally related to treatment / all        | 1 / 1          |  |  |
| deaths causally related to treatment / all             | 0 / 7          |  |  |
| Diarrhoea  |                |  |  |
| subjects affected / exposed                            | 1 / 22 (4.55%) |  |  |
| occurrences causally related to treatment / all        | 1 / 1          |  |  |
| deaths causally related to treatment / all             | 0 / 7          |  |  |
| <b>Respiratory, thoracic and mediastinal disorders</b> |                |  |  |
| Chest infection  |                |  |  |
| subjects affected / exposed                            | 1 / 22 (4.55%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1          |  |  |
| deaths causally related to treatment / all             | 0 / 7          |  |  |
| <b>Renal and urinary disorders</b>                     |                |  |  |
| Acute kidney injury                                    |                |  |  |
| subjects affected / exposed                            | 1 / 22 (4.55%) |  |  |
| occurrences causally related to treatment / all        | 1 / 1          |  |  |
| deaths causally related to treatment / all             | 0 / 7          |  |  |
| Raised creatinine                                      |                |  |  |
| subjects affected / exposed                            | 1 / 22 (4.55%) |  |  |
| occurrences causally related to treatment / all        | 1 / 1          |  |  |
| deaths causally related to treatment / all             | 0 / 7          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Acute kidney injury / creatinine increased      |                |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 7          |  |  |
| Infections and infestations                     |                |  |  |
| Upper respiratory tract infection               |                |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 7          |  |  |
| Soft tissue infection                           |                |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 7          |  |  |
| Urinary tract infection                         |                |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 7          |  |  |
| Lung infection                                  |                |  |  |
| subjects affected / exposed                     | 2 / 22 (9.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 7          |  |  |
| Infection                                       |                |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 7          |  |  |
| Fever   |                |  |  |
| subjects affected / exposed                     | 2 / 22 (9.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 7          |  |  |
| Flu like symptoms                               |                |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 7          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Fever and upper respiratory tract infection     |                |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 7          |  |  |

Frequency threshold for reporting non-serious adverse events: 0.05 %

| <b>Non-serious adverse events</b>                     | Safety population |  |  |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events |                   |  |  |
| subjects affected / exposed                           | 22 / 22 (100.00%) |  |  |
| Vascular disorders                                    |                   |  |  |
| Thromboembolic event                                  |                   |  |  |
| subjects affected / exposed                           | 1 / 22 (4.55%)    |  |  |
| occurrences (all)                                     | 1                 |  |  |
| Hypertension  |                   |  |  |
| subjects affected / exposed                           | 1 / 22 (4.55%)    |  |  |
| occurrences (all)                                     | 1                 |  |  |
| General disorders and administration site conditions  |                   |  |  |
| Fatigue   |                   |  |  |
| subjects affected / exposed                           | 17 / 22 (77.27%)  |  |  |
| occurrences (all)                                     | 17                |  |  |
| Fever   |                   |  |  |
| subjects affected / exposed                           | 3 / 22 (13.64%)   |  |  |
| occurrences (all)                                     | 3                 |  |  |
| Edema limbs   |                   |  |  |
| subjects affected / exposed                           | 5 / 22 (22.73%)   |  |  |
| occurrences (all)                                     | 5                 |  |  |
| Pain in extremity                                     |                   |  |  |
| subjects affected / exposed                           | 5 / 22 (22.73%)   |  |  |
| occurrences (all)                                     | 5                 |  |  |
| Pain  |                   |  |  |
| subjects affected / exposed                           | 2 / 22 (9.09%)    |  |  |
| occurrences (all)                                     | 2                 |  |  |
| Lethargy  |                   |  |  |

|  |  |  |  |
|--|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Localized edema</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Other</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>1 / 22 (4.55%)</p> <p>1</p> <p>1 / 22 (4.55%)</p> <p>1</p> <p>12 / 22 (54.55%)</p> <p>12</p>  |  |  |
| <p>Reproductive system and breast disorders</p> <p>Vaginal discharge</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>1 / 22 (4.55%)</p> <p>1</p>   |  |  |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Epistaxis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hiccups</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pharyngitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Sore throat</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 22 (13.64%)</p> <p>3</p> <p>6 / 22 (27.27%)</p> <p>6</p> <p>5 / 22 (22.73%)</p> <p>5</p> <p>1 / 22 (4.55%)</p> <p>1</p> <p>1 / 22 (4.55%)</p> <p>1</p> <p>1 / 22 (4.55%)</p> <p>1</p> |  |  |
| <p>Psychiatric disorders</p> <p>Depression</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Insomnia</p>   | <p>2 / 22 (9.09%)</p> <p>2</p>   |  |  |

|                                    |                  |  |  |
|------------------------------------|------------------|--|--|
| subjects affected / exposed        | 2 / 22 (9.09%)   |  |  |
| occurrences (all)                  | 2                |  |  |
| Anxiety                            |                  |  |  |
| subjects affected / exposed        | 1 / 22 (4.55%)   |  |  |
| occurrences (all)                  | 1                |  |  |
| Confusion                          |                  |  |  |
| subjects affected / exposed        | 1 / 22 (4.55%)   |  |  |
| occurrences (all)                  | 1                |  |  |
| Irritability                       |                  |  |  |
| subjects affected / exposed        | 1 / 22 (4.55%)   |  |  |
| occurrences (all)                  | 1                |  |  |
| Investigations                     |                  |  |  |
| Platelet count decreased           |                  |  |  |
| subjects affected / exposed        | 15 / 22 (68.18%) |  |  |
| occurrences (all)                  | 15               |  |  |
| White blood cell count decreased   |                  |  |  |
| subjects affected / exposed        | 12 / 22 (54.55%) |  |  |
| occurrences (all)                  | 12               |  |  |
| Alanine aminotransferase increased |                  |  |  |
| subjects affected / exposed        | 3 / 22 (13.64%)  |  |  |
| occurrences (all)                  | 3                |  |  |
| Lymphocyte count decreased         |                  |  |  |
| subjects affected / exposed        | 3 / 22 (13.64%)  |  |  |
| occurrences (all)                  | 3                |  |  |
| Creatinine increased               |                  |  |  |
| subjects affected / exposed        | 6 / 22 (27.27%)  |  |  |
| occurrences (all)                  | 6                |  |  |
| CPK increased                      |                  |  |  |
| subjects affected / exposed        | 2 / 22 (9.09%)   |  |  |
| occurrences (all)                  | 2                |  |  |
| Investigations - other, specify    |                  |  |  |
| subjects affected / exposed        | 3 / 22 (13.64%)  |  |  |
| occurrences (all)                  | 3                |  |  |
| Neutrophil count decreased         |                  |  |  |
| subjects affected / exposed        | 2 / 22 (9.09%)   |  |  |
| occurrences (all)                  | 2                |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| Weight loss                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Aspartate aminotransferase increased            |                 |  |  |
| subjects affected / exposed                     | 2 / 22 (9.09%)  |  |  |
| occurrences (all)                               | 2               |  |  |
| INR increased                                   |                 |  |  |
| subjects affected / exposed                     | 2 / 22 (9.09%)  |  |  |
| occurrences (all)                               | 2               |  |  |
| Activated partial thromboplastin time prolonged |                 |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Alkaline phosphatase increased                  |                 |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Injury, poisoning and procedural complications  |                 |  |  |
| Spinal fracture                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Cardiac disorders                               |                 |  |  |
| Atrial fibrillation                             |                 |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Cardiac disorders - other, specify              |                 |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Ventricular arrhythmia                          |                 |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Nervous system disorders                        |                 |  |  |
| Peripheral sensory neuropathy                   |                 |  |  |
| subjects affected / exposed                     | 8 / 22 (36.36%) |  |  |
| occurrences (all)                               | 8               |  |  |
| Dysgeusia                                       |                 |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed               | 3 / 22 (13.64%)  |  |  |
| occurrences (all)                         | 3                |  |  |
| Dizziness                                 |                  |  |  |
| subjects affected / exposed               | 1 / 22 (4.55%)   |  |  |
| occurrences (all)                         | 1                |  |  |
| Headache                                  |                  |  |  |
| subjects affected / exposed               | 1 / 22 (4.55%)   |  |  |
| occurrences (all)                         | 1                |  |  |
| Nervous system disorders - other, specify |                  |  |  |
| subjects affected / exposed               | 1 / 22 (4.55%)   |  |  |
| occurrences (all)                         | 1                |  |  |
| Peripheral motor neuropathy               |                  |  |  |
| subjects affected / exposed               | 1 / 22 (4.55%)   |  |  |
| occurrences (all)                         | 1                |  |  |
| radiculitis                               |                  |  |  |
| subjects affected / exposed               | 1 / 22 (4.55%)   |  |  |
| occurrences (all)                         | 1                |  |  |
| Blood and lymphatic system disorders      |                  |  |  |
| Anaemia                                   |                  |  |  |
| subjects affected / exposed               | 16 / 22 (72.73%) |  |  |
| occurrences (all)                         | 16               |  |  |
| Hematoma                                  |                  |  |  |
| subjects affected / exposed               | 1 / 22 (4.55%)   |  |  |
| occurrences (all)                         | 1                |  |  |
| Hypokalemia                               |                  |  |  |
| subjects affected / exposed               | 3 / 22 (13.64%)  |  |  |
| occurrences (all)                         | 3                |  |  |
| Oral haemorrhage                          |                  |  |  |
| subjects affected / exposed               | 1 / 22 (4.55%)   |  |  |
| occurrences (all)                         | 1                |  |  |
| Eye disorders                             |                  |  |  |
| Blurred vision                            |                  |  |  |
| subjects affected / exposed               | 1 / 22 (4.55%)   |  |  |
| occurrences (all)                         | 1                |  |  |
| Cataracts                                 |                  |  |  |

|                                 |                  |  |  |
|---------------------------------|------------------|--|--|
| subjects affected / exposed     | 1 / 22 (4.55%)   |  |  |
| occurrences (all)               | 1                |  |  |
| Watering eyes                   |                  |  |  |
| subjects affected / exposed     | 1 / 22 (4.55%)   |  |  |
| occurrences (all)               | 1                |  |  |
| Gastrointestinal disorders      |                  |  |  |
| Diarrhoea                       |                  |  |  |
| subjects affected / exposed     | 13 / 22 (59.09%) |  |  |
| occurrences (all)               | 13               |  |  |
| Nausea                          |                  |  |  |
| subjects affected / exposed     | 15 / 22 (68.18%) |  |  |
| occurrences (all)               | 15               |  |  |
| Vomiting                        |                  |  |  |
| subjects affected / exposed     | 3 / 22 (13.64%)  |  |  |
| occurrences (all)               | 3                |  |  |
| Dry mouth                       |                  |  |  |
| subjects affected / exposed     | 3 / 22 (13.64%)  |  |  |
| occurrences (all)               | 3                |  |  |
| Abdominal pain                  |                  |  |  |
| subjects affected / exposed     | 5 / 22 (22.73%)  |  |  |
| occurrences (all)               | 5                |  |  |
| Enterocolitis infectious        |                  |  |  |
| subjects affected / exposed     | 1 / 22 (4.55%)   |  |  |
| occurrences (all)               | 1                |  |  |
| Dyspepsia                       |                  |  |  |
| subjects affected / exposed     | 2 / 22 (9.09%)   |  |  |
| occurrences (all)               | 2                |  |  |
| Constipation                    |                  |  |  |
| subjects affected / exposed     | 7 / 22 (31.82%)  |  |  |
| occurrences (all)               | 7                |  |  |
| Mucositis                       |                  |  |  |
| subjects affected / exposed     | 2 / 22 (9.09%)   |  |  |
| occurrences (all)               | 2                |  |  |
| Gastroesophageal reflux disease |                  |  |  |
| subjects affected / exposed     | 1 / 22 (4.55%)   |  |  |
| occurrences (all)               | 1                |  |  |

|   |   |  |  |
|---|---|--|--|
| Gastrointestinal disorders - other, specify<br>subjects affected / exposed<br>occurrences (all)   | 1 / 22 (4.55%)<br>1   |  |  |
| Skin and subcutaneous tissue disorders<br>Alopecia<br>subjects affected / exposed<br>occurrences (all)<br><br>Flushing<br>subjects affected / exposed<br>occurrences (all)<br><br>Pruritus<br>subjects affected / exposed<br>occurrences (all)<br><br>Rash maculo-papular<br>subjects affected / exposed<br>occurrences (all)<br><br>Dry skin<br>subjects affected / exposed<br>occurrences (all)<br><br>Skin ulceration<br>subjects affected / exposed<br>occurrences (all)<br><br>allergic rhinitis<br>subjects affected / exposed<br>occurrences (all) | 2 / 22 (9.09%)<br>2<br><br>2 / 22 (9.09%)<br>2<br><br>2 / 22 (9.09%)<br>2<br><br>2 / 22 (9.09%)<br>2<br><br>1 / 22 (4.55%)<br>1<br><br>1 / 22 (4.55%)<br>1<br><br>1 / 22 (4.55%)<br>1 |  |  |
| Renal and urinary disorders<br>Acute kidney injury<br>subjects affected / exposed<br>occurrences (all)<br><br>Hyperuricemia<br>subjects affected / exposed<br>occurrences (all)   | 2 / 22 (9.09%)<br>2<br><br>3 / 22 (13.64%)<br>3   |  |  |
| Endocrine disorders<br>Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)   | 1 / 22 (4.55%)<br>1   |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Bone pain                                       |                 |  |  |
| subjects affected / exposed                     | 5 / 22 (22.73%) |  |  |
| occurrences (all)                               | 5               |  |  |
| Back pain                                       |                 |  |  |
| subjects affected / exposed                     | 4 / 22 (18.18%) |  |  |
| occurrences (all)                               | 4               |  |  |
| Myalgia   |                 |  |  |
| subjects affected / exposed                     | 2 / 22 (9.09%)  |  |  |
| occurrences (all)                               | 2               |  |  |
| Arthralgia                                      |                 |  |  |
| subjects affected / exposed                     | 2 / 22 (9.09%)  |  |  |
| occurrences (all)                               | 2               |  |  |
| neck pain                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Infections and infestations                     |                 |  |  |
| Upper respiratory infection                     |                 |  |  |
| subjects affected / exposed                     | 8 / 22 (36.36%) |  |  |
| occurrences (all)                               | 8               |  |  |
| Lung infection                                  |                 |  |  |
| subjects affected / exposed                     | 3 / 22 (13.64%) |  |  |
| occurrences (all)                               | 3               |  |  |
| Urinary tract infection                         |                 |  |  |
| subjects affected / exposed                     | 3 / 22 (13.64%) |  |  |
| occurrences (all)                               | 3               |  |  |
| Infections and infestations - other, specify    |                 |  |  |
| subjects affected / exposed                     | 4 / 22 (18.18%) |  |  |
| occurrences (all)                               | 4               |  |  |
| Soft tissue infection                           |                 |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Flu like symptoms                               |                 |  |  |
| subjects affected / exposed                     | 3 / 22 (13.64%) |  |  |
| occurrences (all)                               | 3               |  |  |
| Tooth infection                                 |                 |  |  |

|                                    |                  |  |  |
|------------------------------------|------------------|--|--|
| subjects affected / exposed        | 1 / 22 (4.55%)   |  |  |
| occurrences (all)                  | 1                |  |  |
| Metabolism and nutrition disorders |                  |  |  |
| Hyponatraemia                      |                  |  |  |
| subjects affected / exposed        | 6 / 22 (27.27%)  |  |  |
| occurrences (all)                  | 6                |  |  |
| Hypercalcemia                      |                  |  |  |
| subjects affected / exposed        | 2 / 22 (9.09%)   |  |  |
| occurrences (all)                  | 2                |  |  |
| Hypoalbuminaemia                   |                  |  |  |
| subjects affected / exposed        | 4 / 22 (18.18%)  |  |  |
| occurrences (all)                  | 4                |  |  |
| Anorexia                           |                  |  |  |
| subjects affected / exposed        | 14 / 22 (63.64%) |  |  |
| occurrences (all)                  | 14               |  |  |
| Dehydration                        |                  |  |  |
| subjects affected / exposed        | 1 / 22 (4.55%)   |  |  |
| occurrences (all)                  | 1                |  |  |
| Hypomagnesaemia                    |                  |  |  |
| subjects affected / exposed        | 2 / 22 (9.09%)   |  |  |
| occurrences (all)                  | 2                |  |  |
| Hypermagnesemia                    |                  |  |  |
| subjects affected / exposed        | 1 / 22 (4.55%)   |  |  |
| occurrences (all)                  | 1                |  |  |
| Hypernatremia                      |                  |  |  |
| subjects affected / exposed        | 1 / 22 (4.55%)   |  |  |
| occurrences (all)                  | 1                |  |  |
| Hypocalcemia                       |                  |  |  |
| subjects affected / exposed        | 1 / 22 (4.55%)   |  |  |
| occurrences (all)                  | 1                |  |  |
| hyperglycemia                      |                  |  |  |
| subjects affected / exposed        | 5 / 22 (22.73%)  |  |  |
| occurrences (all)                  | 5                |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment     |
|-------------------|---------------|
| 02 December 2011  | Protocol v3.0 |
| 14 March 2012     | Protocol v4.0 |
| 16 August 2013    | Protocol v5   |
| 04 July 2014      | Protocol v6   |
| 11 September 2014 | Protocol v7   |

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported