



## Clinical trial results:

### Adjuvant Urokinase in the Treatment of Malignant Pleural Effusion: The Third Therapeutic Intervention in Malignant Effusion Trial (TIME3-UK). A Randomised Controlled Trial to evaluate whether use of intrapleural Urokinase aids the drainage of multi-septated pleural effusion compared to placebo

#### Summary

EudraCT number	2008-000586-26
Trial protocol	GB
Global end of trial date	26 June 2015

#### Results information

Result version number	v1 (current)
This version publication date	22 July 2016
First version publication date	22 July 2016

#### Trial information

##### Trial identification

Sponsor protocol code	TIME3UK
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##### Additional study identifiers

ISRCTN number	ISRCTN12852177
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Joint Research Office, Block 60, Churchill Hospital, Oxford, United Kingdom, OX3 7LE
Public contact	Dr Eleanor Mishra, Oxford Respiratory Trials Unit University of Oxford Churchill Hospital Headington Oxford OX3 7LE, 01865 225205, eleanor.mishra@gmail.com
Scientific contact	Dr Eleanor Mishra, Oxford Respiratory Trials Unit University of Oxford Churchill Hospital Headington Oxford OX3 7LE, 01865 225205, eleanor.mishra@gmail.com

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 June 2015
Global end of trial reached?	Yes
Global end of trial date	26 June 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

1. Mean daily breathlessness score over 28 days following randomisation (quantified by visual analogue scale (VAS) scores)
2. Time to pleurodesis failure (proportion requiring further pleural fluid drainage with deaths and loss to follow up censored, log rank test). Pleurodesis failure is defined as: either another ipsilateral pleural drainage procedure to control breathlessness or the patient has symptomatic pleural fluid recurrence but another ipsilateral pleural drainage procedure is not performed due to patient refusal, futility or other medical reason e.g. warfarinisation, poor performance status.

Protection of trial subjects:

Patients were closely monitored for any adverse events following the administration of the IMP. Bleeding was the expected adverse event though this was not expected to be a common occurrence. Patients experiencing adverse events were treated according to best clinical practice.

Background therapy:

Following the administration of the IMP and further clinical assessment (chest -xray and pleural fluid drainage charts) all patients underwent talc pleurodesis, administered according to clinical standard operational procedures.

Evidence for comparator:

N/A

Actual start date of recruitment	01 September 2009
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: 71
Worldwide total number of subjects	71
EEA total number of subjects	71

Notes:

### Subjects enrolled per age group

In utero	0
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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)	16
From 65 to 84 years	49
85 years and over	6

## Subject disposition

### Recruitment

Recruitment details:

71 patients were recruited into the trial from September 2009 to June 2014. All patients were recruited as in-patients from 12 centres across the United Kingdom.

### Pre-assignment

Screening details:

Patients screened for the trial were those with a clinically confident diagnosis of pleural malignancy and a chest drain inserted for a pleural effusion. The total number of subjects screened was 692.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Urokinase

Arm description:

intrapleural Urokinase 100,000 IU.

Product name: "Syner-KINASE® 100,000 IU"

3 doses given 8-14 hours apart

Arm type	Experimental
Investigational medicinal product name	Urokinase 100,000 I.U.
Investigational medicinal product code	B01A D04
Other name	Syner-KINASE® 100,000 IU
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Respiratory use

Dosage and administration details:

Treatment (urokinase) limb

Intra-pleural Urokinase (100,000 IU in 20mls normal saline) administered at intervals of between 8-14 hours apart for a total of 3 doses.

<b>Arm title</b>	Placebo
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Arm description:

intra-pleural placebo, diluted in 20ml normal saline solution

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Respiratory use

Dosage and administration details:

Placebo limb

Intra-pleural urokinase placebo (in 20mls normal saline) administered at intervals of between 8-14 hours apart for a total of 3 doses

<b>Number of subjects in period 1</b>	Urokinase	Placebo
Started	36	35
Completed	35	32
Not completed	1	3
other	1	1
Chest drain fell out	-	1
Trial drugs unavaliabile	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Urokinase
Reporting group description: intrapleural Urokinase 100,000 IU. Product name: "Syner-KINASE® 100,000 IU" 3 doses given 8-14 hours apart	
Reporting group title	Placebo
Reporting group description: intra-pleural placebo, diluted in 20ml normal saline solution	

Reporting group values	Urokinase	Placebo	Total
Number of subjects	36	35	71
Age categorical Units: Subjects			
Adults (18-64 years)	9	7	16
From 65-84 years	24	25	49
85 years and over	3	3	6
Age continuous Units: years arithmetic mean standard deviation	69.5 ± 10.48	71.5 ± 8.3	-
Gender categorical Units: Subjects			
Female	13	17	30
Male	23	18	41
WHO Performance Status Units: Subjects			
0-2	21	21	42
3-4	15	14	29
Histological tissue type Units: Subjects			
Mesothelioma	3	4	7
Non-mesothelioma/unknown	33	31	64
Previous pleurodesis Units: Subjects			
No	31	30	61
Yes	5	5	10

### Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: All randomised patients and will include all randomised patients on whom an outcome is available	

<b>Reporting group values</b>	ITT		
Number of subjects	71		
Age categorical Units: Subjects			
Adults (18-64 years)	16		
From 65-84 years	49		
85 years and over	6		
Age continuous Units: years			
arithmetic mean	70.5		
standard deviation	± 9.45		
Gender categorical Units: Subjects			
Female	30		
Male	41		
WHO Performance Status Units: Subjects			
0-2	42		
3-4	29		
Histological tissue type Units: Subjects			
Mesothelioma	7		
Non-mesothelioma/unknown	64		
Previous pleurodesis Units: Subjects			
No	61		
Yes	10		

## End points

### End points reporting groups

Reporting group title	Urokinase
Reporting group description: intrapleural Urokinase 100,000 IU. Product name: "Syner-KINASE® 100,000 IU" 3 doses given 8-14 hours apart	
Reporting group title	Placebo
Reporting group description: intra-pleural placebo, diluted in 20ml normal saline solution	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: All randomised patients and will include all randomised patients on whom an outcome is available	

### Primary: The average breathlessness score over 28 days

End point title	The average breathlessness score over 28 days
End point description:	
End point type	Primary
End point timeframe: From randomisation to day 28	

End point values	Urokinase	Placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	30	33	63	
Units: Vas Score				
arithmetic mean (standard deviation)	38.06 (± 28.36)	38.39 (± 25.13)	38.22 (± 26.66)	

### Statistical analyses

Statistical analysis title	The average breathlessness score over 28 days
Comparison groups	Urokinase v Placebo
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.362
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.8



Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.97
upper limit	4.37

### Primary: Time to pleurodesis failure, up to 12 months

End point title	Time to pleurodesis failure, up to 12 months
End point description:	
End point type	Primary
End point timeframe:	
From randomisation to month 12	

End point values	Urokinase	Placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	35	34	69	
Units: Time to failure				
arithmetic mean (standard deviation)	21.65 (± 9.2)	22.18 (± 17.49)	21.9 (± 13.31)	

### Statistical analyses

Statistical analysis title	Time to pleurodesis failure, up to 12 months
Comparison groups	Urokinase v Placebo
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.648
Method	competing risk analysis
Parameter estimate	subdistribution hazard ratio (SHR)
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	2.72

### Secondary: All-cause mortality up to 12 months

End point title	All-cause mortality up to 12 months
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End point description:

End point type	Secondary
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End point timeframe:

From randomisation to 12 months

End point values	Urokinase	Placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	36	35	71	
Units: Days to death				
arithmetic mean (standard deviation)				
Died	94.42 (± 99.05)	67.89 (± 68.25)	80.35 (± 84.51)	

### Statistical analyses

Statistical analysis title	All-cause mortality up to 12 months
Comparison groups	Urokinase v Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	0.93

### Secondary: Length of hospital stay (measured as time from randomisation until discharge)

End point title	Length of hospital stay (measured as time from randomisation until discharge)
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End point description:

End point type	Secondary
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End point timeframe:

randomisation until discharge from hospital

End point values	Urokinase	Placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	35	34	69	
Units: Length of hospital stay in days				
arithmetic mean (standard deviation)	6.15 ( $\pm$ 2.73)	8.67 ( $\pm$ 6.47)	7.35 ( $\pm$ 5)	

## Statistical analyses

Statistical analysis title	Length of hospital stay
Comparison groups	Urokinase v Placebo
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049
Method	competing risk analysis
Parameter estimate	subdistribution hazard (SHR)
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	2.56

## Secondary: Patients self-reported overall quality of life at enrolment calculated from patient's response to Q30 on the EORTC QLQ-30

End point title	Patients self-reported overall quality of life at enrolment calculated from patient's response to Q30 on the EORTC QLQ-30
End point description:	
End point type	Secondary
End point timeframe:	
From enrolment, day 28, 3 months, 6 months and 12 months	

End point values	Urokinase	Placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	36	34	70	
Units: Quality of life				
arithmetic mean (standard deviation)	39.39 ( $\pm$ 22.29)	34.23 ( $\pm$ 28.42)	36.88 ( $\pm$ 25.4)	

## Statistical analyses

Statistical analysis title	Overall quality of life
Statistical analysis description:	
Patients self-reported overall quality of life at enrolment, day 28, 3 months, 6 months and 12 months calculated from patient's response to Q30 on the EORTC QLQ-30 and transformed to a percentage	
Comparison groups	Urokinase v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.171
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	7.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.18
upper limit	17.89

## Secondary: The proportion of patients that had any systemic bleeding (from time of randomisation until day of pleurodesis)

End point title	The proportion of patients that had any systemic bleeding (from time of randomisation until day of pleurodesis)
End point description:	
End point type	Secondary
End point timeframe:	
from time of randomisation until day of pleurodesis	

End point values	Urokinase	Placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	36	35	71	
Units: Number of patients				
unobtainable	0	1	1	
Systemic Bleeding	0	1	1	
No systemic bleeding	36	33	69	

## Statistical analyses

No statistical analyses for this end point

## Secondary: The proportion of patients that had any new intrapleural bleeding (from time of randomisation until day of pleurodesis)

End point title	The proportion of patients that had any new intrapleural
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End point description:

End point type	Secondary
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End point timeframe:

from time of randomisation until day of pleurodesis

End point values	Urokinase	Placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	36	35	71	
Units: Number of Patients				
New intrapleural bleeding	0	0	0	
No new intrapleural bleeding	36	34	70	
Unobtainable	0	1	1	

### Statistical analyses

No statistical analyses for this end point

### Secondary: The average amount patients were bothered by their breathlessness over 28 days

End point title	The average amount patients were bothered by their breathlessness over 28 days
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End point description:

End point type	Secondary
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End point timeframe:

From randomisation to day 28

End point values	Urokinase	Placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	30	33	63	
Units: VAS score				
arithmetic mean (standard deviation)	34.47 (± 28.95)	35.28 (± 29.36)	34.86 (± 28.91)	

### Statistical analyses

Statistical analysis title	The average amount bothered by breathlessness
Comparison groups	Urokinase v Placebo

Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.101
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-6.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.25
upper limit	1.36

### Secondary: Radiographic improvement in the area of the pleural effusion on day two (the day of pleurodesis)

End point title	Radiographic improvement in the area of the pleural effusion on day two (the day of pleurodesis)
End point description:	
End point type	Secondary
End point timeframe:	
From randomisation to day 2	

End point values	Urokinase	Placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	26	21	47	
Units: Radiographic improvement				
arithmetic mean (standard deviation)	22.62 (± 15.39)	44.23 (± 23.62)	33.27 (± 22.12)	

### Statistical analyses

<b>Statistical analysis title</b>	Radiographic improvement in pleural effusion
Comparison groups	Urokinase v Placebo
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	co-efficient
Point estimate	-19.28

Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.74
upper limit	-10.81

**Secondary: The proportion of patients achieving a clinically significant decrease in VAS (19mm) over 28 days.**

End point title	The proportion of patients achieving a clinically significant decrease in VAS (19mm) over 28 days.
End point description:	
End point type	Secondary
End point timeframe:	
From randomisation to day 28	

End point values	Urokinase	Placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	24	19	43	
Units: Number of patients				
>=19 mm decrease	6	4	10	
<19 mm decrease	18	15	33	

**Statistical analyses**

Statistical analysis title	proportion achieving clinical decrease in VAS
Comparison groups	Urokinase v Placebo
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.761
Method	Chi-squared

**Secondary: Volume of pleural fluid drained (mls) whilst the drain is in situ**

End point title	Volume of pleural fluid drained (mls) whilst the drain is in situ
End point description:	
End point type	Secondary
End point timeframe:	
Randomisation to day 3	

<b>End point values</b>	Urokinase	Placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	24	19	43	
Units: Volume of Fluid drained				
arithmetic mean (standard deviation)	357.5 (± 643.72)	257.11 (± 402.28)	313.14 (± 546.65)	

### Statistical analyses

<b>Statistical analysis title</b>	Volume of pleural fluid drained
Comparison groups	Urokinase v Placebo
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.237
Method	Regression, Linear
Parameter estimate	co-efficient
Point estimate	168.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-110.63
upper limit	447.94

### Secondary: Patients that have symptomatic pleural fluid recurrence but do not have another pleural drainage procedure

End point title	Patients that have symptomatic pleural fluid recurrence but do not have another pleural drainage procedure
End point description:	
End point type	Secondary
End point timeframe:	
From randomisation to month 12	

<b>End point values</b>	Urokinase	Placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	36	35	71	
Units: Number of Patients				
Symptomatic and no drainage	4	0	4	
Not : symptomatic and no drainage	32	35	37	



## Statistical analyses

No statistical analyses for this end point

### Secondary: Patients self-reported health status calculated from patient's response to Q29 on the EORTC QLQ-30

End point title	Patients self-reported health status calculated from patient's response to Q29 on the EORTC QLQ-30
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End point description:

End point type	Secondary
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End point timeframe:

From enrolment, day 28, 3 months, 6 months and 12 months

End point values	Urokinase	Placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	36	34	70	
Units: Health Status				
arithmetic mean (standard deviation)	37.75 ( $\pm$ 22.96)	36.4 ( $\pm$ 24.13)	37.09 ( $\pm$ 23.37)	

## Statistical analyses

Statistical analysis title	Patients self-reported health status
Comparison groups	Urokinase v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.758
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.64
upper limit	11.87

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

During days 0-3 inclusive all SAEs, excluding reactions to talc pleurodesis, were reported to the sponsor within 24 hours knowledge of the event.

After day 3, only SAEs possibly be related to the trial drug were reported to the sponsor within 24 hours

Adverse event reporting additional description:

During in-patient stay, AEs and SAEs were collected by research staff for days 0-3 and day 3 onwards until discharge from hospital. Following discharge from hospital, Adverse Events were captured at 4 weeks, 3, 6 and 12 month follow-ups. SAEs were reported by patients and captured by research staff through monitoring admissions.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

### Reporting groups

Reporting group title	Urokinase
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Reporting group description:

intrapleural Urokinase 100,000 IU.

Product name: "Syner-KINASE® 100,000 IU"

White powder for solution for injection or infusion.

Reporting group title	Placebo
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Reporting group description:

intra-pleural placebo, diluted in 20ml normal saline solution

Serious adverse events	Urokinase	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 36 (8.33%)	3 / 35 (8.57%)	
number of deaths (all causes)	31	35	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Death	Additional description: In the protocol only deaths within the first 3 days are reported as SAEs. Deaths after this time were reported on the CRF forms.		
subjects affected / exposed	1 / 36 (2.78%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Injury, poisoning and procedural complications			
Wound dehiscence			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal			

disorders			
Pleuritic pain			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (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			
Pleural infection			
subjects affected / exposed	1 / 36 (2.78%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Urokinase	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	
Gastrointestinal disorders			
haemorrhage			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 April 2009	<p>Protocol v1.1 -change of PI at the Oxford Centre for Respiratory Medicine.</p> <p>We propose to change from 30ml normal saline vials to 20ml vials as 30ml are unavailable in the UK and the use of the vials imported from the United States would increase the costs of the trial. We also propose to remove lateral CXR and the chest pain VAS questionnaire as these are not essential for the study.</p> <p>We have added the collection of blood and pleural fluid samples on day 1 and day 2 after the enrolment and we have removed "Baseline VAS Questionnaire" phrase from the discharge column and inserted it in the trial entry column as this is when the baseline VAS will be measured.</p> <p>We also propose to add a new questionnaire - "Multidimensional dyspnoea profile" (for Oxford site only) which is a validated questionnaire developed at Harvard Medical School</p>
24 June 2009	<p>Protocol v1.2</p> <p>The CTA has been amended with the change of the packaging/labelling company to LC2 which will be responsible for the final QP release .</p>
26 August 2009	<p>SA03-Protocol v1.3</p> <ol style="list-style-type: none"><li>1. Amendment of the consent form and the Patient Information Sheet to include information about the Medical Research Information Service follow-up.</li><li>2. Removal of CRDQ questionnaire from the study.</li><li>3. Change of the MRC performance status to WHO performance status.</li><li>4. Change of the trial mobile phone number.</li><li>5. Addition of the second VAS breathlessness measurement at baseline (protocol &amp; VAS booklet).</li><li>6. Addition of chemotherapy-naïve patients with small cell lung cancer, lymphoma or breast cancer to the exclusion list.</li><li>7. Change from 15ml of 2% lignocaine local anaesthetic to 30ml 1% lignocaine local anaesthetic - in the Appendix 2 SOP for the performance of talc pleurodesis.</li><li>8. Change of the clinical coordinator</li><li>9. Removal of the total blood white cell count <math>&lt;1.0 \times 10^9</math> from the exclusion list.</li><li>10. Change of the definition of the pleurodesis failure.</li><li>11. Change of the definition of the primary outcomes.</li></ol>

19 November 2009	<p>SA04- protocol v1.4</p> <ol style="list-style-type: none"> <li>1. Redefinition of one of the primary endpoints and clarification of the pleurodesis efficacy definition.</li> <li>2. Addition of "Known underlying trapped lung of sufficient severity that pleurodesis is futile" to the exclusion criteria and rewording of the exclusion criteria referring to chemotherapy responsive tumours.</li> <li>3. Clarification of the day of pleurodesis (pleurodesis is performed on day 2 not on day 3) and the days when trial procedures are performed.</li> <li>4. Modification of the analysis plan.</li> <li>5. Change of the drug accountability procedures.</li> <li>6. Deletion of "at discharge" phrase from the Follow-up table; deletion of "until death" from the patients' follow-up in the protocol and GP letter.</li> <li>7. Inclusion of the list of the Trial Steering Committee and the Data Monitoring Committee members for the trial and confirmation of the CTA reference number.</li> <li>8. Updating the confidentiality section in the PIS and consent</li> </ol>
25 March 2010	<p>Protocol V1.5</p> <p>Removal of all references to the "Dyspnoea questionnaire" from the protocol as the Principal Investigator has deemed that this questionnaire does not serve the purpose it was designed for.</p>
19 August 2010	<p>Protocol v1.6</p> <p>The eligibility criteria in the protocol is being changed from 'histocytologically proven cancer' to 'clinically proven cancer'.</p> <p>Addition of VAS (breathlessness) data collection at 3, 6 &amp; 12 months.</p>
03 March 2011	<p>Protocol v2.0</p> <p>Change of CI</p>
15 April 2011	<p>Protocol v3.0</p> <p>Widening of the following inclusion criteria with the following point to help increase the recruitment rate for the trial and to reflect current clinical practice.</p> <p>c. Radiologically proven pleural malignancy as diagnosed in normal clinical practice on thoracic CT in the absence of histocytological proof</p> <p>-A chest radiograph showing &gt;15% hemithorax area occupied by effusion OR</p> <p>-Septated effusion on thoracic ultrasound with a basal parietal to visceral depth of &gt;2cm</p> <p>Removal of the following exclusion criteria</p> <p>Highly chemotherapy responsive tumours (such as small cell lung cancer, lymphoma or breast cancer) unless the patient has already undergone chemotherapy</p>
29 August 2011	<p>Protocol v4.0</p> <ul style="list-style-type: none"> <li>- Interval between drug doses confirmed as 8-14 hours apart.</li> <li>- Recommended timings for baseline VAS measurements given to ensure consistency throughout all trial sites</li> </ul>

11 April 2013	<p>Protocol v5.0</p> <ul style="list-style-type: none"> <li>-Addition of text to confirm that patients may be contacted by telephone if they cannot attend a follow-up visit</li> <li>-Clarification of procedures regarding loss to follow-up and withdrawal</li> <li>-Re-wording of the safety reporting section to provide clarification on safety reporting procedures.</li> <li>-Removal of appendices (two SOPs). The 'talc slurry pleurodesis' is already supplied in the Investigator Site File. The SOP entitled 'Assessment of a reported probable SAE' is for ORTU use only and will be kept with the departmental SOPs.</li> </ul>
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Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported