IPC-PLUS TRIAL SUPPLEMENTARY APPENDIX

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METHODS AND ANALYSIS PLAN

Trial oversight, conduct and registration

The trial was sponsored and monitored by North Bristol NHS Trust, and was conducted in accordance with the standards laid out by both the Declaration of Helsinki and the International conference on harmonization guidance on good clinical practice.

The study was prospectively registered on publicly-accessible databases (registration numbers EudraCT 2012-000599-40 and ISRCTN73255764) and was adopted onto the UK National Institute for Health Research's Clinical Research Network Portfolio.

Full trial inclusion criteria.

1. Symptomatic malignant pleural effusion, agreed at appropriate local / regional level to require an IPC, defined as pleural fluid in the context of any of the following:
    a. Histocytologically proven pleural malignancy
    b. Otherwise unexplained pleural effusion in the context of clinically proven cancer elsewhere
    c. Radiologically proven pleural malignancy as diagnosed in normal clinical practice on thoracic CT in the absence of histocytological proof
2. Expected survival greater than 2 months and WHO/ECOG performance status of 2 or better. Patients with a PS of 3 may be included if it is felt that removal of pleural fluid would improve their performance status to 2 or better.
3. Written informed consent to trial participation.

Full trial exclusion criteria.

1. Age < 18 years.
2. Females who are pregnant or lactating.
3. Patient unable to provide informed consent.
4. Previous attempts at pleurodesis within the last 56 days on same side as effusion requiring management.
5. Previously documented adverse reaction to talc or lidocaine.

6. Community services unable to drain indwelling pleural catheter at least twice per week.
7. Evidence of extensive lung entrapment on CXR or CT, or significant fluid loculation on ultrasound scan, to a level which would normally be a contraindication to attempted talc pleurodesis or IPC insertion.
8. Other contraindication to indwelling pleural catheter insertion
9. Patient has no access to a telephone

Changes to original protocol and statistical analysis plan

The TSC sanctioned the all versions of the protocol, statistical analysis plan, and any subsequent amendments. The separate, fully independent DSMC also met at regular intervals to review the study and sanction ongoing recruitment.

Inclusion and exclusion criteria

Exclusion criterion 9 was updated from that stated in the original protocol as part of amendment SA01 (09/07/2012). This amendment specified that patients must have access to a telephone to be eligible for the study.

Inclusion criterion 2 was updated from that stated in the original protocol (version 1.0, date 10/04/2014) as part of amendment SA06 (05/02/2014). This amendment clarified the WHO/ECOG performance status requirements for trial participants.

Exclusion criterion 4 was updated from that stated in the original protocol as part of amendment SA06. This amendment allowed patients who had had a previous attempt at pleurodesis to be included in the study (05/02/2014).

Interim analysis

The original analysis plan stipulated that an interim analysis for efficacy be performed after 100 patients had been recruited, using the O'Brien-Fleming stopping rule for the primary endpoint. This stopping rule required a significance threshold for the primary outcome of 0.048 at final analysis. However, because patient recruitment was better than anticipated at the time of the 100th patient being recruited, the TSC felt that by the time data would be ready for the interim analysis (i.e. after the follow-up was complete for the 100th patient, and the primary outcome had been adjudicated by two independent clinicians), the overall sample size target of 154 patients would be almost completed, rendering an interim analysis unnecessary.

Therefore, the IDMC and TSC recommended that the interim analysis not be undertaken, and that the significance threshold for the final analysis be set at 0.05. This change was implemented to the trial protocol in version 6.0 (9/9/16), as part of substantial amendment SA7 (approved 7/10/16).

Changes to primary outcome measure

Amendment SA03 (date 14/12/2012, approved 10/01/2013) revised the primary outcome measure to define successful pleurodesis as the sequential collection of 50mls of fluid rather than 20mls. This was amended, with the approval of the TSC, as it became clear that the drainage bottles being used in the study were unable to provide accurate measurements below 50mls of fluid. At the time of this amendment being approved, seven patients had been enrolled into the study

Other changes

The following deviations were decided before analysis of trial data began, and the trial statistician and all other study investigators were unaware of results by treatment arm.

- The Statistical Analysis Plan (SAP) specified that analyses would adjust for the volume of pleural fluid removed in the first 10 days post IPC as a continuous variable. Because the continuous value was not recorded for all patients, this has been changed to adjustment for the binary variable used in the minimisation procedure (≤1999 vs. ≥2000).
- Analysis of outcome variables collected at multiple time-points during follow-up (chest pain and breathlessness VAS scores, quality of life measured using QLQ-C30, quality of life measured using EQ-5D, size of pleural effusion, and degree of septation) was changed from including time-point as a continuous variable in the statistical model to including time-point as a categorical variable in the analysis. This change was made to ensure that separate treatment effects could be accurately estimated at each time-point.
- The SAP specified that analysis of the size of pleural effusion and the degree of septation outcomes would be via an ordered logistic regression mixed-effects model. This was changed to an ordered logistic regression model with robust standard errors to account for clustering of multiple time-points within participants. This change was made due to the lack of availability of ordered logistic regression mixed-effects models in Stata 12.
- The sensitivity analysis for missing data specified in the SAP did not work well for competing risk time-to-event models. We have therefore used a simplified sensitivity

analysis based on best and worst case scenarios to examine the maximum impact that missing data could have on results.

The following deviations were decided after analysis of trial data began, and the trial statistician was aware of results by treatment arm, but before other study investigators were aware of results by treatment arm.

- The SAP specified that the analysis for the outcome 'further pleural procedures within 10 weeks' would adjust for the minimisation factors. However, due to the low event rate (7 events total), adjustment for these factors would lead to over-stratification of the analysis model. Therefore, the analysis was unadjusted.

Randomization

Randomization was performed using a centralized, computer-based system hosted by Sealed Envelope Ltd (London, United Kingdom). In order to randomize, sites called the trial co-ordinating unit in Bristol who took verbal confirmation of suitability before entering data onto the randomization server via a web portal. Once known, treatment allocation was communicated to sites immediately, both verbally over the telephone and via automated emails sent to the local hospital pharmacy, principal investigator, and wider trial team.

The treatment allocation took place in a 1:1 ratio using minimization with a random component. The minimization factors were:

- Volume of pleural fluid removed between IPC insertion and randomization (≤1999 mls vs ≥2000 mls)
- Malignancy subtype (Ovarian and breast vs mesothelioma vs other)
- Day 10 (randomization) chest x-ray appearance (expanded with no evidence of trapped lung vs evidence of trapped lung but fits the criteria for randomization)

Trial database

Trial data were entered and stored in an electronic database designed and hosted by the Clinical Trials Evaluation Unit at the University of Bristol, United Kingdom.

Administration of trial treatment

For the purposes of trial treatment, investigators were advised to counsel patients as to the nature of the instillation procedure whilst keeping them unaware of their treatment allocation. The trial was therefore conducted in a single-blind fashion.

All trial medications, including 0.9% saline, were stored in monitored, temperature-controlled conditions at each local site. The appropriate substances were released to the trial team upon receipt of the randomization email and an appropriate prescription.

A standard operating procedure was used for all trial drug administration. Aseptic technique was required at all times. Administration of trial treatment took place as follows:

Preparation

1. Out of sight of the patient, the following were prepared:
    a. A clear syringe containing 50mls of 0.9% saline solution, labelled "flush"
    b. A clear syringe containing 3mg/kg of 1% lidocaine (to a maximum of 250mg), labelled "local anaesthetic"
    c. An opaque syringe containing either 4g sterile talc made into a slurry with 50mls 0.9% saline solution; or 50mls 0.9% saline solution alone (placebo), labelled "X"
2. Patients could be given prophylactic analgesia using non-NSAID medication.
3. The IPC was undressed and the patient positioned so that the catheter could be accessed by the trial team without it being visible to the patient. This usually entailed the patient lying on, or sitting on the edge of, a bed with their catheter angled behind them.

Administration

1. A drainage adaptor line was attached to a 3-way tap, before being connected to the IPC one-way valve.
2. A small amount of "flush" was used to clear the line, before the local anesthetic was administered, followed by another flush. The valve connector was disconnected, effectively clamping the drain.
3. After approximately 10 minutes, the connector apparatus was re-attached and the opaque syringe containing the trial drug was agitated.

4. The trial medication was administered over 2-5 minutes, with enough flush to ensure no visible trace was left in the IPC line.

Post-administration

1. The IPC was re-dressed as per standard practice
2. The patient was prescribed sufficient simple analgesia as necessary, and observed for no less than 2 hours before being discharged home.
3. Community services were contacted to ensure a drainage would take place between 12 and 36 hours post instillation.

Pleurodesis outcome assessments

Primary outcome

The primary outcome measure for this trial was the number of patients with successful pleurodesis at 5 weeks post randomisation.

Successful pleurodesis was defined as the collection of less than, or equal to, 50mls of pleural fluid on three consecutive occasions, with chest opacification on the side of the IPC less than 25% on a chest radiograph taken after the third consecutive occasion of collection less than 50mls, and within the 10 week follow-up period. All chest radiographs were reviewed at the end of the study by 2 independent pulmonologists with expertise in pleural disease, both of whom were blind to treatment allocation. Information on drainage volumes was collected in the community and during follow-up visits. All three occasions of collection less than 50mls had to occur within the 10 week follow-up period.

Patients who drained less than 50mls of fluid on three or more occasions but who continued to have greater than 25% pleural opacification on chest x-ray due to pleural fluid (as proven by the presence of either a moderate or large effusion on contemporaneous thoracic ultrasound), were defined as having an unsuccessful pleurodesis. If there was clinical suspicion that the drain may have been blocked then appropriate attempts to resolve this could be made.

The achievement of pleurodesis was dated to the first drainage of less than or equal to 50mls. Even if patients achieved the requirements for pleurodesis during the trial period, they continued to receive fortnightly follow-up as originally planned until the 70-day follow-up period was complete.

Patients who died during the 10-week trial period were assessed for whether they achieved pleurodesis success prior to death using the same criteria as defined above.

Successful pleurodesis by measurement of total volume over time

As part of a secondary analysis, patients who recorded drainages totalling less than or equal to 250mls over two consecutive weeks during their follow-up period (with appropriate radiological findings as described above) were also defined as having a successful pleurodesis. The period of two consecutive weeks began with any drainage which was undertaken during the post-randomisation trial period, and ended two weeks later on the same day of the week. The drainage volume recorded on the final day was included in the total volume for the two week period. Patients were to be drained no less frequently than twice per week.

For patients who successfully drained less than or equal to 250mls of fluid in a two week period, the date of pleurodesis was defined as the day of the first drainage in that period. All drainages which counted towards the total volume must have occurred within the study period.

Patients who died during the follow-up period were also assessed for pleurodesis using measurements collected prior to death. The clinical and radiological parameters used to define successful pleurodesis by volume over time remained the same as those described above.

Secondary outcome assessments – measures and analyses

Secondary outcome measures detailed descriptions

- Self-reported quality of life status, measured at 14, 28, 42, 56, and 70 days, using the EQ-5D health questionnaire
- Self-reported quality of life status, measured at 14, 28, 42, 56, and 70 days using the QLQ-C30 questionnaire
- Self-reported VAS scores, measured daily from randomisation to 10 weeks post-randomisation, for thoracic pain
- Self-reported VAS scores, measured daily from randomisation to 10 weeks post-randomisation, for breathlessness
- Total volume of pleural fluid drained from randomisation to 10 weeks post-randomisation
- All-cause mortality up to 10 weeks post randomisation.
- Number of hospital inpatient bed-days required from randomisation to 10 weeks post-randomisation

- Overall size of pleural effusion (none, small, moderate, large) at 14, 28, 42, 56, and 70 days
- Degree of septation of pleural fluid (none, light, moderate, heavy) at 14, 28, 42, 56, and 70 days.
- Pleurodesis success at 10 weeks post randomisation
- Pleurodesis success at 5 weeks, as defined by the total volume of fluid collected over a 2 week period
- Pleurodesis success at 10 weeks, as defined by the total volume of fluid collected over a 2 week period
- Further pleural procedures from randomisation to 10 weeks post-randomisation
- Adverse events from randomisation to 10 weeks post-randomisation
- Serious adverse events from randomisation to 10 weeks post-randomisation

Secondary outcome analyses methods

- All-cause mortality up to 10 weeks post randomisation was analysed using a logistic regression model .
- Self-reported VAS scores for thoracic pain and breathlessness were analysed using a mixed-effects linear regression model, with an unstructured correlation matrix between different time-points. A treatment-by-time interaction was included as a fixed-factor in the model. The analysis was adjusted for the baseline value of thoracic pain (in addition to the minimisation factors). Missing baseline values of thoracic pain were imputed using mean imputation.
- The total volume of pleural fluid drained from randomisation to 10 weeks post-randomisation was analysed using a linear regression model.
- The number of hospital inpatient bed-days required from randomisation to 10 weeks post-randomisation was analysed using a negative binomial regression model. The number of days of follow-up was included in the model as an offset (i.e. the model included a term for the log-transformed number of days of follow-up for each patient, with the parameter constrained to one).
- The overall size of the pleural effusion and degree of fluid loculation were analysed using an ordered logistic regression model, with a treatment-by-time interaction. The baseline value of the outcome was included in the model as a covariate (in

addition to the minimization factors). Robust standard errors were used to account for correlation between different time-points.

- Self-reported quality of life status using the EQ-5D and QLQ-C30 questionnaires was analysed using the same approach as the self-reported VAS scores.
- Further pleural procedures were analysed using logistic regression model.
- Adverse events and serious adverse events were analysed using a logistic regression model.

Clarification of size of pleural effusion

The overall size of any effusion was determined using a standardised data capture tool, which was completed by the physician performing any trial-related thoracic ultrasound scans. Effusion size was categorised as one of the following in all cases:

- None
- Small (fluid present only in basal area)
- Moderate (Effusion affects less than half of the hemithorax, but more than just the basal area
- Large (Effusion affects more than half of the hemithorax)

Clarification of degree of pleural fluid septation

- No septation was defined as the absence of visible septation on ultrasound.
- Light septation was defined as a collection with 3 or fewer septations visible on ultrasound at the maximally septated area.
- Moderate septation was defined as a collection with 4-9 septations visible at the maximally septated area.
- Heavy septation was defined as a collection with more than 9 septations visible at the maximally septated area.

Clarification of further pleural procedures

- A further pleural procedure was defined as any of the following (provided it took place on the side of the trial intervention):
- Therapeutic aspiration of >100mls of fluid

- Insertion of an intercostal drain for fluid drainage
- Repeat insertion of an indwelling pleural catheter
- Medical or surgical thoracoscopy

Additional analyses

In addition to the main trial outcomes, comprehensive data regarding health economic outcomes were also collected during the study period. Analysis of health economic and exploratory outcomes (including pleural manometry the time of IPC insertion) were not specified in the a priori statistical analysis plan and will take place separate to the main trial which is reported here.

Primary outcome pre-specified subgroup analyses

Subgroup analyses were performed for the primary outcome using an interaction test (i.e. an interaction term between the treatment and the baseline covariate was added to the regression model), and was considered statistically significant at the 5% level.

The following subgroup analyses were pre-specified in the analysis plan:

- Patients receiving chemotherapy at baseline vs those not receiving chemotherapy at baseline
- Previous radiotherapy to chest vs no previous radiotherapy to chest
- WHO performance status 0-1 vs 2-3
- Patients on NSAIDS at baseline vs those not on NSAIDS at baseline.
- Presence of trapped lung at baseline vs. no trapped lung
- Volume of pleural fluid removed in first 10 days post IPC (≤1999 mls vs. ≥2000 mls)

Missing data

The primary outcome was considered missing if the patient had fewer than 3 pleural drainage measurements. If the patient had 3 or more consecutive pleural drainage measurements of less than 50mls of fluid, but does not have an x-ray for chest opacification taken after the 3rd measurement, they were also considered missing. Pleurodesis success at 10 weeks, and pleurodesis success at 5 and 10 weeks based on total volume drained over 2 weeks were assessed similarly.

EQ-5D, QLQ-C30, thoracic pain, breathlessness, overall size of the pleural effusion, and degree of septation of pleural fluid was considered missing if no post-randomisation measurements were recorded.

Further pleural procedures, number of days in hospital, adverse events, and serious adverse events were considered missing if the patient attended no follow-up visits, and outcome records are not available.

All-cause mortality was considered missing if we were unable to obtain information on whether the patient was alive at the end of follow-up.

RESULTS

Primary outcome sensitivity analyses

The primary analysis assumed that missing data was *missing-at-random,* i.e. that conditional on the variables included in the analysis model (treatment arm, minimisation factors) the outcomes for patients with missing data were not different to the outcomes for patients with observed data. We have performed several sensitivity analyses to assess the robustness of our results to departures from this assumption. There were 6/76 (8%) patients with missing data in the placebo group, and 9/78 (12%) in the talc group.

We assessed four different scenarios:

1. All patients with missing data achieved successful pleurodesis (i.e. missing data = success)
2. No patients with missing data achieved successful pleurodesis (i.e. missing data = failure)
3. All placebo patients with missing data achieved successful pleurodesis, and no talc patients with missing data achieved successful pleurodesis (i.e. missing data = success (placebo), missing data = failure (talc))
4. No placebo patients with missing data achieved successful pleurodesis, and all talc patients with missing data achieved successful pleurodesis (i.e. missing data = failure (placebo), missing data = success (talc))

Note that the last two scenarios are the most extreme situations that could occur in practice, and are extremely implausible. They are shown only to denote the maximum possible impact of the missing data on the results.

When missing data was set to successful pleurodesis, we set the time to pleurodesis at 15 days. When missing data was set to no successful pleurodesis, we set the censoring time as 35 days.

Results are shown in the graph below, with the treatment effect estimate remaining relatively unchanged for the first two scenarios, and only minor changes for the last two scenarios. In all scenarios, the treatment effect estimate is consistent with benefit from talc.

Outcome definition

The primary outcome was defined as missing if patients have 3 or more consecutive pleural drainage measures of less than 50mls of fluid, but no x-ray for chest opacification taken after the 3rd measurement. We had planned to assess the sensitivity of this definition by re-analyzing the primary outcome by including these patients without an x-ray after their 3rd successful measurement as having had a successful pleurodesis. However, there were no cases where this occurred.

Post-hoc primary outcome analysis of performance status

Post-hoc analysis of performance status suggested a difference in participants with scores of 0 (HR 1.97, 95% CI 0.32 to 12.17) and 1 (HR 4.07, 95% CI 1.55 to 10.71) compared to 2 (HR 0.56, 95% CI 0.19 to 1.60) or 3 (HR not estimable) (p-value for interaction <0.001) for the primary outcome

Post-hoc sensitivity analysis to adjust for baseline imbalance of LMWH

We conducted a post-hoc sensitivity analysis to assess whether the baseline imbalance between treatment groups had any effect on results. We re-analyzed the primary outcome while including LMWH as a covariate in the time-to-event regression model. Results were not materially affected (HR 2.01, 95% CI 1.12 to 3.62, p=0.02).

Post-hoc sensitivity analysis to adjust for baseline imbalance of chemotherapy

We conducted a post-hoc sensitivity analysis to assess whether the baseline imbalance between treatment groups had any effect on results. We re-analyzed the primary outcome while including baseline chemotherapy as a covariate in the time-to-event regression model. Results were not materially affected (HR 2.31, 95% CI 1.29 to 4.12, p=0.005).

ADVERSE EVENTS

Events relating to IPC and IPC use

At each follow-up assessment, patients were asked if certain events relating to their IPC or the drainage of the IPC had occurred since the previous trial visit. Where necessary, these events could also be reported as adverse or serious adverse events if judged to be so by the principal investigator.

Serious adverse events

Serious adverse events were defined as any untoward medical occurrence or effect that;

- Resulted in death
- Was life-threatening
- Required hospitalisation, or prolongation of existing inpatients' hospitalisation
- Resulted in persistent or significant disability or incapacity

Assessment and reporting of serious events took place in accordance with the Sponsor's standard operating procedures, except where the event was expected.

Expected adverse events in the setting of this study were defined to be:

- Death due to underlying malignancy
- Admission due to underlying malignancy
- New fever after instillate
- New mild tachycardia after instillate (≤20 beats per minute over baseline)
- New pleuritic chest pain after instillate requiring simple analgesia (simple analgesia is defined as any medication which is not a morphine derivative or equivalent)
- New tachypnoea after instillate (increase in respiratory rate of ≥5 breaths per minute over baseline)
- New hypoxia after instillate (to saturation of ≤92% on air, or to a level requiring additional supplemental oxygen)
- Mild transient cough, chest pain or discomfort reasonably associated with drainage of the IPC requiring no analgesia or use of patient's standard analgesia only

FIGURES

Figure S1 – Trial procedures outline

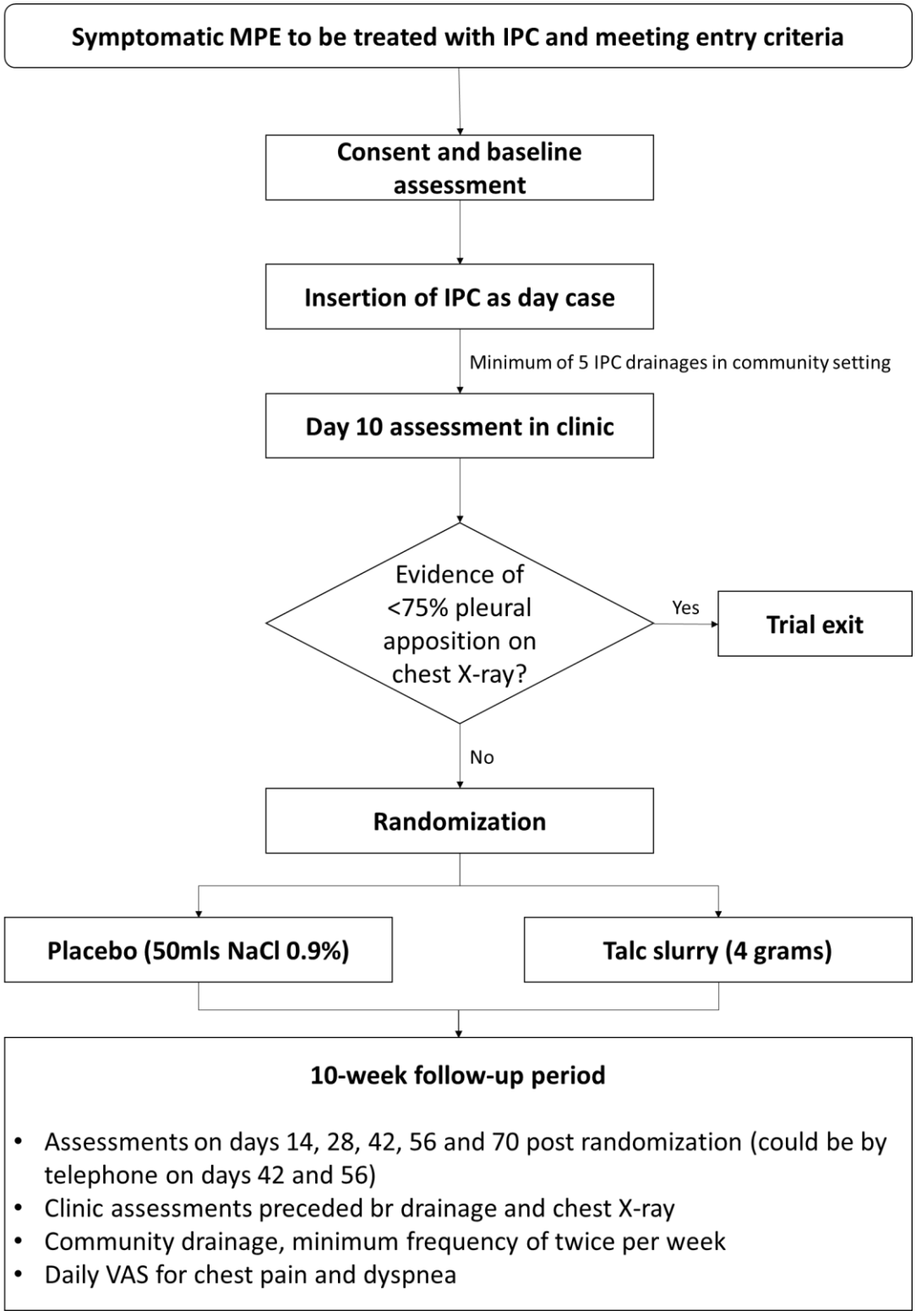
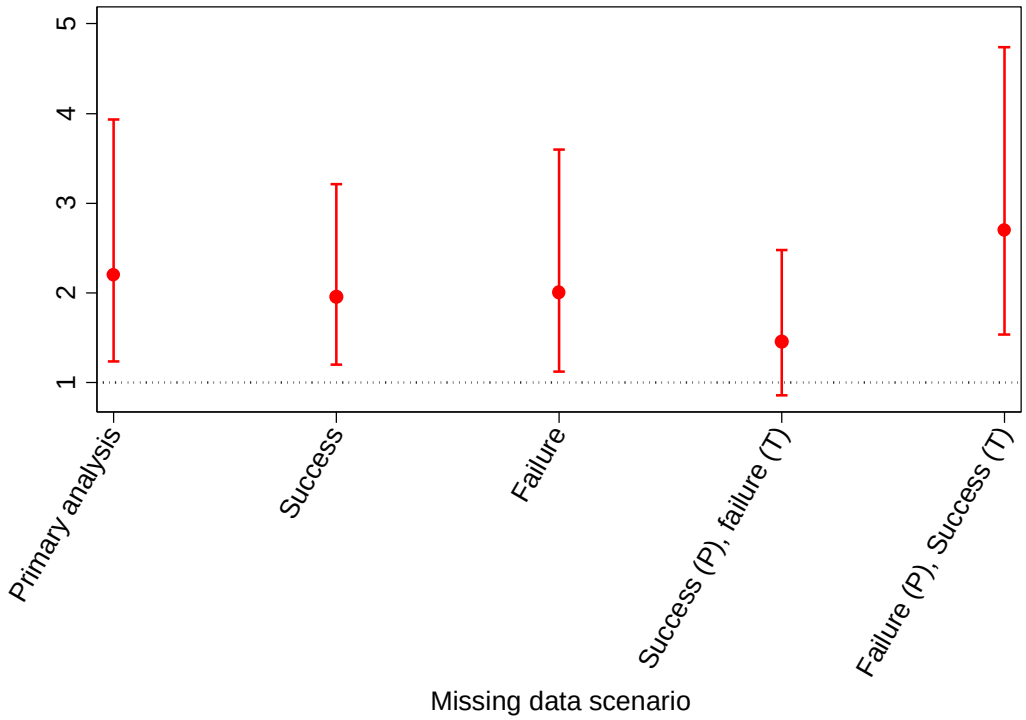
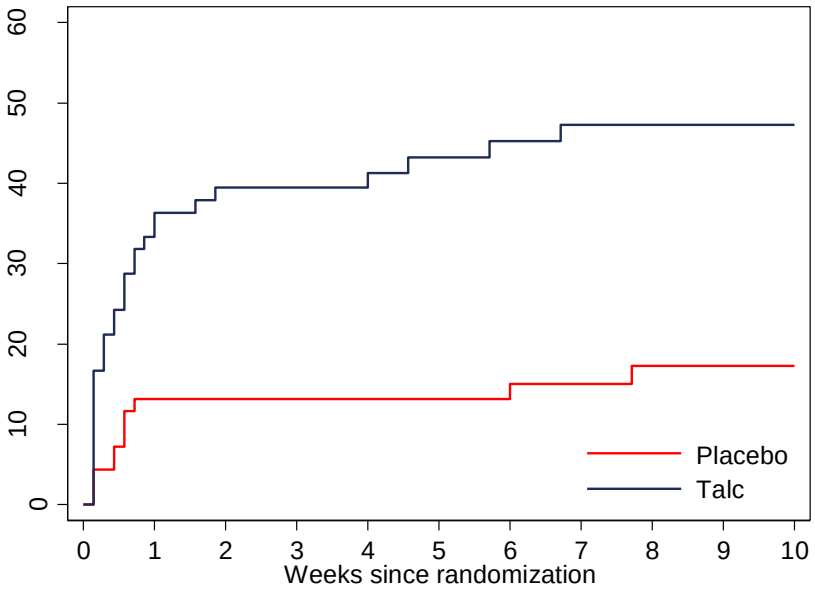


Figure S2 – Graph demonstrating sensitivity analyses



*P=placebo, T=talc. X-axis categories demonstrate outcome if missing data allocated to groups described

Figure S3 – Survival curve for pleurodesis success using secondary definition



Number at risk											
Placebo	69	59	56	52	50	47	45	40	36	33	17
Talc	66	44	39	35	33	29	28	25	24	23	11

Figure S4 – VAS chest pain change from baseline (days 1 to 14)

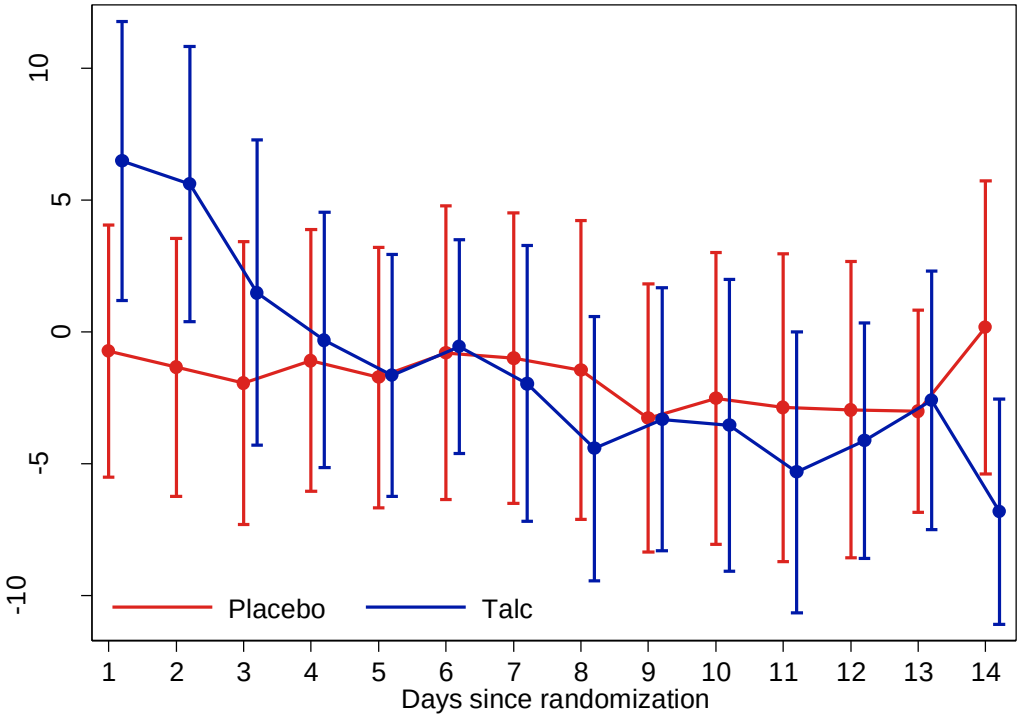


Figure S5 – VAS chest pain change from baseline (days 14 to 70)

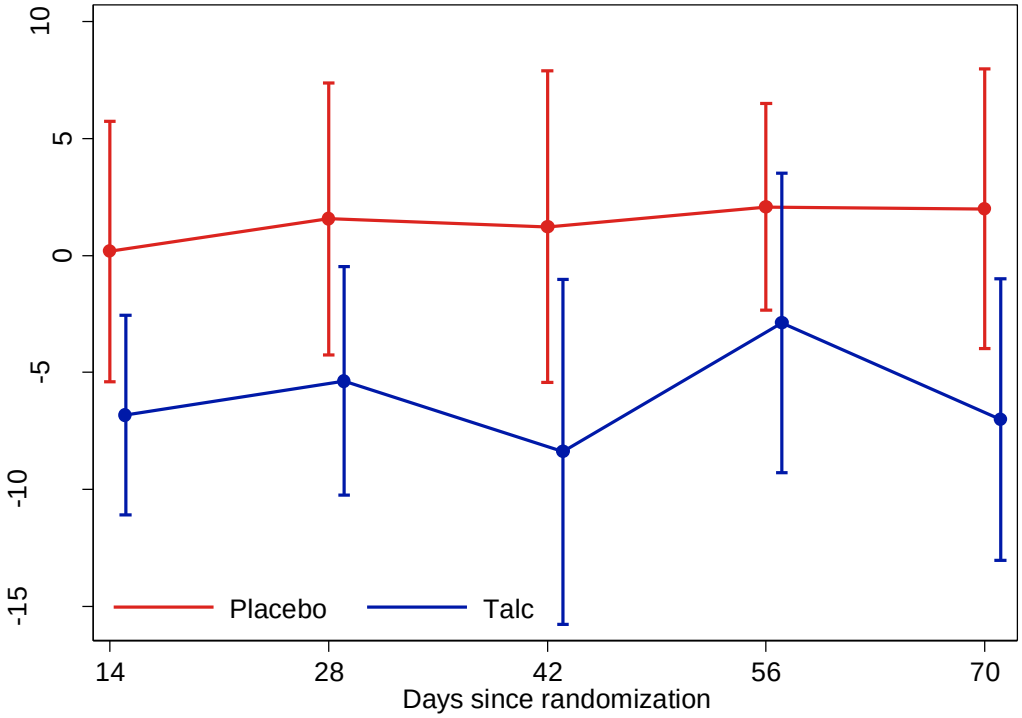


Figure S6 – VAS chest pain treatment effect difference

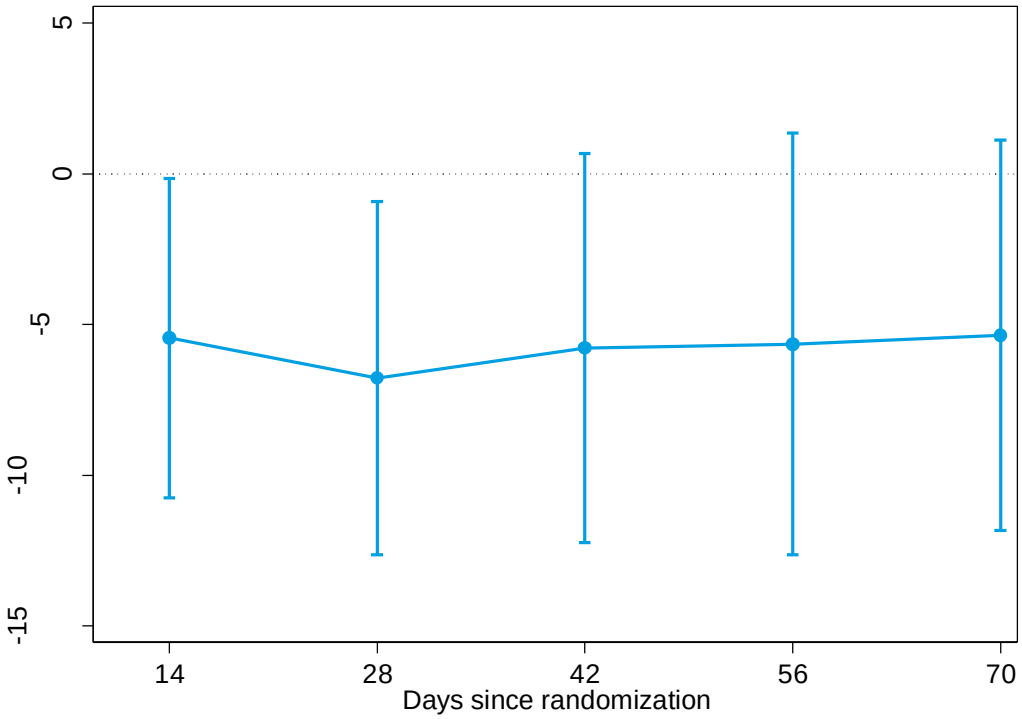


Figure S7 – VAS dyspnea change from baseline (days 1 to 14)

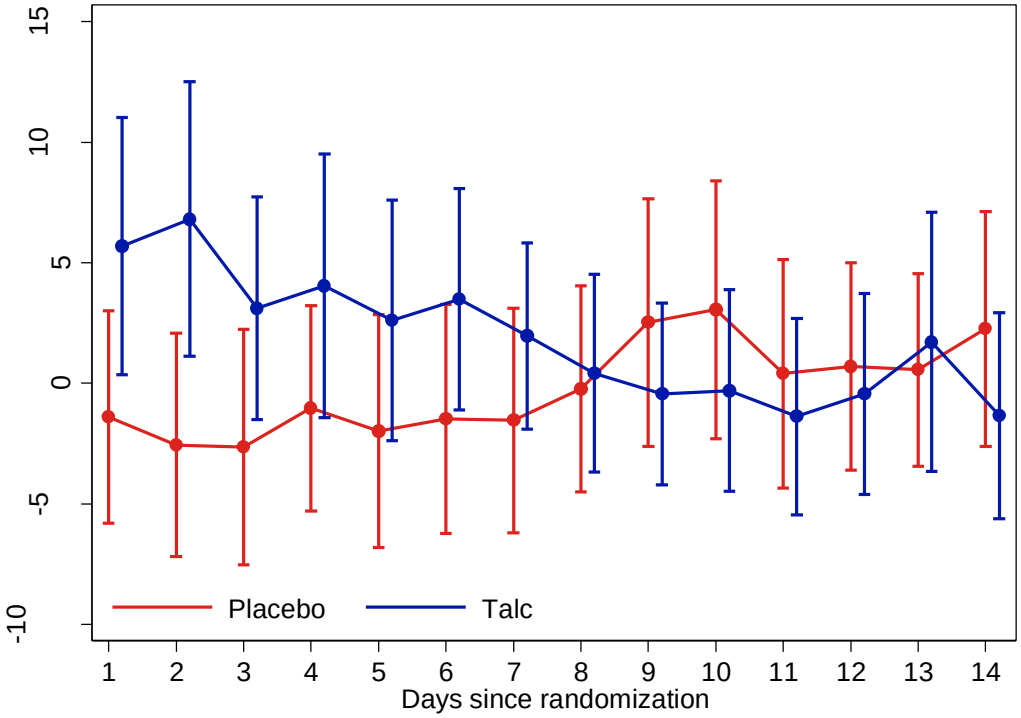


Figure S8 – VAS dyspnea change from baseline (days 14 to 70)

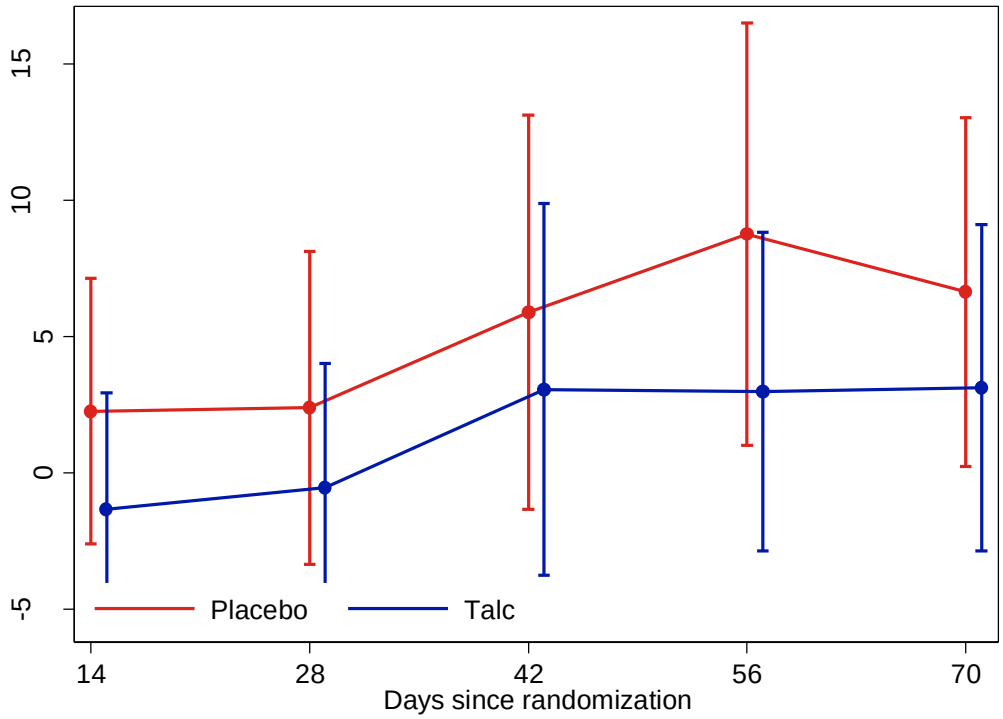


Figure S9 – VAS dyspnea treatment effect difference

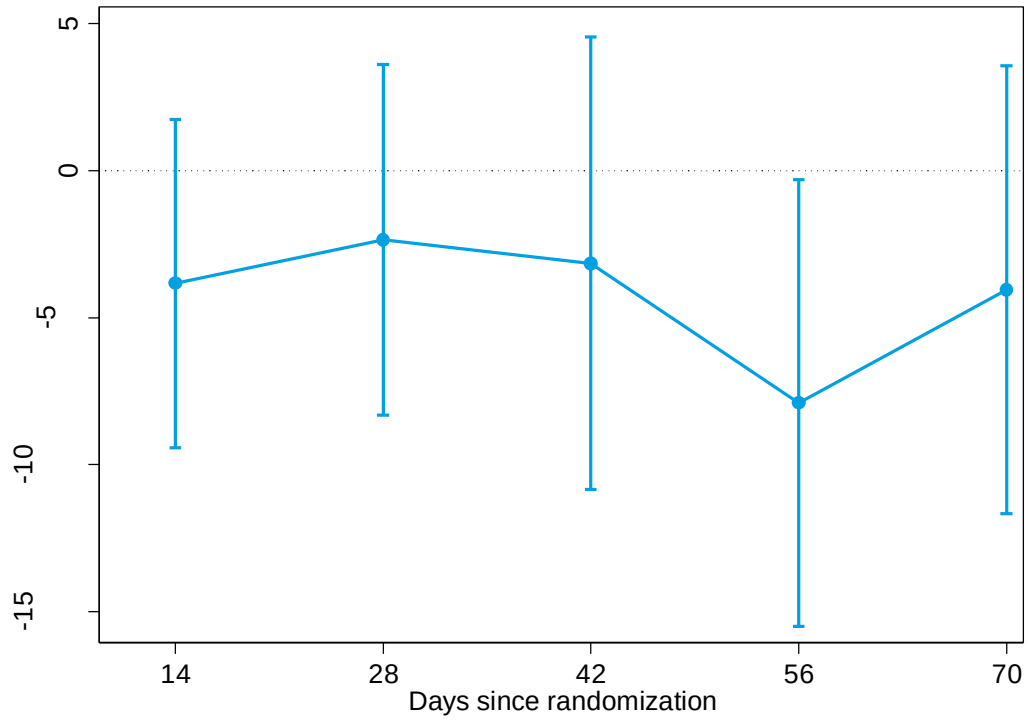


Figure S10 – EQ-5D-5L change from baseline

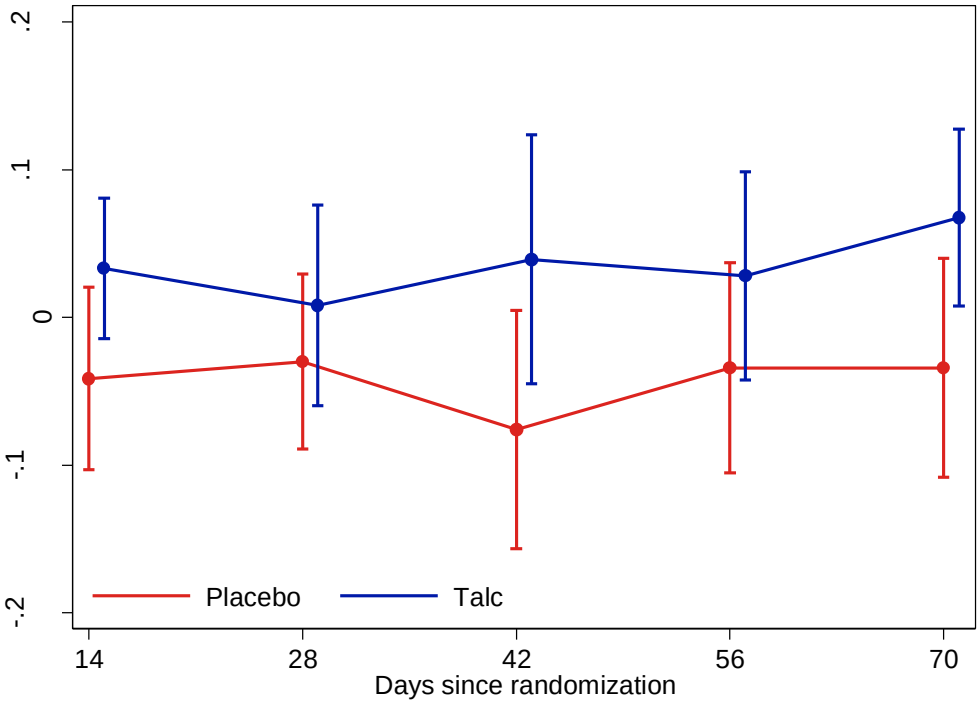


Figure S11 – EQ-5D-5L treatment effect difference

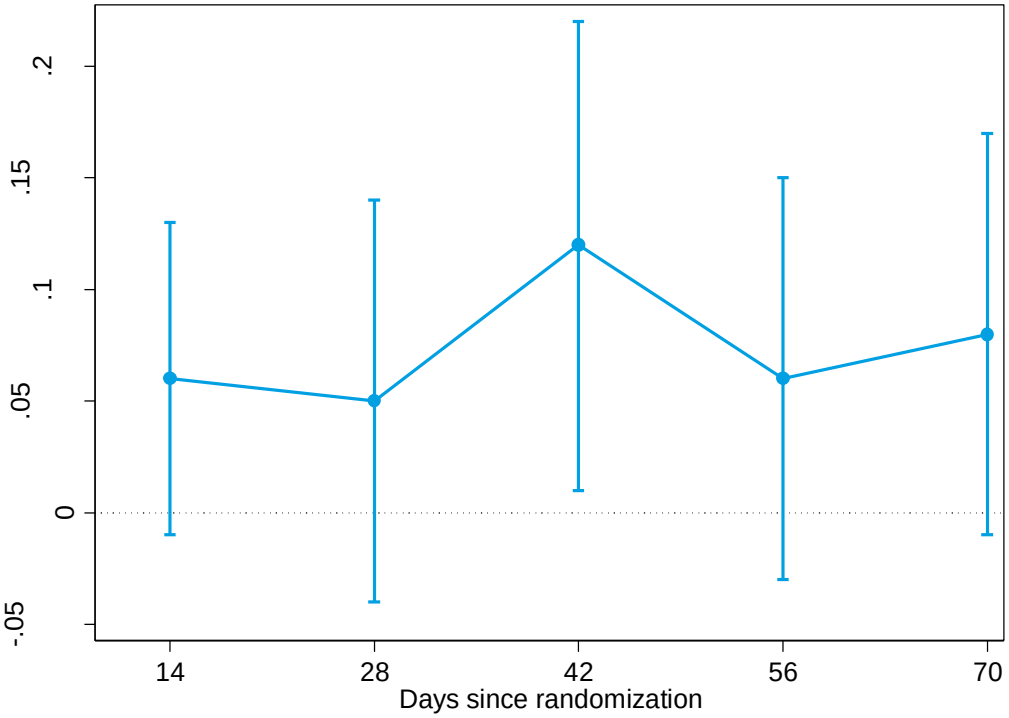


Figure S12 – QLQ-C30 change from baseline

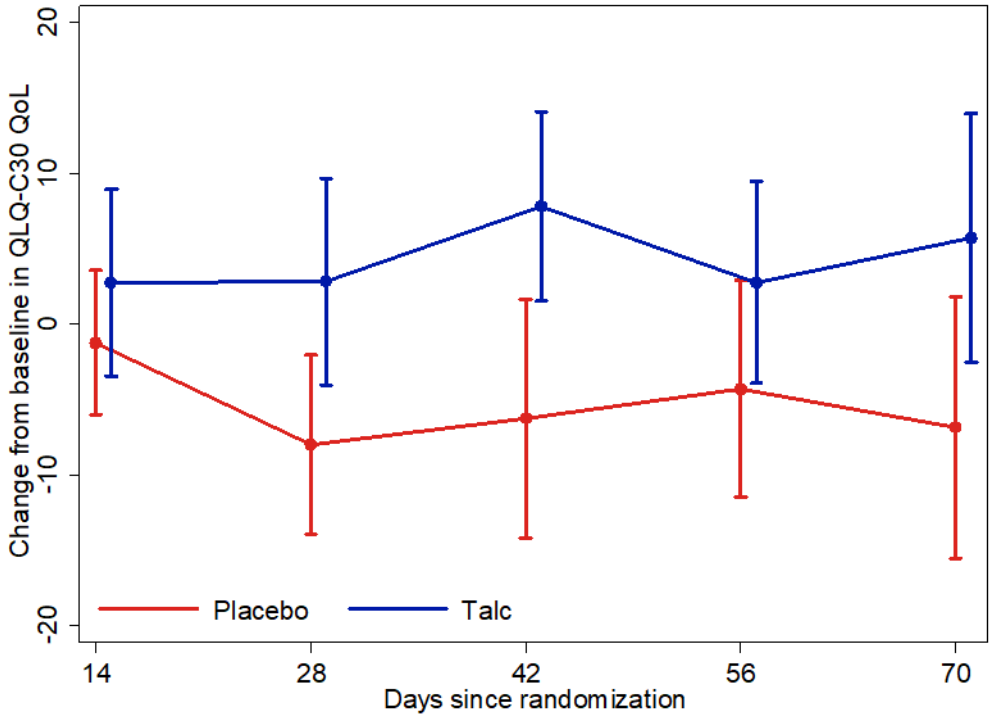
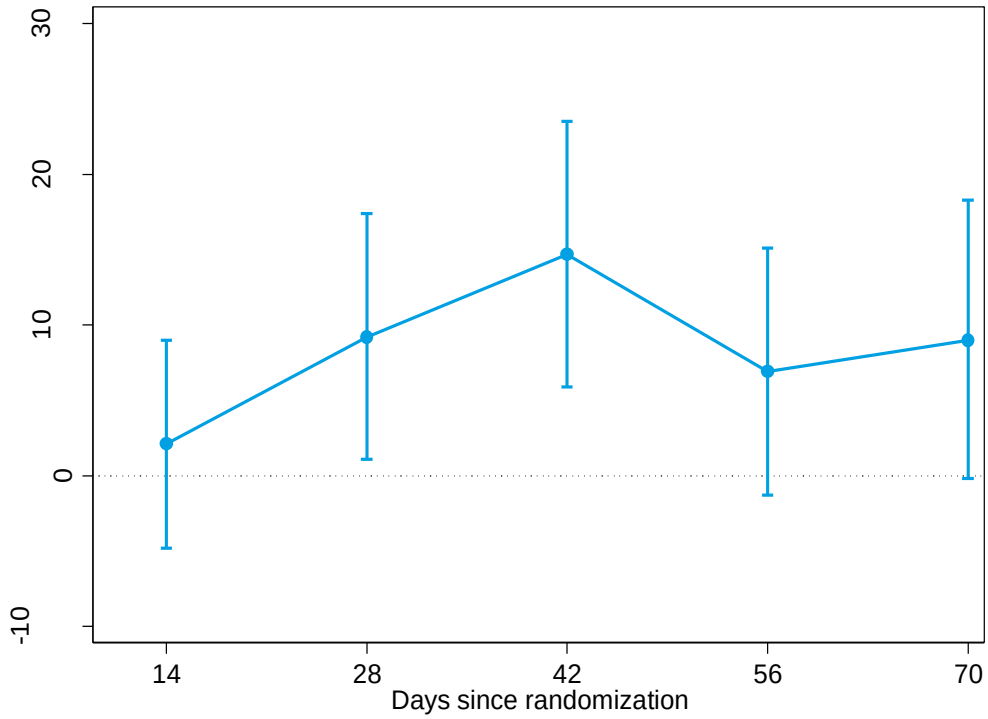


Figure S13 – QLQ-C30 treatment effect difference



TABLES

Table S1 – Full baseline characteristics

Characteristic	Placebo n=76 (% unless stated)	Talc n=78 (% unless stated)	Missing data	
			Placebo	Talc
Mean age (standard deviation)	68.7 (10.1)	67.7 (12.7)	0	0
Female	39 (51)	44 (56)	0	0
Right sided effusion	42 (55)	44 (56)	0	0
Duration of symptoms			0	0
<1 month	24 (32)	14 (18)	-	-
1-2 months	30 (39)	35 (45)	-	-
>2 months	22 (29)	29 (37)	-	-
ECOG performance score			1	1
0	10 (13)	8 (10)	-	-
1	33 (44)	38 (49)	-	-
2	16 (21)	23 (30)	-	-
3	16 (21)	8 (10)	-	-
Smoking status			2	1
Never smoked	30 (41)	25 (32)	-	-
Current smoker	8 (11)	7 (9)	-	-
Ex-smoker	36 (49)	45 (58)	-	-
Cancer type			0	0
Lung	25 (33)	20 (26)	-	-
Breast	16 (21)	15 (19)	-	-
Mesothelioma	10 (13)	13 (17)	-	-
Ovarian	5 (7)	6 (8)	-	-
Renal	4 (5)	5 (6)	-	-
Colorectal	5 (7)	1 (1)	-	-
Lymphoma	0 (0)	5 (6)	-	-
Gastro-oesophageal	2 (3)	2 (3)	-	-
Prostate	1 (1)	2 (3)	-	-
Unknown	0 (0)	3 (4)	-	-
Not specified	3 (4)	3 (4)	-	-
Other	5 (7)	3 (4)	-	-
Removed ≥2000mls fluid prior to randomisation	61 (80)	61 (78)	0	0
<25% lung entrapment at randomization	14 (18)	16 (21)	0	0
At least one pleural intervention in previous three months	55 (72)	59 (76)	0	0
Median number of pleural interventions in previous three months (IQR)	1 (0, 2)	1 (1, 2)	0	0
Type of pleural intervention in previous three months			0	0

Diagnostic tap	20 (26)	18 (23)	-	-
Therapeutic tap	39 (51)	42 (54)	-	-
Image-guided biopsy	1 (1)	2 (3)	-	-
Chest drain	5 (7)	7 (9)	-	-
IPC	0 (0)	1 (1)	-	-
Medical thoracoscopy	4 (5)	4 (5)	-	-
VATS	0 (0)	1 (1)	-	-
Size of effusion (TUS) at randomisation			0	0
None	23 (30)	26 (33)	-	-
Small	49 (64)	46 (59)	-	-
Moderate	4 (5)	6 (8)	-	-
Degree of septation (TUS) at randomisation			0	0
None	63 (83)	61 (78)	-	-
Light	9 (12)	8 (10)	-	-
Moderate	3 (4)	7 (9)	-	-
Heavy	1 (1)	2 (3)	-	-
Co-morbidities				
COPD/asthma	9 (12)	10 (13)	1	0
Interstitial lung disease	0 (0)	1 (1)	2	0
Bronchiectasis	1 (1)	0 (0)	2	0
Pulmonary hypertension	0 (0)	0 (0)	2	0
Pulmonary emboli	7 (9)	4 (5)	2	0
Other respiratory co-morbidity	0 (0)	3 (4)	2	0
Ischaemic heart disease	5 (7)	6 (8)	2	0
Atrial fibrillation	5 (7)	7 (9)	2	0
Heart failure	0 (0)	3 (4)	2	0
Other cardiac co-morbidity	8 (11)	7 (9)	2	0
Medications at baseline				
Oral glucocorticoids	13 (17)	7 (9)	1	1
Non-steroidal anti-inflammatory drugs	14 (19)	11 (14)	1	1
Paracetamol	46 (61)	46 (60)	1	1
Weak opiates	19 (25)	19 (25)	1	1
Strong opiates	18 (24)	22 (29)	1	1
Clopidogrel	3 (5)	2 (3)	12	5
Low molecular weight heparin*	12 (17)	4 (5)	4	3
Warfarin	3 (5)	4 (6)	12	5
Other anticoagulant	1 (2)	3 (4)	14	4
Anticancer treatments at baseline				
Radiotherapy	14 (19)	19 (24)	1	0
Hormone therapy	9 (12)	7 (9)	0	0
Chemotherapy	6 (8)	15 (19)	0	0
Other anti-cancer therapy	4 (5)	4 (5)	0	0
Started chemotherapy during trial	27 (39)	21 (33)	0	0

*A statistically significant imbalance (p = 0.034) was noted was in patients receiving anticoagulation therapy with low molecular weight heparin. No other statistically significant baseline imbalances were identified.

Table S2 – Full pleurodesis results table

	Number included in analysis		Summary measure			
Outcome	**Placebo n=76 (%)**	**Talc n=78 (%)**	**Placebo**	**Talc**	**Treatment effect (talc vs. placebo) (Hazard ratio, 95% CI)**	**P-value**
Pleurodesis success at 5 weeks (primary outcome)	70 (92)	69 (88)	-	-		
Failure	-	-	50 (71)	35 (51)	-	-
Success	-	-	16 (23)	30 (43)	2.20 (1.23, 3.92)	0.008
Died before success	-	-	4 (6)	4 (6)	-	-
Pleurodesis success at 10 weeks (secondary outcome)	70 (92)	69 (88)				
Failure	-	-	42 (60)	30 (43)	-	-
Success	-	-	19 (27)	35 (51)	2.24 (1.31, 3.85)	0.003
Died before success	-	-	9 (13)	4 (6)	-	-

Table S3 – Pre-specified subgroup analyses

Subgroup	**Placebo**	**Talc**	**Hazard ratio (95% CI)**	**P-value for interaction**
Chemotherapy				Not estimable
No	16/64 (25)	24/56 (43)	Not estimable	-
Yes	0/6 (0)	6/13 (46)	Not estimable	-
Radiotherapy				0.90
No	12/57 (21)	21/51 (41)	2.11 (1.06, 4.22)	-
Yes	4/12 (33)	9/18 (50)	2.30 (0.74, 7.13)	-
WHO score				0.07
0-1	7/41 (17)	22/44 (50)	3.52 (1.55, 7.97)	-
2-3	9/28 (32)	8/25 (32)	1.10 (0.43, 2.81)	-
NSAIDS				0.72
No	13/56 (23)	25/60 (42)	2.10 (1.12, 3.94)	-
Yes	3/13 (23)	5/9 (56)	2.80 (0.67, 11.76)	-
Trapped lung				0.40
No	15/56 (27)	25/54 (46)	1.99 (1.08, 3.66)	-
Yes	1/14 (7)	5/15 (33)	5.18 (0.60, 44.76)	-
Fluid removed before randomisation				0.24
≤1999	6/15 (40)	7/15 (47)	1.30 (0.48, 3.50)	-
≥2000	10/55 (18)	23/54 (43)	2.75 (1.32, 5.73)	-

Post hoc analyses of primary outcome

Table S4 – Pleurodesis success with no requirement for chest x-ray success

	Summary measure			
Outcome	**Placebo**	**Talc**	**Treatment effect (talc vs. placebo) (95% CI)**	**P-value**
Pleurodesis success at 5 weeks (no requirement for x-ray success)	20 (28)	33 (48)	1.88 (1.08, 3.29)	0.03

Outcome is defined as 3 or more drainage values of less than or equal to 50mls within 5 weeks, with no requirement for x-ray success.

Table S5 – Re-classifying patients with further pleural procedures as 'failure'

	Hazard ratio (95% CI)	**P-value**
Pleurodesis success (5 weeks)	2.11 (1.18, 3.78)	0.01
Pleurodesis success (10 weeks)	2.00 (1.15, 1.69)	0.01

Table S6 – Amount of fluid drained before randomisation

Subgroup	**Placebo**	**Talc**	**Hazard ratio (95% CI)**	**P-value for interaction**
Amount drained				0.53
<1500	5/13 (38)	5/11 (45)	1.12 (0.38, 3.26)	-
1500-3000	3/17 (18)	13/24 (54)	3.88 (1.10, 13.66)	-
3000-4500	6/29 (21)	9/25 (36)	2.10 (0.75, 5.86)	-
>4500	2/11 (18)	3/9 (33)	1.97 (0.33, 11.65)	-

Table S7 – ECOG score (0 vs. 1 vs. 2 vs. 3)

Subgroup	Placebo	Talc	Hazard ratio (95% CI)	P-value for interaction
ECOG score				<0.001
0	2/10 (20)	3/8 (38)	1.97 (0.32, 12.17)	-
1	5/31 (16)	19/36 (53)	4.07 (1.55, 10.71)	-
2	9/15 (60)	6/18 (33)	0.56 (0.19, 1.60)	-
3	0/13 (0)	2/7 (29)	Not estimable	-

Secondary outcome analyses

Table S8 – Secondary definition of pleurodesis

	Number included in analysis		Summary measure			
Outcome	**Placebo n=76 (%)**	**Talc n=78 (%)**	**Placebo**	**Talc**	**Treatment effect (talc vs. placebo) (Hazard ratio, 95% CI)**	**P-value**
Pleurodesis success at 5 weeks (based on total fluid drained over 2 week period)	70 (92)	67 (86)				
Failure	-	-	57 (81)	35 (52)	-	-
Success	-	-	9 (13)	28 (42)	3.78 (1.81, 7.90)	<0.001
Died before success	-	-	4 (6)	4 (6)	-	-
Pleurodesis success at 10 weeks (based on total fluid drained over 2 week period)	69 (91)	66 (85)	-	-		
Failure	-	-	49 (71)	31 (47)	-	-
Success	-	-	11 (16)	30 (45)	3.43 (1.74, 6.75)	<0.001
Died before success	-	-	9 (13)	5 (8)	-	-

Table S9 – Other secondary outcomes

	Number included in analysis		Summary measure			
Outcome	**Placebo n=76 (%)**	**Talc n=78 (%)**	**Placebo**	**Talc**	**Treatment effect (talc vs. placebo) (95% CI)**	**P-value**
Further pleural procedures within 10 weeks	73 (96)	71 (91)	2 (3)	5 (7)	Odds ratio 2.69 (0.50, 14.34)	0.25
Total fluid drained over 10 weeks	71 (93)	71 (91)	3640 (845, 7605)	1350 (340, 5680)	Difference in means -826 (-2587, 935)	0.36
Mortality within 10 weeks	67 (88)	67 (86)	14 (21)	7 (10)	Odds ratio 0.45 (0.17, 1.24)	0.13
Hospital bed days	75 (99)	73 (94)	3.0 (5.2)	4.1 (7.9)	Rate ratio 1.16 (0.50, 2.70)	0.74

Table S10 – Data summary for patients requiring further pleural procedures

Further pleural procedure?	Treatment arm	Achieved pleurodesis?	Time of pleurodesis (days)	Time of further pleural procedure (days)	Further pleural procedure before or after pleurodesis success?
Yes	Placebo	No	-	28	-
Yes	Placebo	No	-	42	-
Yes	Talc	No	-	Missing	-
Yes	Talc	No	-	21	-
Yes	Talc	Yes	40	70	After
Yes	Talc	Yes	36	48	After
Yes	Talc	Yes	19	14	Before

Table S11 – Ultrasound outcomes

	Number included in analysis			
Outcome	**Placebo (n=76)**	**Talc (n=78)**	**Odds ratio* (talc vs. placebo) (95% CI)**	**P-value**
Effusion size	67 (88)	66 (85)	-	-
14 days	-	-	1.50 (0.76, 2.97)	0.24
28 days	-	-	1.26 (0.58, 2.75)	0.55
42 days	-	-	0.79 (0.27, 2.37)	0.68
56 days	-	-	0.75 (0.31, 1.83)	0.53
70 days	-	-	1.23 (0.52, 2.90)	0.63
Degree of septation	67 (88)	66 (85)	-	-
14 days	-	-	1.88 (0.86, 4.13)	0.11
28 days	-	-	1.20 (0.54, 2.69)	0.65
42 days	-	-	0.78 (0.31, 2.00)	0.61
56 days	-	-	0.66 (0.24, 1.80)	0.42
70 days	-	-	0.57 (0.25, 1.30)	0.18

*Odds ratio >1 indicates talc is associated with larger effusion sizes/greater septation, while an odds ratio <1 indicates talc is associated with smaller effusion sizes/less septation.

Table S12 – Symptom scores – chest pain VAS

Time point	Number included in analysis		Summary measure			
	Placebo (n=76)	Talc (n=78)	Placebo	Talc	Difference in means (talc vs. placebo) (95% CI)	P-value
	67 (88)	66 (85)				
14 days	-	-	0.2 (22.3)	-6.8 (17.2)	-5.4 (-10.7, -0.1)	0.04
28 days	-	-	1.6 (21.7)	-5.4 (19.1)	-6.8 (-12.6, -0.9)	0.02
42 days	-	-	1.2 (19.4)	-8.4 (23.7)	-5.8 (-12.2, 0.7)	0.08
56 days	-	-	2.1 (12.4)	-2.9 (18.6)	-5.6 (-12.6, 1.4)	0.11
70 days	-	-	2.0 (19.0)	-7.0 (21.9)	-5.4 (-11.8, 1.1)	0.11

Table S13 – Symptom scores –VAS dyspnea

Time point	Number included in analysis		Summary measure			
	Placebo (n=76)	Talc (n=78)	Placebo	Talc	Difference in means (talc vs. placebo) (95% CI)	P-value
	67 (88)	66 (85)			-	-
14 days	-	-	2.3 (19.5)	-1.3 (17.1)	-3.8 (-9.4, 1.8)	0.18
28 days	-	-	2.4 (21.4)	-0.5 (17.6)	-2.3 (-8.3, 3.6)	0.44
42 days	-	-	5.9 (20.7)	3.1 (21.6)	-3.1 (-10.8, 4.5)	0.42
56 days	-	-	8.7 (21.8)	3.0 (16.7)	-7.9 (-15.5, -0.3)	0.04
70 days	-	-	6.6 (20.3)	3.1 (21.5)	-4.0 (-11.7, 3.6)	0.30

Table S14 – Quality of life – EQ-5D-5L

Time point	Number included in analysis		Summary measure			
	Placebo (n=76)	Talc (n=78)	Placebo	Talc	Difference in means (talc vs. placebo) (95% CI)	P-value
	68 (89)	67 (86)				
14 days	-	-	-0.04 (0.24)	0.03 (0.19)	0.06 (-0.01, 0.13)	0.09
28 days	-	-	-0.03 (0.22)	0.01 (0.27)	0.05 (-0.04, 0.14)	0.31
42 days	-	-	-0.08 (0.28)	0.04 (0.32)	0.12 (0.01, 0.22)	0.03
56 days	-	-	-0.03 (0.23)	0.03 (0.26)	0.06 (-0.03, 0.15)	0.20
70 days	-	-	-0.03 (0.23)	0.07 (0.22)	0.08 (-0.01, 0.17)	0.07

Table S15 – Quality of life – QLQ-C30

Time point	Number included in analysis		Summary measure			
	Placebo (n=76)	Talc (n=78)	Placebo	Talc	Difference in means (talc vs. placebo) (95% CI)	P-value
	58 (76)	58 (74)	-	-	-	-
14 days	-	-	-1.2 (16.5)	2.8 (22.7)	2.1 (-4.8, 9.0)	0.55
28 days	-	-	-8.0 (20.0)	2.8 (24.2)	9.2 (1.1, 17.4)	0.03
42 days	-	-	-6.3 (26.1)	7.8 (21.9)	14.7 (5.9, 23.5)	0.001
56 days	-	-	-4.3 (22.1)	2.8 (22.3)	6.9 (-1.3, 15.1)	0.10
70 days	-	-	-6.8 (24.4)	5.7 (27.4)	9.0 (-0.2, 18.3)	0.06

Table S16 – Post-hoc test for average treatment effects*

Outcome	Treatment effect estimate (95% CI)	P-value
Chest pain (VAS)	-5.7 (-9.8, -1.6)	0.007
Breathlessness (VAS)	-3.6 (-8.5, 1.3)	0.15
QLQ-C30	6.9 (1.2, 12.6)	0.02
EQ-5D	0.07 (0.00, 0.14)	0.04

*This analysis compares the average outcomes across all time-points (14, 28, 42, 56, and 70 days) across the two treatment arms. It can be interpreted as the difference in average outcomes during follow-up.

Table S17 – IPC events recorded at follow-up assessments

	Placebo (n=76)	Talc (n=78)
Drained removed	14/73 (19)	33/73 (45)
Reason for drain removal		
Wound infection	2	1
Pleural infection	2	0
Drainage cessation	11	30
Uncontrolled pain	1	1
Other	0	2
Any IPC complication	34/71 (48)	30/70 (43)
Reason for complication		
Drainage stopped due to pain	27	23
Drainage stopped due to syncope	1	0
Drainage stopped due to cough	4	3
Drainage stopped due to tube blockage	1	5
Missed drainage due to inadequate team support	1	2
Other	7	4
Any drain site abnormalities	9/71 (13)	19/67 (28)
Reason for abnormality		
Wound infection	5	6
Malignant infiltration	0	1
Drain site leakage	1	1
Other	5	11

Table S18 – Number of IPC drainages

Number of drainage recordings	Placebo (n=76)	Talc (n=78)
Mean (SD)	14.9 (10.5)	13.8 (10.1)
Median (IQR)	15 (6, 21)	12 (6, 19)

Adverse events – additional information

Table S19 – Adverse events

	Number included in analysis		Summary measure			
Outcome	**Placebo (n=76)**	**Talc (n=78)**	**Placebo**	**Talc**	**Odds ratio (talc vs. placebo) (95% CI)**	**P-value**
Total number of adverse events	76 (100)	78 (100)	58	65	-	-
Number of patients with at least one adverse event	76 (100)	78 (100)	33 (43)	32 (41)	0.90 (0.47, 1.71)	0.74
Number of adverse events	76 (100)	78 (100)	-	-	-	-
0	-	-	43 (57)	46 (59)	-	-
1	-	-	17 (22)	19 (24)	-	-
2	-	-	11 (14)	7 (9)	-	-
3	-	-	1 (1)	1 (1)	-	-
4	-	-	4 (5)	1 (1)	-	-
5	-	-	0 (0)	0 (0)	-	-
6	-	-	0 (0)	3 (4)	-	-
7	-	-	0 (0)	1 (1)	-	-
Relatedness to trial	58/58	64/65	-	-		
Definitely related	-	-	5	12		
Possibly related	-	-	2	17		
Probably related	-	-	1	1		
Unrelated	-	-	50	34		

Table S20 – Serious adverse events

	Number included in analysis		Summary measure			
Outcome	**Placebo (n=76)**	**Talc (n=78)**	**Placebo**	**Talc**	**Odds ratio (talc vs. placebo) (95% CI)**	**P-value**
Total number of serious adverse events	76 (100)	78 (100)	28	22	-	-
Number of patients with at least one serious adverse event	76 (100)	78 (100)	21 (28)	18 (23)	0.78 (0.37, 1.62)	0.50
Number of serious adverse events	76 (100)	78 (100)	-	-	-	-
0	-	-	55 (72)	60 (77)	-	-
1	-	-	15 (20)	15 (19)	-	-
2	-	-	5 (7)	2 (3)	-	-
3	-	-	1 (1)	1 (1)	-	-
Relatedness to trial	27/28	21/22	-	-		
Definitely unrelated	-	-	25	15		
Unlikely related	-	-	0	3		
Possibly related	-	-	1	1		
Probably related	-	-	0	0		
Definitely related	-	-	1	2		