



## Clinical trial results:

### ALERT: A phase II study of alternating eribulin and hormonal therapy in pre-treated ER+ve breast cancer

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-004112-11 |
| Trial protocol           | GB             |
| Global end of trial date | 24 July 2018   |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 01 February 2020 |
| First version publication date | 01 February 2020 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | C/31/2014 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02681523 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Imperial College London  |
| Sponsor organisation address | Du Cane Road, London, United Kingdom, W12 ONN                            |
| Public contact               | Anna Kasim, Imperial College London, 44 2033130648, alert@imperial.ac.uk |
| Scientific contact           | Anna Kasim, Imperial College London, 44 2033130648, alert@imperial.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                       | 17 December 2018 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 24 July 2018     |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 24 July 2018     |
| Was the trial ended prematurely?                     | Yes              |

Notes:

## General information about the trial

Main objective of the trial:

To assess the efficacy of Eribulin when prescribed in alternating cycles with an Aromatase Inhibitor (AI) in patients with locally advanced or metastatic breast cancer, based on progression free survival (PFS).

Protection of trial subjects:

A Joint Trial Steering Committee (TSC) and Independent Data Monitoring Committee (IDMC) was set up to provide overall supervision for the study and to ensure it was conducted in accordance with Good Clinical Practice (GCP) and provided advice through its independent chairman. The joint TSC/IDMC also monitored the study progress and the committee members met in confidence at regular intervals as they saw fit but at least annually. Following each meeting they reported their findings and recommendations to the chief investigator (CI) and sponsor (CRUK Cancer Clinical Trials Unit) and the Trial Statistician. The joint TSC/IDMC consisted of two clinicians (not entering patients into the study), an independent statistician and an independent chairman, who gave recommendations and decided on continuing or stopping the study, or modifying the protocol.

Background therapy:

Non-Investigational Medicinal Product - Aromatase inhibitors (AIs): anastrozole 1mg, exemestane 25mg or letrozole 2.5mg once daily for 9 weeks.

Evidence for comparator:

Eribulin is standard of care for women with advanced breast cancer. In contrast to premenopausal women, in whom most of the oestrogen is produced in the ovaries, in postmenopausal women oestrogen is mainly produced in peripheral tissues of the body. Because some breast cancers respond to oestrogen, lowering oestrogen production at the site of the cancer (i.e. the adipose tissue of the breast) with AIs has been proven to be an effective treatment for hormone-sensitive breast cancer in postmenopausal women.

AIs work by inhibiting the action of the enzyme aromatase, which converts androgens into oestrogens by a process called aromatization. As oestrogen receptor positive (ER+ve) breast cancers are stimulated by oestrogens, decreasing their production is a way of suppressing recurrence of the breast tumour tissue. The main source of oestrogen is the ovaries in premenopausal women, while in post-menopausal women most of the body's oestrogen is produced in peripheral tissues (outside the central nervous system (CNS)), and also a few CNS sites in various regions within the brain.

Therefore, by alternating eribulin with AIs, we will examine in this pilot study whether there may be breakthrough relapse during the AI therapy or if we can extend the duration that eribulin may be used for. Importantly, blood based biomarkers, the tumour derived fraction of circulating free DNA (ctDNA), and circulating tumour cells will be measured.

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 23 February 2016 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United Kingdom: 8 |
| Worldwide total number of subjects   | 8                 |
| EEA total number of subjects         | 8                 |

Notes:

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**Subjects enrolled per age group**

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|   |   |
|---|---|
| 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)                      | 8 |
| From 65 to 84 years                       | 0 |
| 85 years and over                         | 0 |

## Subject disposition

### Recruitment

Recruitment details:

This was a single-centre, single arm, open label, non-randomised, phase II pilot study. The study recruited 8 female patients with ER+ve locally advanced or metastatic breast cancer who have received at least one chemotherapy agent in the metastatic setting.

### Pre-assignment

Screening details:

Each patient underwent a full screening assessment to confirm study eligibility. Patients who met all inclusion criteria (and none of the exclusion criteria) were enrolled onto the study. This included patients who have progressed after at least one chemotherapy regimen for advanced or metastatic disease.

### Pre-assignment period milestones

|                              |   |
|------------------------------|---|
| Number of subjects started   | 8 |
| Number of subjects completed |   |

### Period 1

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

Blinding implementation details:

No blinding - open label IMP

### Arms

|           |       |
|-----------|-------|
| Arm title | Arm 1 |
|-----------|-------|

Arm description:

Subjects were intravenously administered eribulin 1.23mg/m<sup>2</sup> (0.97mg/m<sup>2</sup> or 0.62mg/m<sup>2</sup> in patients with Child-Pugh A and Child-Pugh B respectively) on day 1 and day 8 of 21 day cycles.

This was then alternated with an AI inhibitor, orally once daily for 9 weeks, followed again by 21 day eribulin cycles and finally a further 9 weeks of the same AI treatment.

|  |  |
|--|--|
| Arm type                               | Experimental                                       |
| Investigational medicinal product name | Eribulin   |
| Investigational medicinal product code |  |
| Other name                             | Halaven  |
| Pharmaceutical forms                   | Concentrate and solvent for solution for injection |
| Routes of administration               | Intravenous use                                    |

Dosage and administration details:

1.23mg/m<sup>2</sup> on day 1 and day 8 for every 21 day cycles.

|  |                                      |
|--|--------------------------------------|
| Investigational medicinal product name | Aromatase Inhibitor                  |
| Investigational medicinal product code |                                      |
| Other name                             | Letrozole, exemestane or anastrozole |
| Pharmaceutical forms                   | Tablet                               |
| Routes of administration               | Oral use                             |

Dosage and administration details:

Aromatase inhibitor (NIMP) was prescribed under investigator discretion. Subjects were prescribed either:

Anastrozole 1mg tablets, letrozole 2.5mg tablets or exemestane 25mg tablets.

| <b>Number of subjects in period 1</b> | Arm 1 |
|---------------------------------------|-------|
| Started                               | 8     |
| Completed                             | 6     |
| Not completed                         | 2     |
| Adverse event, non-fatal              | 1     |
| Patient non-compliance                | 1     |

## Baseline characteristics

### Reporting groups

|   |               |
|---|---------------|
| Reporting group title   | Overall Trial |
| Reporting group description:  |               |
| Thirteen subjects were screened for eligibility and eight of these patients were recruited to the study. Six subsequently completed study and two were withdrawn. |               |

| Reporting group values  | Overall Trial | Total |  |
|---|---------------|-------|--|
| Number of subjects  | 8             | 8     |  |
| Age categorical   |               |       |  |
| Subjects aged 18 year and over were included in the study     |               |       |  |
| 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)  | 8             | 8     |  |
| From 65-84 years  | 0             | 0     |  |
| 85 years and over   | 0             | 0     |  |
| Age continuous  |               |       |  |
| Subjects aged 18 year and over were included in the trial     |               |       |  |
| Units: years  |               |       |  |
| median  | 50            |       |  |
| inter-quartile range (Q1-Q3)                                  | 48 to 57      | -     |  |
| Gender categorical  |               |       |  |
| Female patients   |               |       |  |
| Units: Subjects   |               |       |  |
| Female  | 8             | 8     |  |
| Male  | 0             | 0     |  |
| Ethnicity   |               |       |  |
| Subjects of all ethnicity were included.                      |               |       |  |
| Units: Subjects   |               |       |  |
| White   | 6             | 6     |  |
| Turkish   | 1             | 1     |  |
| Middle Eastern  | 1             | 1     |  |
| Mixed   | 0             | 0     |  |
| Asian   | 0             | 0     |  |
| Black   | 0             | 0     |  |
| Other ethnic group  | 0             | 0     |  |
| Eastern Cooperative Oncology Group (ECOG) Performance Status  |               |       |  |
| An ECOG Performance Assessment was performed for each subject |               |       |  |
| Units: Subjects   |               |       |  |
| ECOG Performance Status 1                                     | 4             | 4     |  |
| ECOG Performance Status 0                                     | 4             | 4     |  |

|  |   |   |  |
|--|---|---|--|
| ECOG Performance Status 2  | 0 | 0 |  |
| ECOG Performance Status 3  | 0 | 0 |  |
| ECOG Performance Status 4  | 0 | 0 |  |
| ECOG Performance Status 5  | 0 | 0 |  |
| Smoking Status   |   |   |  |
| Smoking Status for all subjects were collected   |   |   |  |
| Units: Subjects  |   |   |  |
| Never  | 3 | 3 |  |
| Former   | 3 | 3 |  |
| Current  | 1 | 1 |  |
| No Information   | 1 | 1 |  |
| Tumour Type  |   |   |  |
| The tumour type for all subjects was assessed using CT or MRI scans of the chest, abdomen and pelvis.              |   |   |  |
| Units: Subjects  |   |   |  |
| Invasive Ductal Carcinoma  | 8 | 8 |  |
| ER Status  |   |   |  |
| The oestrogen receptor status for all subjects was assessed histologically and was ER positive for study enrolment |   |   |  |
| Units: Subjects  |   |   |  |
| Allred   | 3 | 3 |  |
| Other  | 5 | 5 |  |
| PgR Status   |   |   |  |
| Units: Subjects  |   |   |  |
| Positive   | 7 | 7 |  |
| Negative   | 0 | 0 |  |
| Unknown  | 1 | 1 |  |
| HER2 Status  |   |   |  |
| Units: Subjects  |   |   |  |
| Zero   | 5 | 5 |  |
| 1+   | 1 | 1 |  |
| 2+   | 0 | 0 |  |
| 3+   | 0 | 0 |  |
| Not done   | 2 | 2 |  |
| Primary Tumour Stage   |   |   |  |
| Units: Subjects  |   |   |  |
| Stage I  | 1 | 1 |  |
| Stage IIA  | 1 | 1 |  |
| Stage IIIA   | 1 | 1 |  |
| Stage IIIC   | 1 | 1 |  |
| No information   | 4 | 4 |  |
| Primary Tumour Grade   |   |   |  |
| Units: Subjects  |   |   |  |
| G1   | 1 | 1 |  |
| G2   | 5 | 5 |  |
| G3   | 2 | 2 |  |
| Prior Chemotherapy   |   |   |  |
| Units: Subjects  |   |   |  |
| Yes  | 8 | 8 |  |
| No   | 0 | 0 |  |
| Prior Radiotherapy   |   |   |  |
| Units: Subjects  |   |   |  |

|  |              |   |  |
|--|--------------|---|--|
| Yes  | 8            | 8 |  |
| No   | 0            | 0 |  |
| Prior Endocrine Therapy_ Tamoxifen<br>Units: Subjects      |              |   |  |
| Tamoxifen  | 8            | 8 |  |
| Prior Surgery<br>Units: Subjects                           |              |   |  |
| Yes  | 8            | 8 |  |
| No   | 0            | 0 |  |
| Prior Endocrine Therapy_ Exemestane<br>Units: Subjects     |              |   |  |
| Exemestane   | 5            | 5 |  |
| No Exemestane  | 3            | 3 |  |
| Endocrine Therapy_ Letrozole and<br>Units: Subjects        |              |   |  |
| Letrozole  | 3            | 3 |  |
| Anastrozole  | 5            | 5 |  |
| Body Mass Index  |              |   |  |
| Body Mass Index was assessed and reported for all subjects |              |   |  |
| Units: kg/m2   |              |   |  |
| median   | 26.5         |   |  |
| full range (min-max)                                       | 20.3 to 31.6 | - |  |
| Primary Tumour Size<br>Units: mm                           |              |   |  |
| median   | 28           |   |  |
| full range (min-max)                                       | 25 to 40     | - |  |



## End points

### End points reporting groups

|                       |       |
|-----------------------|-------|
| Reporting group title | Arm 1 |
|-----------------------|-------|

Reporting group description:

Subjects were intravenously administered eribulin 1.23mg/m<sup>2</sup> (0.97mg/m<sup>2</sup> or 0.62mg/m<sup>2</sup> in patients with Child-Pugh A and Child-Pugh B respectively) on day 1 and day 8 of 21 day cycles.

This was then alternated with an AI inhibitor, orally once daily for 9 weeks, followed again by 21 day eribulin cycles and finally a further 9 weeks of the same AI treatment.

### Primary: Progression Free Survival (PFS) at fixed time points

|                 |   |
|-----------------|---|
| End point title | Progression Free Survival (PFS) at fixed time points <sup>[1]</sup> |
|-----------------|---|

End point description:

The median PRS at the end of the study was 235 days. The mean PFS could not be calculated at 3 months, as no patients experienced disease progression at Follow-up.

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

End point timeframe:

PFS rate was measured at fixed time points of 3, 6 and 9 months (as estimated by the Kaplan-Meier Curve).

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: The median Progression-Free Survival (PFS) Rate was calculated based on the time from study enrolment to the first evidence of progression for each patient. Patients were censored at the last follow-up date if they are lost to follow-up, withdrawn from the study or not progressed at the end of the study.

| End point values                | Arm 1           |  |  |  |
|---------------------------------|-----------------|--|--|--|
| Subject group type              | Reporting group |  |  |  |
| Number of subjects analysed     | 8               |  |  |  |
| Units: Days                     |                 |  |  |  |
| 3 months - cannot be calculated | 0               |  |  |  |
| 6 months                        | 202             |  |  |  |
| 9 months                        | 235             |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Clinical Benefit Rate (CBR)

|                 |                             |
|-----------------|-----------------------------|
| End point title | Clinical Benefit Rate (CBR) |
|-----------------|-----------------------------|

End point description:

Only 6 patients had at least one tumour assessment during the study period.

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

End point timeframe:

Clinical Benefit Rate (CBR), defined as proportion whose best overall response, according Response

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | Arm 1           |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 6               |  |  |  |
| Units: Observed CBR         |                 |  |  |  |
| Stable disease              | 3               |  |  |  |
| Partial response            | 3               |  |  |  |
| Complete response           | 0               |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Safety and Tolerability

|                        |  |
|------------------------|--|
| End point title        | Safety and Tolerability  |
| End point description: | Safety and tolerability as assessed by adverse events (AE) and serious adverse events (SAEs) according to the Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.03) |
| End point type         | Secondary  |
| End point timeframe:   | Collected from consent to follow-up for subjects who received at least one dose of study treatment.  |

|                               |                 |  |  |  |
|-------------------------------|-----------------|--|--|--|
| <b>End point values</b>       | Arm 1           |  |  |  |
| Subject group type            | Reporting group |  |  |  |
| Number of subjects analysed   | 8               |  |  |  |
| Units: AE and SAEs            |                 |  |  |  |
| Mild                          | 71              |  |  |  |
| Moderate                      | 39              |  |  |  |
| Severe                        | 17              |  |  |  |
| Life threatening or disabling | 2               |  |  |  |
| Death                         | 0               |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs and SAEs) were collected from consent to end of follow up for all patients, followed up according to local practice until stabilised or resolved, 9 months.

Adverse event reporting additional description:

All Adverse event were collected electronically in the eCRF.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 22.0 |
|--------------------|------|

### Reporting groups

|                       |      |
|-----------------------|------|
| Reporting group title | Arm1 |
|-----------------------|------|

Reporting group description:

Treatment Arm

| Serious adverse events                               | Arm1           |  |  |
|--|----------------|--|--|
| Total subjects affected by serious adverse events    |                |  |  |
| subjects affected / exposed                          | 5 / 8 (62.50%) |  |  |
| number of deaths (all causes)                        | 0              |  |  |
| number of deaths resulting from adverse events       | 0              |  |  |
| Nervous system disorders                             |                |  |  |
| Ischaemia cerebrovascular                            |                |  |  |
| subjects affected / exposed                          | 1 / 8 (12.50%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General disorders and administration site conditions |                |  |  |
| Mucositis  |                |  |  |
| subjects affected / exposed                          | 1 / 8 (12.50%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Gastrointestinal disorders                           |                |  |  |
| Vomiting   |                |  |  |
| subjects affected / exposed                          | 1 / 8 (12.50%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Respiratory, thoracic and mediastinal disorders      |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Dyspnea   |                |  |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory distress syndrome                   |                |  |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Neutropenic sepsis                              |                |  |  |
| subjects affected / exposed                     | 2 / 8 (25.00%) |  |  |
| occurrences causally related to treatment / all | 1 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Metabolism and nutrition disorders              |                |  |  |
| Hypercalcaemia                                  |                |  |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| <b>Non-serious adverse events</b>                     | Arm1            |  |  |
|---|-----------------|--|--|
| Total subjects affected by non-serious adverse events |                 |  |  |
| subjects affected / exposed                           | 8 / 8 (100.00%) |  |  |
| Vascular disorders                                    |                 |  |  |
| Flushing  |                 |  |  |
| subjects affected / exposed                           | 2 / 8 (25.00%)  |  |  |
| occurrences (all)                                     | 2               |  |  |
| General disorders and administration site conditions  |                 |  |  |
| Fatigue   |                 |  |  |
| subjects affected / exposed                           | 5 / 8 (62.50%)  |  |  |
| occurrences (all)                                     | 6               |  |  |
| Influenza like illness                                |                 |  |  |
| subjects affected / exposed                           | 1 / 8 (12.50%)  |  |  |
| occurrences (all)                                     | 1               |  |  |
| Mucosal inflammation                                  |                 |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 8 (12.50%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Oedema peripheral                               |                |  |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Pain  |                |  |  |
| subjects affected / exposed                     | 3 / 8 (37.50%) |  |  |
| occurrences (all)                               | 4              |  |  |
| Peripheral swelling                             |                |  |  |
| subjects affected / exposed                     | 3 / 8 (37.50%) |  |  |
| occurrences (all)                               | 3              |  |  |
| Pyrexia   |                |  |  |
| subjects affected / exposed                     | 2 / 8 (25.00%) |  |  |
| occurrences (all)                               | 2              |  |  |
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| Cough   |                |  |  |
| subjects affected / exposed                     | 3 / 8 (37.50%) |  |  |
| occurrences (all)                               | 3              |  |  |
| Dyspnoea  |                |  |  |
| subjects affected / exposed                     | 4 / 8 (50.00%) |  |  |
| occurrences (all)                               | 6              |  |  |
| Nasopharyngitis                                 |                |  |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Oropharyngeal pain                              |                |  |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Pleural effusion                                |                |  |  |
| subjects affected / exposed                     | 2 / 8 (25.00%) |  |  |
| occurrences (all)                               | 2              |  |  |
| Tonsillar erythema                              |                |  |  |
| subjects affected / exposed                     | 1 / 8 (12.50%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Investigations                                  |                |  |  |

|  |                     |  |  |
|--|---------------------|--|--|
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)                   | 2 / 8 (25.00%)<br>2 |  |  |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)                 | 2 / 8 (25.00%)<br>2 |  |  |
| Blood alkaline phosphatase<br>subjects affected / exposed<br>occurrences (all)                           | 1 / 8 (12.50%)<br>1 |  |  |
| Blood cholesterol increased<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 8 (12.50%)<br>1 |  |  |
| Grip strength decreased<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 8 (12.50%)<br>1 |  |  |
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)                           | 1 / 8 (12.50%)<br>1 |  |  |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)                             | 1 / 8 (12.50%)<br>1 |  |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                                     | 1 / 8 (12.50%)<br>1 |  |  |
| White blood cell count decreased<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 8 (12.50%)<br>1 |  |  |
| Cardiac disorders<br>Palpitations<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 8 (12.50%)<br>1 |  |  |
| Nervous system disorders<br>Ageusia<br>subjects affected / exposed<br>occurrences (all)<br><br>Dizziness | 2 / 8 (25.00%)<br>2 |  |  |

|                                      |                |  |  |
|--------------------------------------|----------------|--|--|
| subjects affected / exposed          | 2 / 8 (25.00%) |  |  |
| occurrences (all)                    | 2              |  |  |
| Headache                             |                |  |  |
| subjects affected / exposed          | 1 / 8 (12.50%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Neuropathy peripheral                |                |  |  |
| subjects affected / exposed          | 4 / 8 (50.00%) |  |  |
| occurrences (all)                    | 4              |  |  |
| Paraesthesia                         |                |  |  |
| subjects affected / exposed          | 1 / 8 (12.50%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Sciatica                             |                |  |  |
| subjects affected / exposed          | 1 / 8 (12.50%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Cognitive disorder                   |                |  |  |
| subjects affected / exposed          | 1 / 8 (12.50%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Blood and lymphatic system disorders |                |  |  |
| Lymphadenopathy                      |                |  |  |
| subjects affected / exposed          | 2 / 8 (25.00%) |  |  |
| occurrences (all)                    | 2              |  |  |
| Neutropenia                          |                |  |  |
| subjects affected / exposed          | 1 / 8 (12.50%) |  |  |
| occurrences (all)                    | 2              |  |  |
| Ear and labyrinth disorders          |                |  |  |
| Ear pain                             |                |  |  |
| subjects affected / exposed          | 2 / 8 (25.00%) |  |  |
| occurrences (all)                    | 2              |  |  |
| Gastrointestinal disorders           |                |  |  |
| Abdominal distension                 |                |  |  |
| subjects affected / exposed          | 3 / 8 (37.50%) |  |  |
| occurrences (all)                    | 3              |  |  |
| Abdominal pain upper                 |                |  |  |
| subjects affected / exposed          | 1 / 8 (12.50%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Abdominal pain                       |                |  |  |

|                             |                |  |  |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 2 / 8 (25.00%) |  |  |
| occurrences (all)           | 2              |  |  |
| Ascites                     |                |  |  |
| subjects affected / exposed | 1 / 8 (12.50%) |  |  |
| occurrences (all)           | 1              |  |  |
| Constipation                |                |  |  |
| subjects affected / exposed | 4 / 8 (50.00%) |  |  |
| occurrences (all)           | 4              |  |  |
| Diarrhoea                   |                |  |  |
| subjects affected / exposed | 1 / 8 (12.50%) |  |  |
| occurrences (all)           | 1              |  |  |
| Dry mouth                   |                |  |  |
| subjects affected / exposed | 1 / 8 (12.50%) |  |  |
| occurrences (all)           | 1              |  |  |
| Dyspepsia                   |                |  |  |
| subjects affected / exposed | 1 / 8 (12.50%) |  |  |
| occurrences (all)           | 1              |  |  |
| Heartburn/burping           |                |  |  |
| subjects affected / exposed | 1 / 8 (12.50%) |  |  |
| occurrences (all)           | 1              |  |  |
| Melaena                     |                |  |  |
| subjects affected / exposed | 1 / 8 (12.50%) |  |  |
| occurrences (all)           | 1              |  |  |
| Mouth ulceration            |                |  |  |
| subjects affected / exposed | 2 / 8 (25.00%) |  |  |
| occurrences (all)           | 2              |  |  |
| Nausea                      |                |  |  |
| subjects affected / exposed | 4 / 8 (50.00%) |  |  |
| occurrences (all)           | 4              |  |  |
| Oral pain                   |                |  |  |
| subjects affected / exposed | 1 / 8 (12.50%) |  |  |
| occurrences (all)           | 1              |  |  |
| Rectal haemorrhage          |                |  |  |
| subjects affected / exposed | 1 / 8 (12.50%) |  |  |
| occurrences (all)           | 1              |  |  |
| Teeth and gum darkening     |                |  |  |



|   |   |  |  |
|---|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Teeth and gum thinning</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>1 / 8 (12.50%)</p> <p>1</p> <p>1 / 8 (12.50%)</p> <p>1</p> <p>1 / 8 (12.50%)</p> <p>1</p>                                |  |  |
| <p>Hepatobiliary disorders</p> <p>Hepatic pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hepatomegaly</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>1 / 8 (12.50%)</p> <p>1</p> <p>2 / 8 (25.00%)</p> <p>2</p>   |  |  |
| <p>Skin and subcutaneous tissue disorders</p> <p>Alopecia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hyperhidrosis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pruritus</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Skin striae</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>6 / 8 (75.00%)</p> <p>6</p> <p>1 / 8 (12.50%)</p> <p>1</p> <p>1 / 8 (12.50%)</p> <p>1</p> <p>1 / 8 (12.50%)</p> <p>1</p> |  |  |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Muscle spasms</p>  | <p>3 / 8 (37.50%)</p> <p>3</p> <p>2 / 8 (25.00%)</p> <p>2</p>   |  |  |

|                                    |                |  |  |
|------------------------------------|----------------|--|--|
| subjects affected / exposed        | 1 / 8 (12.50%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Musculoskeletal pain               |                |  |  |
| subjects affected / exposed        | 1 / 8 (12.50%) |  |  |
| occurrences (all)                  | 2              |  |  |
| Pain in jaw                        |                |  |  |
| subjects affected / exposed        | 1 / 8 (12.50%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Infections and infestations        |                |  |  |
| Ear infection                      |                |  |  |
| subjects affected / exposed        | 2 / 8 (25.00%) |  |  |
| occurrences (all)                  | 2              |  |  |
| Neutropenic sepsis                 |                |  |  |
| subjects affected / exposed        | 1 / 8 (12.50%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Oral herpes                        |                |  |  |
| subjects affected / exposed        | 1 / 8 (12.50%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Vaginal infection                  |                |  |  |
| subjects affected / exposed        | 1 / 8 (12.50%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Metabolism and nutrition disorders |                |  |  |
| Decreased appetite                 |                |  |  |
| subjects affected / exposed        | 1 / 8 (12.50%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Diabetes mellitus                  |                |  |  |
| subjects affected / exposed        | 1 / 8 (12.50%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Hypercalcaemia                     |                |  |  |
| subjects affected / exposed        | 1 / 8 (12.50%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Hypoalbuminaemia                   |                |  |  |
| subjects affected / exposed        | 1 / 8 (12.50%) |  |  |
| occurrences (all)                  | 1              |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 17 September 2015 | <p>Substantial Amendment 01 was made to include the following:</p> <ul style="list-style-type: none"><li>• Amendment to the inclusion and exclusion criteria in the number/type of prior lines of therapy and clarification that only site of measurable disease is required.</li><li>• Change to primary, secondary and translational endpoints</li><li>• Included action to take in case of pregnancy</li><li>• Inclusion of serum albumin to biochemistry tests, the removal of troponin I measurement, units of measurements corrected and a change to blood volume collected for translational samples.</li><li>• Clarification of the location of translational sample analysis</li><li>• Change from obligatory to optional tissue sample collection</li><li>• Other minor administrative updates and amendments to wording/typographical errors, including potential risks, the naming of the coordinating centre, change in statistician, updated sponsor details and the change in the naming of the end of study visit.</li></ul> |
| 25 July 2017      | <p>Substantial Amendment 02 was made to include the following:</p> <ul style="list-style-type: none"><li>• Change in chief investigator (CI) and principal investigator (PI)</li><li>• Change in contact details for the CI and PI, reflected in the protocol and GP letter.</li><li>• Administrative updates to reflect staff changes, including the Trial Coordinator, Clinical Trial Manager, Sponsor and member of the Protocol Development Group.</li><li>• Change to treatment schedule to allow +/- 1 week window for week 18 assessments allowing them to take place during week 19 eribulin treatment.</li></ul>  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

This was a pilot study planned to recruit 12 patients. Due to slow recruitment, the study was terminated early after the recruitment of 8 patients. Of the patients recruited, 6 completed the study.

Notes: