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:

Results analysis stage

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:

General information about the trial

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:

Population of trial subjects

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:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	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
Arm title	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.

Arm title	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.

Number of subjects in period 1	Pravastatin	Placebo
Started	422	424
Completed	422	424

Baseline characteristics

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	

Reporting group values	Pravastatin	Placebo	Total
Number of subjects	422	424	846
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (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 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			
subjects affected / exposed	10 / 422 (2.37%)	3 / 424 (0.71%)	
occurrences causally related to treatment / all	0 / 10	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Valvular heart disease			
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	
Vasovagal episode			
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	
Nervous system disorders			
Ataxia			
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	
CNS ischemia			
subjects affected / exposed	3 / 422 (0.71%)	4 / 424 (0.94%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disturbance			
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	
Confusion			
subjects affected / exposed	14 / 422 (3.32%)	9 / 424 (2.12%)	
occurrences causally related to treatment / all	0 / 16	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	7 / 422 (1.66%)	1 / 424 (0.24%)	
occurrences causally related to treatment / all	0 / 7	0 / 1	
deaths causally related to 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	
Gastrointestinal disorders			
Anorexia			
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	
Constipation			
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	
Dehydration			
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	
Diarrhoea			
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	
Dysphagia			
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	
Esophagitis			
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	
GI - 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	
Haemorrhoids			

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

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

subjects affected / exposed	113 / 422 (26.78%)	115 / 424 (27.12%)	
occurrences (all)	113	115	
Respiratory, thoracic and mediastinal disorders			
Dyspnea	Additional description: CTCAE v3.0 - SOC = Pulmonary / upper respiratory Occurrences not reported. Value displayed is the number of patients affected		
subjects affected / exposed	145 / 422 (34.36%)	148 / 424 (34.91%)	
occurrences (all)	145	148	
Cough	Additional description: CTCAE v3.0 - SOC = Pulmonary / upper respiratory Occurrences not reported. Value displayed is the number of patients affected		
subjects affected / exposed	125 / 422 (29.62%)	115 / 424 (27.12%)	
occurrences (all)	125	115	
Skin and subcutaneous tissue disorders			
Alopecia	Additional description: CTCAE v3.0 - SOC = dermatology Occurrences not reported. Value displayed is the number of patients affected		
subjects affected / exposed	148 / 422 (35.07%)	146 / 424 (34.43%)	
occurrences (all)	148	146	
Urticaria	Additional description: CTCAE v3.0 - SOC = Dermatology / skin Occurrences not reported. Value displayed is the number of patients affected		
subjects affected / exposed	45 / 422 (10.66%)	62 / 424 (14.62%)	
occurrences (all)	45	62	
Renal and urinary disorders			
Renal	Additional description: Occurrences not reported. Value displayed is the number of patients affected		
subjects affected / exposed	43 / 422 (10.19%)	53 / 424 (12.50%)	
occurrences (all)	43	53	
Musculoskeletal and connective tissue disorders			
Myalgia / myositis	Additional description: Occurrences not reported. Value displayed is the number of patients affected		
subjects affected / exposed	74 / 422 (17.54%)	77 / 424 (18.16%)	
occurrences (all)	74	77	
Infections and infestations			
Infection	Additional description: Occurrences not reported. Value displayed is the number of patients affected		
subjects affected / exposed	248 / 422 (58.77%)	276 / 424 (65.09%)	
occurrences (all)	248	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	- EDTA and C&G method included for measuring GFR formula and WRIGHT formula removed, and "GFR > 50mls/min as measured by EDTA OR GFR > 40mls/min as measured by the C&G formula" included - Stratification: "and by participating site" removed - Baseline supply clarified "3 months of pravastatin or placebo (3 x 30 tablets)". - GFR to be capped at 130ml/min with maximum Carboplatin dose of 1000mg
27 November 2007	Addition of a patient card
22 June 2009	- Inclusion criteria - Change: The timing of the baseline CT scan has been increased from 28 to 31days - Inclusion criteria - a definition has been added of what is consider limited disease within this trial. - Exclusion criteria - The wording in this section has been changed to clarify that patients are only ineligible when the LFTs reach 3 x ULN. - Exclusion criteria - a sentence has been added, to state that patients who have received methotrexate for arthritis can be entered into the trial. - 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. - Dose modifications - The ANC level at which to delay chemotherapy for a week has been changed to <1.0 ANC as a lower limit, with provision for sites to use <1.5 as a cut off point if this is as per local practice. - 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.
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: