



## Clinical trial results:

### A multicentre phase III randomised double blind placebo controlled trial of pravastatin added to first-line chemotherapy in patients with small cell lung cancer

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2005-005821-71   |
| Trial protocol           | GB               |
| Global end of trial date | 13 November 2013 |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 13 October 2016 |
| First version publication date | 13 October 2016 |

#### Trial information

##### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | UCL/05/129 |
|-----------------------|------------|

##### Additional study identifiers

|                                    |                |
|------------------------------------|----------------|
| ISRCTN number                      | ISRCTN56306957 |
| ClinicalTrials.gov id (NCT number) | NCT00433498    |
| WHO universal trial number (UTN)   | -              |

Notes:

##### Sponsors

|                              |                                                                                                            |
|------------------------------|------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | University College London                                                                                  |
| Sponsor organisation address | Gower Street, London, United Kingdom, WC1E 6BT                                                             |
| Public contact               | Trial Coordinator, Cancer Research UK & UCL Cancer Trials Centre, 0044 02076799747, ctc.lungstar@ucl.ac.uk |
| Scientific contact           | Trial Coordinator, Cancer Research UK & UCL Cancer Trials Centre, 0044 02076799974, ctc.lungstar@ucl.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:

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**Results analysis stage**

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|                                                      |                  |
|------------------------------------------------------|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 30 October 2015  |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 13 November 2013 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 13 November 2013 |
| Was the trial ended prematurely?                     | No               |

Notes:

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**General information about the trial**

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Main objective of the trial:

To determine in patients with SCLC if survival is affected by the addition of pravastatin to either cisplatin/etoposide or carboplatin/etoposide.

Protection of trial subjects:

Dose modification guidance in place to allow for dose reductions.

Guidance for management of adverse events in place

Regular assessments of adverse events during treatment and follow-up

Background therapy:

None

Evidence for comparator:

All patients were randomised to receive either 'chemotherapy and pravastatin' OR 'chemotherapy and placebo'.

The choice of chemotherapy (either cisplatin and etoposide OR carboplatin and etoposide) was determined as per local practice and are the standard drugs used in this patient population.

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 19 February 2007 |
| 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**

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | United Kingdom: 846 |
| Worldwide total number of subjects   | 846                 |
| EEA total number of subjects         | 846                 |

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) | 412 |
| From 65 to 84 years  | 432 |
| 85 years and over    | 2   |

## Subject disposition

### Recruitment

Recruitment details:

All patients were recruited between 19 February 2007 and 31/01/2012

### Pre-assignment

Screening details:

All screening assessments were performed up to 21 days prior to randomisation (CT scan were performed up to 31 days prior to randomisation).

### Period 1

|                              |                                                 |
|------------------------------|-------------------------------------------------|
| Period 1 title               | Overall trial (overall period)                  |
| Is this the baseline period? | Yes                                             |
| Allocation method            | Randomised - controlled                         |
| Blinding used                | Double blind                                    |
| Roles blinded                | Investigator, Monitor, Carer, Assessor, Subject |

Blinding implementation details:

Use of a matched placebo

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | Pravastatin |
|------------------|-------------|

Arm description:

Chemotherapy (cisplatin and etoposide or carboplatin and etoposide) + pravastatin

|                                        |                                       |
|----------------------------------------|---------------------------------------|
| Arm type                               | Active comparator                     |
| Investigational medicinal product name | cisplatin or carboplatin              |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

According to local guidelines - for a maximum of 6 cycles

|                                        |                                                                |
|----------------------------------------|----------------------------------------------------------------|
| Investigational medicinal product name | Etoposide                                                      |
| Investigational medicinal product code |                                                                |
| Other name                             |                                                                |
| Pharmaceutical forms                   | Capsule, soft, Concentrate for solution for injection/infusion |
| Routes of administration               | Intravenous use, Oral use                                      |

Dosage and administration details:

According to local guidelines - for a maximum of 6 cycles

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

Dosage and administration details:

40mg daily for a maximum of 24 months.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Matched placebo

|                                        |                                       |
|----------------------------------------|---------------------------------------|
| Arm type                               | Placebo                               |
| Investigational medicinal product name | cisplatin or carboplatin              |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

According to local guidelines - for a maximum of 6 cycles

|                                        |                                                                |
|----------------------------------------|----------------------------------------------------------------|
| Investigational medicinal product name | Etoposide                                                      |
| Investigational medicinal product code |                                                                |
| Other name                             |                                                                |
| Pharmaceutical forms                   | Capsule, soft, Concentrate for solution for injection/infusion |
| Routes of administration               | Intravenous use, Oral use                                      |

Dosage and administration details:

According to local guidelines - for a maximum of 6 cycles

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

Dosage and administration details:

Daily for a maximum of 24 months.

| <b>Number of subjects in period 1</b> | Pravastatin | Placebo |
|---------------------------------------|-------------|---------|
| Started                               | 422         | 424     |
| Completed                             | 422         | 424     |

## Baseline characteristics

### Reporting groups

|                                                                                                                   |             |
|-------------------------------------------------------------------------------------------------------------------|-------------|
| Reporting group title                                                                                             | Pravastatin |
| Reporting group description:<br>Chemotherapy (cisplatin and etoposide or carboplatin and etoposide) + pravastatin |             |
| Reporting group title                                                                                             | Placebo     |
| Reporting group description:<br>Matched placebo                                                                   |             |

| Reporting group values                                | Pravastatin | Placebo | Total |
|-------------------------------------------------------|-------------|---------|-------|
| Number of subjects                                    | 422         | 424     | 846   |
| Age categorical<br>Units: Subjects                    |             |         |       |
| In utero                                              | 0           | 0       | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0           | 0       | 0     |
| Newborns (0-27 days)                                  | 0           | 0       | 0     |
| Infants and toddlers (28 days-23 months)              | 0           | 0       | 0     |
| Children (2-11 years)                                 | 0           | 0       | 0     |
| Adolescents (12-17 years)                             | 0           | 0       | 0     |
| Adults (18-64 years)                                  | 200         | 212     | 412   |
| From 65-84 years                                      | 221         | 211     | 432   |
| 85 years and over                                     | 1           | 1       | 2     |
| Gender categorical<br>Units: Subjects                 |             |         |       |
| Female                                                | 203         | 210     | 413   |
| Male                                                  | 219         | 214     | 433   |

## End points

### End points reporting groups

|                                                                                   |             |
|-----------------------------------------------------------------------------------|-------------|
| Reporting group title                                                             | Pravastatin |
| Reporting group description:                                                      |             |
| Chemotherapy (cisplatin and etoposide or carboplatin and etoposide) + pravastatin |             |
| Reporting group title                                                             | Placebo     |
| Reporting group description:                                                      |             |
| Matched placebo                                                                   |             |

### Primary: Overall Survival

|                        |                  |
|------------------------|------------------|
| End point title        | Overall Survival |
| End point description: |                  |
| End point type         | Primary          |
| End point timeframe:   |                  |
| 01/10/2015             |                  |

| End point values            | Pravastatin     | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 422             | 424             |  |  |
| Units: Subjects             |                 |                 |  |  |
| Dead                        | 381             | 377             |  |  |

|                            |                                 |
|----------------------------|---------------------------------|
| Attachments (see zip file) | Overall survival/km_plot_os.png |
|----------------------------|---------------------------------|

### Statistical analyses

|                                         |                       |
|-----------------------------------------|-----------------------|
| Statistical analysis title              | Hazard ratio          |
| Comparison groups                       | Pravastatin v Placebo |
| Number of subjects included in analysis | 846                   |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | superiority           |
| P-value                                 | = 0.9                 |
| Method                                  | Regression, Cox       |
| Parameter estimate                      | Hazard ratio (HR)     |
| Point estimate                          | 1.01                  |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | 0.88                  |
| upper limit                             | 1.16                  |

## Secondary: Progression Free Survival

|                 |                           |
|-----------------|---------------------------|
| End point title | Progression Free Survival |
|-----------------|---------------------------|

End point description:

Progressed or died.

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

End point timeframe:

01/10/2015

| End point values            | Pravastatin     | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 422             | 424             |  |  |
| Units: Subjects             |                 |                 |  |  |
| Progressed                  | 395             | 392             |  |  |

|                            |                                           |
|----------------------------|-------------------------------------------|
| Attachments (see zip file) | Progression-free survival/km_plot_pfs.png |
|----------------------------|-------------------------------------------|

## Statistical analyses

|                                         |                       |
|-----------------------------------------|-----------------------|
| Statistical analysis title              | Hazard ratio          |
| Comparison groups                       | Pravastatin v Placebo |
| Number of subjects included in analysis | 846                   |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | superiority           |
| P-value                                 | = 0.81                |
| Method                                  | Regression, Cox       |
| Parameter estimate                      | Hazard ratio (HR)     |
| Point estimate                          | 0.98                  |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | 0.85                  |
| upper limit                             | 1.13                  |



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From informed consent and 28 days post last trial treatment administration

Adverse event reporting additional description:

01/10/2015

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

### Dictionary used

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

|                    |   |
|--------------------|---|
| Dictionary version | 3 |
|--------------------|---|

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Pravastatin |
|-----------------------|-------------|

Reporting group description:

Chemotherapy (cisplatin and etoposide or carboplatin and etoposide) + pravastatin

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Matched placebo

| Serious adverse events                            | Pravastatin        | Placebo            |  |
|---------------------------------------------------|--------------------|--------------------|--|
| Total subjects affected by serious adverse events |                    |                    |  |
| subjects affected / exposed                       | 221 / 422 (52.37%) | 213 / 424 (50.24%) |  |
| number of deaths (all causes)                     | 381                | 377                |  |
| number of deaths resulting from adverse events    | 2                  | 0                  |  |
| Vascular disorders                                |                    |                    |  |
| Peripheral arterial ischemia                      |                    |                    |  |
| subjects affected / exposed                       | 0 / 422 (0.00%)    | 1 / 424 (0.24%)    |  |
| occurrences causally related to treatment / all   | 0 / 0              | 0 / 1              |  |
| deaths causally related to treatment / all        | 0 / 0              | 0 / 0              |  |
| Thrombosis/thrombus/embolism                      |                    |                    |  |
| subjects affected / exposed                       | 14 / 422 (3.32%)   | 20 / 424 (4.72%)   |  |
| occurrences causally related to treatment / all   | 2 / 16             | 0 / 21             |  |
| deaths causally related to treatment / all        | 1 / 3              | 0 / 0              |  |
| Vascular - other                                  |                    |                    |  |
| subjects affected / exposed                       | 0 / 422 (0.00%)    | 3 / 424 (0.71%)    |  |
| occurrences causally related to treatment / all   | 0 / 0              | 0 / 3              |  |
| deaths causally related to treatment / all        | 0 / 0              | 0 / 0              |  |
| Visceral arterial ischemia                        |                    |                    |  |

|                                                      |                  |                  |  |
|------------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                          | 1 / 422 (0.24%)  | 0 / 424 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| General disorders and administration site conditions |                  |                  |  |
| Death not associated with CTCAE term                 |                  |                  |  |
| subjects affected / exposed                          | 1 / 422 (0.24%)  | 5 / 424 (1.18%)  |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 5            |  |
| deaths causally related to treatment / all           | 0 / 1            | 0 / 5            |  |
| Fatigue                                              |                  |                  |  |
| subjects affected / exposed                          | 11 / 422 (2.61%) | 4 / 424 (0.94%)  |  |
| occurrences causally related to treatment / all      | 0 / 11           | 0 / 4            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Fever                                                |                  |                  |  |
| subjects affected / exposed                          | 8 / 422 (1.90%)  | 6 / 424 (1.42%)  |  |
| occurrences causally related to treatment / all      | 0 / 9            | 0 / 6            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Insomnia                                             |                  |                  |  |
| subjects affected / exposed                          | 0 / 422 (0.00%)  | 1 / 424 (0.24%)  |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Pain                                                 |                  |                  |  |
| subjects affected / exposed                          | 35 / 422 (8.29%) | 25 / 424 (5.90%) |  |
| occurrences causally related to treatment / all      | 1 / 38           | 2 / 27           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Weight loss                                          |                  |                  |  |
| subjects affected / exposed                          | 1 / 422 (0.24%)  | 0 / 424 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Immune system disorders                              |                  |                  |  |
| Allergic reaction                                    |                  |                  |  |
| subjects affected / exposed                          | 1 / 422 (0.24%)  | 0 / 424 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| Respiratory, thoracic and mediastinal disorders |                  |                  |  |
| ARDS                                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 422 (0.00%)  | 1 / 424 (0.24%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cough                                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 422 (0.24%)  | 3 / 424 (0.71%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dyspnea                                         |                  |                  |  |
| subjects affected / exposed                     | 23 / 422 (5.45%) | 26 / 424 (6.13%) |  |
| occurrences causally related to treatment / all | 0 / 25           | 1 / 31           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Hypoxia                                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 422 (0.00%)  | 1 / 424 (0.24%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pleural effusion                                |                  |                  |  |
| subjects affected / exposed                     | 3 / 422 (0.71%)  | 4 / 424 (0.94%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumonitis                                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 422 (0.47%)  | 1 / 424 (0.24%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumothorax                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 422 (0.24%)  | 3 / 424 (0.71%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pulmonary - Other                               |                  |                  |  |
| subjects affected / exposed                     | 3 / 422 (0.71%)  | 2 / 424 (0.47%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

|                                                 |                 |                  |  |
|-------------------------------------------------|-----------------|------------------|--|
| Pulmonary fibrosis                              |                 |                  |  |
| subjects affected / exposed                     | 0 / 422 (0.00%) | 1 / 424 (0.24%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Investigations                                  |                 |                  |  |
| Bilirubin                                       |                 |                  |  |
| subjects affected / exposed                     | 1 / 422 (0.24%) | 0 / 424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Cardiac disorders                               |                 |                  |  |
| Cardiac Arrhythmia - Other                      |                 |                  |  |
| subjects affected / exposed                     | 3 / 422 (0.71%) | 2 / 424 (0.47%)  |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Cardiac General - Other                         |                 |                  |  |
| subjects affected / exposed                     | 1 / 422 (0.24%) | 2 / 424 (0.47%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| Cardiac ischemia/infarction                     |                 |                  |  |
| subjects affected / exposed                     | 2 / 422 (0.47%) | 10 / 424 (2.36%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 11           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2            |  |
| Hypotension                                     |                 |                  |  |
| subjects affected / exposed                     | 1 / 422 (0.24%) | 2 / 424 (0.47%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Left ventricular systolic dysfunction           |                 |                  |  |
| subjects affected / exposed                     | 1 / 422 (0.24%) | 0 / 424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| Pericarditis                                    |                 |                  |  |
| subjects affected / exposed                     | 0 / 422 (0.00%) | 1 / 424 (0.24%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |

|                                                            |                  |                 |  |
|------------------------------------------------------------|------------------|-----------------|--|
| Supraventricular arrhythmia<br>subjects affected / exposed | 10 / 422 (2.37%) | 3 / 424 (0.71%) |  |
| occurrences causally related to<br>treatment / all         | 0 / 10           | 0 / 3           |  |
| deaths causally related to<br>treatment / all              | 0 / 0            | 0 / 0           |  |
| Valvular heart disease<br>subjects affected / exposed      | 1 / 422 (0.24%)  | 0 / 424 (0.00%) |  |
| occurrences causally related to<br>treatment / all         | 0 / 1            | 0 / 0           |  |
| deaths causally related to<br>treatment / all              | 0 / 0            | 0 / 0           |  |
| Vasovagal episode<br>subjects affected / exposed           | 1 / 422 (0.24%)  | 1 / 424 (0.24%) |  |
| occurrences causally related to<br>treatment / all         | 0 / 1            | 0 / 1           |  |
| deaths causally related to<br>treatment / all              | 0 / 0            | 0 / 0           |  |
| Nervous system disorders                                   |                  |                 |  |
| Ataxia<br>subjects affected / exposed                      | 1 / 422 (0.24%)  | 1 / 424 (0.24%) |  |
| occurrences causally related to<br>treatment / all         | 0 / 1            | 0 / 1           |  |
| deaths causally related to<br>treatment / all              | 0 / 0            | 0 / 0           |  |
| CNS ischemia<br>subjects affected / exposed                | 3 / 422 (0.71%)  | 4 / 424 (0.94%) |  |
| occurrences causally related to<br>treatment / all         | 0 / 3            | 0 / 4           |  |
| deaths causally related to<br>treatment / all              | 0 / 0            | 0 / 0           |  |
| Cognitive disturbance<br>subjects affected / exposed       | 1 / 422 (0.24%)  | 1 / 424 (0.24%) |  |
| occurrences causally related to<br>treatment / all         | 0 / 1            | 0 / 1           |  |
| deaths causally related to<br>treatment / all              | 0 / 0            | 0 / 0           |  |
| Confusion<br>subjects affected / exposed                   | 14 / 422 (3.32%) | 9 / 424 (2.12%) |  |
| occurrences causally related to<br>treatment / all         | 0 / 16           | 0 / 9           |  |
| deaths causally related to<br>treatment / all              | 0 / 0            | 0 / 0           |  |
| Dizziness<br>subjects affected / exposed                   | 7 / 422 (1.66%)  | 1 / 424 (0.24%) |  |
| occurrences causally related to<br>treatment / all         | 0 / 7            | 0 / 1           |  |
| deaths causally related to<br>treatment / all              | 0 / 0            | 0 / 0           |  |
| Memory impairment                                          |                  |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 422 (0.00%) | 1 / 424 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mood alteration                                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 422 (0.47%) | 1 / 424 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neurology - Other                               |                 |                 |  |
| subjects affected / exposed                     | 3 / 422 (0.71%) | 2 / 424 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neuropathy: cranial                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 422 (0.24%) | 0 / 424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neuropathy-motor                                |                 |                 |  |
| subjects affected / exposed                     | 2 / 422 (0.47%) | 1 / 424 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neuropathy-sensory                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 422 (0.24%) | 1 / 424 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Personality                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 422 (0.24%) | 0 / 424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Seizure                                         |                 |                 |  |
| subjects affected / exposed                     | 6 / 422 (1.42%) | 8 / 424 (1.89%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 9           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Speech impairment                               |                 |                 |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 422 (0.24%)  | 3 / 424 (0.71%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Syncope (fainting)                              |                  |                  |  |
| subjects affected / exposed                     | 4 / 422 (0.95%)  | 3 / 424 (0.71%)  |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tremor                                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 422 (0.24%)  | 0 / 424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood and lymphatic system disorders            |                  |                  |  |
| Blood - other                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 422 (0.00%)  | 2 / 424 (0.47%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haematoma                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 422 (0.24%)  | 0 / 424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemoglobin                                     |                  |                  |  |
| subjects affected / exposed                     | 24 / 422 (5.69%) | 26 / 424 (6.13%) |  |
| occurrences causally related to treatment / all | 0 / 28           | 0 / 32           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Haemorrhage                                     |                  |                  |  |
| subjects affected / exposed                     | 4 / 422 (0.95%)  | 3 / 424 (0.71%)  |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Haemorrhage pulmonary                           |                  |                  |  |
| subjects affected / exposed                     | 4 / 422 (0.95%)  | 5 / 424 (1.18%)  |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Haemorrhage, GI                                 |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 4 / 422 (0.95%)  | 1 / 424 (0.24%)  |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| INR (Int. normalized ratio of prothrombin time) |                  |                  |  |
| subjects affected / exposed                     | 1 / 422 (0.24%)  | 0 / 424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Leukocytes                                      |                  |                  |  |
| subjects affected / exposed                     | 7 / 422 (1.66%)  | 5 / 424 (1.18%)  |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymphatics - Other                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 422 (0.24%)  | 0 / 424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymphopenia                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 422 (0.00%)  | 1 / 424 (0.24%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neutrophils                                     |                  |                  |  |
| subjects affected / exposed                     | 32 / 422 (7.58%) | 27 / 424 (6.37%) |  |
| occurrences causally related to treatment / all | 0 / 36           | 0 / 31           |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 1            |  |
| Oedema: head and neck                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 422 (0.24%)  | 1 / 424 (0.24%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oedema: limb                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 422 (0.00%)  | 2 / 424 (0.47%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Platelets                                       |                  |                  |  |



|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 16 / 422 (3.79%) | 12 / 424 (2.83%) |  |
| occurrences causally related to treatment / all | 0 / 19           | 0 / 15           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| <b>Gastrointestinal disorders</b>               |                  |                  |  |
| <b>Anorexia</b>                                 |                  |                  |  |
| subjects affected / exposed                     | 6 / 422 (1.42%)  | 2 / 424 (0.47%)  |  |
| occurrences causally related to treatment / all | 0 / 7            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Constipation</b>                             |                  |                  |  |
| subjects affected / exposed                     | 5 / 422 (1.18%)  | 11 / 424 (2.59%) |  |
| occurrences causally related to treatment / all | 1 / 5            | 1 / 12           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Dehydration</b>                              |                  |                  |  |
| subjects affected / exposed                     | 3 / 422 (0.71%)  | 8 / 424 (1.89%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            |  |
| <b>Diarrhoea</b>                                |                  |                  |  |
| subjects affected / exposed                     | 19 / 422 (4.50%) | 15 / 424 (3.54%) |  |
| occurrences causally related to treatment / all | 2 / 20           | 4 / 16           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Dysphagia</b>                                |                  |                  |  |
| subjects affected / exposed                     | 5 / 422 (1.18%)  | 7 / 424 (1.65%)  |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Esophagitis</b>                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 422 (0.24%)  | 0 / 424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>GI - other</b>                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 422 (0.24%)  | 0 / 424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Haemorrhoids</b>                             |                  |                  |  |

|                                                 |                  |                  |
|-------------------------------------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 422 (0.24%)  | 0 / 424 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| heartburn                                       |                  |                  |
| subjects affected / exposed                     | 1 / 422 (0.24%)  | 0 / 424 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| Mucositis (clinical exam)                       |                  |                  |
| subjects affected / exposed                     | 1 / 422 (0.24%)  | 1 / 424 (0.24%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| Mucositis (functional/symptomatic)              |                  |                  |
| subjects affected / exposed                     | 0 / 422 (0.00%)  | 1 / 424 (0.24%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| Nausea                                          |                  |                  |
| subjects affected / exposed                     | 13 / 422 (3.08%) | 13 / 424 (3.07%) |
| occurrences causally related to treatment / all | 0 / 14           | 1 / 16           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| Obstruction GI                                  |                  |                  |
| subjects affected / exposed                     | 0 / 422 (0.00%)  | 1 / 424 (0.24%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| Oesophagitis                                    |                  |                  |
| subjects affected / exposed                     | 0 / 422 (0.00%)  | 2 / 424 (0.47%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| Stricture, Gianotti-Crosti syndrome             |                  |                  |
| subjects affected / exposed                     | 0 / 422 (0.00%)  | 1 / 424 (0.24%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| Taste alteration                                |                  |                  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 422 (0.00%)  | 1 / 424 (0.24%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ulcer, GI                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 422 (0.00%)  | 1 / 424 (0.24%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vomiting                                        |                  |                  |  |
| subjects affected / exposed                     | 24 / 422 (5.69%) | 19 / 424 (4.48%) |  |
| occurrences causally related to treatment / all | 3 / 28           | 0 / 20           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Hepatobiliary disorders                         |                  |                  |  |
| Cholecystitis                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 422 (0.24%)  | 1 / 424 (0.24%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatobiliary - Other                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 422 (0.24%)  | 0 / 424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Liver dysfunction                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 422 (0.00%)  | 2 / 424 (0.47%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin and subcutaneous tissue disorders          |                  |                  |  |
| Rash                                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 422 (0.00%)  | 1 / 424 (0.24%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal and urinary disorders                     |                  |                  |  |
| Fistula, GU                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 422 (0.24%)  | 0 / 424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Perforation, GU                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 422 (0.00%) | 1 / 424 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal - Other                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 422 (0.24%) | 1 / 424 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal failure                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 422 (0.24%) | 0 / 424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary frequency                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 422 (0.24%) | 0 / 424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary retention                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 422 (0.00%) | 4 / 424 (0.94%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endocrine disorders                             |                 |                 |  |
| Antidiuretic hormone                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 422 (0.24%) | 0 / 424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetes                                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 422 (0.00%) | 1 / 424 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Fracture                                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 422 (0.00%) | 2 / 424 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                  |                   |  |
|-------------------------------------------------|------------------|-------------------|--|
| Muscle weakness                                 |                  |                   |  |
| subjects affected / exposed                     | 4 / 422 (0.95%)  | 2 / 424 (0.47%)   |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Musculoskeletal - Other                         |                  |                   |  |
| subjects affected / exposed                     | 4 / 422 (0.95%)  | 1 / 424 (0.24%)   |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Osteoporosis                                    |                  |                   |  |
| subjects affected / exposed                     | 1 / 422 (0.24%)  | 0 / 424 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Infections and infestations                     |                  |                   |  |
| Colitis, infectious                             |                  |                   |  |
| subjects affected / exposed                     | 2 / 422 (0.47%)  | 0 / 424 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Febrile neutropenia                             |                  |                   |  |
| subjects affected / exposed                     | 22 / 422 (5.21%) | 18 / 424 (4.25%)  |  |
| occurrences causally related to treatment / all | 0 / 25           | 0 / 19            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| infection - other                               |                  |                   |  |
| subjects affected / exposed                     | 41 / 422 (9.72%) | 52 / 424 (12.26%) |  |
| occurrences causally related to treatment / all | 0 / 48           | 0 / 56            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1             |  |
| Infection (clinically documented)               |                  |                   |  |
| subjects affected / exposed                     | 29 / 422 (6.87%) | 31 / 424 (7.31%)  |  |
| occurrences causally related to treatment / all | 0 / 31           | 0 / 31            |  |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 2             |  |
| Infection with normal ANC                       |                  |                   |  |
| subjects affected / exposed                     | 12 / 422 (2.84%) | 4 / 424 (0.94%)   |  |
| occurrences causally related to treatment / all | 0 / 13           | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Infection with unknown ANC                      |                  |                   |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 422 (0.24%) | 1 / 424 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infection, opportunistic                        |                 |                 |  |
| subjects affected / exposed                     | 5 / 422 (1.18%) | 1 / 424 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| CPK                                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 422 (0.24%) | 0 / 424 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Hypercalcemia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 422 (0.24%) | 1 / 424 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperglycemia                                   |                 |                 |  |
| subjects affected / exposed                     | 2 / 422 (0.47%) | 1 / 424 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoglycemia                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 422 (0.24%) | 0 / 424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypokalemia                                     |                 |                 |  |
| subjects affected / exposed                     | 4 / 422 (0.95%) | 2 / 424 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypernatremia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 422 (0.00%) | 1 / 424 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypomagnesemia                                  |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 422 (0.00%) | 2 / 424 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyponatremia                                    |                 |                 |  |
| subjects affected / exposed                     | 8 / 422 (1.90%) | 6 / 424 (1.42%) |  |
| occurrences causally related to treatment / all | 0 / 11          | 2 / 11          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Metabolic/Lab - Other                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 422 (0.00%) | 1 / 424 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| Non-serious adverse events                            | Pravastatin                                                                                                                                      | Placebo            |  |
|-------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                                                                                                                                                  |                    |  |
| subjects affected / exposed                           | 392 / 422 (92.89%)                                                                                                                               | 401 / 424 (94.58%) |  |
| Investigations                                        |                                                                                                                                                  |                    |  |
| Thrombocytopenia                                      | Additional description: CTCAE v3.0 - SOC = coagulation<br>Occurrences not reported. Value displayed is the number of patients affected           |                    |  |
| subjects affected / exposed                           | 156 / 422 (36.97%)                                                                                                                               | 141 / 424 (33.25%) |  |
| occurrences (all)                                     | 156                                                                                                                                              | 141                |  |
| Elevated ALT / AST                                    | Additional description: CTCAE v3.0- SOC = Metabolic / laboratory<br>Occurrences not reported. Value displayed is the number of patients affected |                    |  |
| subjects affected / exposed                           | 118 / 422 (27.96%)                                                                                                                               | 122 / 424 (28.77%) |  |
| occurrences (all)                                     | 118                                                                                                                                              | 122                |  |
| Nervous system disorders                              |                                                                                                                                                  |                    |  |
| Dizziness                                             | Additional description: CTCAE v3.0 - SOC = Neurology<br>Occurrences not reported. Value displayed is the number of patients affected             |                    |  |
| subjects affected / exposed                           | 51 / 422 (12.09%)                                                                                                                                | 40 / 424 (9.43%)   |  |
| occurrences (all)                                     | 51                                                                                                                                               | 40                 |  |
| Neuropathy                                            | Additional description: CTCAE v3.0 - SOC = neurology<br>Occurrences not reported. Value displayed is the number of patients affected             |                    |  |
| subjects affected / exposed                           | 44 / 422 (10.43%)                                                                                                                                | 52 / 424 (12.26%)  |  |
| occurrences (all)                                     | 44                                                                                                                                               | 52                 |  |
| Blood and lymphatic system disorders                  |                                                                                                                                                  |                    |  |
| Anaemia                                               | Additional description: CTCAE v3.03 - SOC = Blood / bone marrow<br>Occurrences not reported. Value displayed is the number of patients affected  |                    |  |

|                                                         |                                                                                                                                                |                           |  |
|---------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|--|
| subjects affected / exposed<br>occurrences (all)        | 309 / 422 (73.22%)<br>309                                                                                                                      | 0 / 424 (0.00%)<br>0      |  |
| Neutropenia                                             | Additional description: CTCAE v3.0 - SOC = Blood / bone marrow<br>Occurrences not reported. Value displayed is the number of patients affected |                           |  |
| subjects affected / exposed<br>occurrences (all)        | 293 / 422 (69.43%)<br>293                                                                                                                      | 296 / 424 (69.81%)<br>296 |  |
| Leukopenia                                              | Additional description: CTCAE v3.0 - SOC = Blood / bone marrow<br>Occurrences not reported. Value displayed is the number of patients affected |                           |  |
| subjects affected / exposed<br>occurrences (all)        | 216 / 422 (51.18%)<br>216                                                                                                                      | 209 / 424 (49.29%)<br>209 |  |
| General disorders and administration<br>site conditions |                                                                                                                                                |                           |  |
| Fatigue                                                 | Additional description: Occurrences not reported. Value displayed is the number<br>of patients affected                                        |                           |  |
| subjects affected / exposed<br>occurrences (all)        | 287 / 422 (68.01%)<br>287                                                                                                                      | 273 / 424 (64.39%)<br>273 |  |
| Pain                                                    | Additional description: CTCAE v3.0 - SOC = pain<br>Occurrences not reported. Value displayed is the number of patients affected                |                           |  |
| subjects affected / exposed<br>occurrences (all)        | 235 / 422 (55.69%)<br>235                                                                                                                      | 221 / 424 (52.12%)<br>221 |  |
| Gastrointestinal disorders                              |                                                                                                                                                |                           |  |
| Nausea                                                  | Additional description: Occurrences not reported. Value displayed is the number<br>of patients affected                                        |                           |  |
| subjects affected / exposed<br>occurrences (all)        | 241 / 422 (57.11%)<br>241                                                                                                                      | 231 / 424 (54.48%)<br>231 |  |
| Constipation                                            | Additional description: Occurrences not reported. Value displayed is the number<br>of patients affected                                        |                           |  |
| subjects affected / exposed<br>occurrences (all)        | 214 / 422 (50.71%)<br>214                                                                                                                      | 187 / 424 (44.10%)<br>187 |  |
| Anorexia                                                | Additional description: Occurrences not reported. Value displayed is the number<br>of patients affected                                        |                           |  |
| subjects affected / exposed<br>occurrences (all)        | 196 / 422 (46.45%)<br>196                                                                                                                      | 148 / 424 (34.91%)<br>148 |  |
| Mucositis/Stomatitis                                    | Additional description: Occurrences not reported. Value displayed is the number<br>of patients affected                                        |                           |  |
| subjects affected / exposed<br>occurrences (all)        | 193 / 422 (45.73%)<br>193                                                                                                                      | 149 / 424 (35.14%)<br>149 |  |
| Vomiting                                                | Additional description: Occurrences not reported. Value displayed is the number<br>of patients affected                                        |                           |  |
| subjects affected / exposed<br>occurrences (all)        | 139 / 422 (32.94%)<br>139                                                                                                                      | 123 / 424 (29.01%)<br>123 |  |
| Diarrhoea                                               | Additional description: Occurrences not reported. Value displayed is the number<br>of patients affected                                        |                           |  |



|                                                  |                                                                                                                                                          |                           |  |
|--------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|--|
| subjects affected / exposed<br>occurrences (all) | 113 / 422 (26.78%)<br>113                                                                                                                                | 115 / 424 (27.12%)<br>115 |  |
| Respiratory, thoracic and mediastinal disorders  |                                                                                                                                                          |                           |  |
| Dyspnea                                          | Additional description: CTCAE v3.0 - SOC = Pulmonary / upper respiratory<br>Occurrences not reported. Value displayed is the number of patients affected |                           |  |
| subjects affected / exposed<br>occurrences (all) | 145 / 422 (34.36%)<br>145                                                                                                                                | 148 / 424 (34.91%)<br>148 |  |
| Cough                                            | Additional description: CTCAE v3.0 - SOC = Pulmonary / upper respiratory<br>Occurrences not reported. Value displayed is the number of patients affected |                           |  |
| subjects affected / exposed<br>occurrences (all) | 125 / 422 (29.62%)<br>125                                                                                                                                | 115 / 424 (27.12%)<br>115 |  |
| Skin and subcutaneous tissue disorders           |                                                                                                                                                          |                           |  |
| Alopecia                                         | Additional description: CTCAE v3.0 - SOC = dermatology<br>Occurrences not reported. Value displayed is the number of patients affected                   |                           |  |
| subjects affected / exposed<br>occurrences (all) | 148 / 422 (35.07%)<br>148                                                                                                                                | 146 / 424 (34.43%)<br>146 |  |
| Urticaria                                        | Additional description: CTCAE v3.0 - SOC = Dermatology / skin<br>Occurrences not reported. Value displayed is the number of patients affected            |                           |  |
| subjects affected / exposed<br>occurrences (all) | 45 / 422 (10.66%)<br>45                                                                                                                                  | 62 / 424 (14.62%)<br>62   |  |
| Renal and urinary disorders                      |                                                                                                                                                          |                           |  |
| Renal                                            | Additional description: Occurrences not reported. Value displayed is the number of patients affected                                                     |                           |  |
| subjects affected / exposed<br>occurrences (all) | 43 / 422 (10.19%)<br>43                                                                                                                                  | 53 / 424 (12.50%)<br>53   |  |
| Musculoskeletal and connective tissue disorders  |                                                                                                                                                          |                           |  |
| Myalgia / myositis                               | Additional description: Occurrences not reported. Value displayed is the number of patients affected                                                     |                           |  |
| subjects affected / exposed<br>occurrences (all) | 74 / 422 (17.54%)<br>74                                                                                                                                  | 77 / 424 (18.16%)<br>77   |  |
| Infections and infestations                      |                                                                                                                                                          |                           |  |
| Infection                                        | Additional description: Occurrences not reported. Value displayed is the number of patients affected                                                     |                           |  |
| subjects affected / exposed<br>occurrences (all) | 248 / 422 (58.77%)<br>248                                                                                                                                | 276 / 424 (65.09%)<br>276 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 04 August 2004    | Correction of drug name - lipostat to pravastatin                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 06 September 2006 | Consent form – Changing date and version number of PIS in consent form                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 29 January 2007   | <ul style="list-style-type: none"><li>- EDTA and C&amp;G method included for measuring GFR formula and WRIGHT formula removed, and "GFR &gt; 50mls/min as measured by EDTA OR GFR &gt; 40mls/min as measured by the C&amp;G formula" included</li><li>- Stratification: "and by participating site" removed</li><li>- Baseline supply clarified "3 months of pravastatin or placebo (3 x 30 tablets)".</li><li>- GFR to be capped at 130ml/min with maximum Carboplatin dose of 1000mg</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 27 November 2007  | Addition of a patient card                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 22 June 2009      | <ul style="list-style-type: none"><li>- Inclusion criteria - Change: The timing of the baseline CT scan has been increased from 28 to 31days</li><li>- Inclusion criteria - a definition has been added of what is consider limited disease within this trial.</li><li>- Exclusion criteria - The wording in this section has been changed to clarify that patients are only ineligible when the LFTs reach 3 x ULN.</li><li>- Exclusion criteria - a sentence has been added, to state that patients who have received methotrexate for arthritis can be entered into the trial.</li><li>- A list has been added for all the data that is required at the time of randomisation and one for data that is required, but acceptable to send post randomisation.</li><li>- Dose modifications - The ANC level at which to delay chemotherapy for a week has been changed to &lt;1.0 ANC as a lower limit, with provision for sites to use &lt;1.5 as a cut off point if this is as per local practice.</li><li>- Criteria for stopping pravastatin/placebo - a paragraph has been added to make it clear that a patient can restart the pravastatin/placebo after a period off study drug.</li></ul> |
| 19 September 2011 | Following receipt of the MHRA Safety Update volume 5, issue 2, September 2011, giving new information on the risk of rhabdomyolysis should fusidic acid be used in combination with statins, all sites were advise that fusidic acid must not be used concurrently with pravastatin. Sites were asked to check whether any LungStar patients were being prescribed fusidic acid and, if so, to take action to temporarily stop pravastatin for a minimum of 7 days after stopping fusidic acid. The protocol, Patient Information Sheet (PIS), GP Letter and Patient Card were updated in line with the guidance from the MHRA Safety Update.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

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.

AEs reported at each assessment was based on worst grade observed.

Occurrences not reported for Adverse Events. Value displayed is the number of patients affected

Notes: