APPROVALS

Clinical Trial Report

Title:

TC-021-IM TachoSil versus standard surgical treatment for air leakage in pulmonary lobectomy

ID:

TC-021-IM

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Fredrik Bendiksen correctness and completeness	Approved 27.Mar.2009 15:30:55
Henrik Steen Andersen compliance with statistical principles	Approved 27.Mar.2009 21:13:57

Document ID: C00013351

Version: 2.0

Clinical Trial Report Signatures

Title: An open, randomised, prospective, multi-centre, parallel-group trial to compare efficacy and safety of TachoSil® versus standard surgical treatment in patients undergoing pulmonary lobectomy for lung malignancy and requiring treatment for air leakage

Trial ID: TC-021-IM

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

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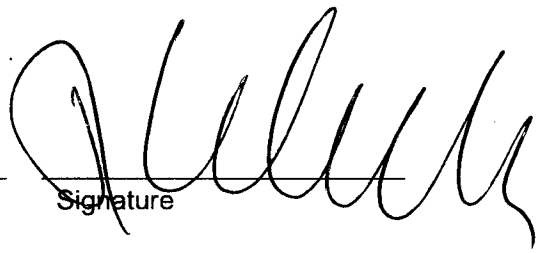
Signature

Date report last modified: 27 March 2009

Published Date: 30 April 2009
Document ID: C00013351
Published Page 2 of 203

Clinical Trial Report

Title: An open, randomised, prospective, multi-centre, parallel-group trial to compare efficacy and safety of TachoSil® versus standard surgical treatment in patients undergoing pulmonary lobectomy for lung malignancy and requiring treatment for air leakage

Short Title: TachoSil® versus standard surgical treatment for air leakage in pulmonary lobectomy

Trial ID: TC-021-IM

Sponsor: Nycomed
Clinical Trial Operations
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Trial phase: Therapeutic confirmatory, Phase IIIb

Date of trial initiation: 27 Jan 2006
Date of trial completion: 23 Mar 2007

This trial was conducted in accordance with Good Clinical Practice (GCP)

Date of final report, version 2.0: 27 March 2009

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For signatures, see separate page

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List of Abbreviations and Definition of Terms Used in the Report

AE:	Adverse Event
AT:	As Treated
AUC:	Area under the Curve
BPWG:	Working Group on Blood Products
BTPS:	Body Temperature (37^{o}C) and Pressure (P_B) Saturated with water vapour
CA:	Competent Authority
CI:	Confidence Interval
CHMP:	Committee for Proprietary Medicinal Products
CIOMS:	Council for International Organisations of Medical Sciences
CPV:	Central Pharmacovigilance
CRF:	Case Report Form
CRO:	Contract Research Organisation

CS:	Clinically Significant
CTM:	Co-ordinating Trial Manager
CV:	Curriculum Vitae
CDU:	Chest Drainage Unit
DHP:	Data Handling Plan
DVP:	Data Validation Plan
EC:	Ethics Committee
ECG:	Electrocardiogram
FEV-1:	Forced Expiratory Volume – 1 second
GCP:	Good Clinical Practice
GMP:	Good Manufacturing Practice
ICH:	International Conference on Harmonisation
INR:	International Normalised Ratio
ITT:	Intention-To-Treat
IUD:	Intrauterine Device
IVRS:	Interactive Voice Response System
Min:	Minute
NCS:	Not Clinically Significant
OR:	Odds Ratio
PDS:	Polydioxanone
PP:	Per-Protocol
RBC:	Red Blood Cells
RV:	Residual Volume
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
SD:	Standard deviation
SE:	Sampling Error
SmPC:	Summary of Product Characteristics
TachoSil:	TachoSil®
TLC:	Total Lung Capacity
Trial ID:	Trial Identification Number

1 Ethics

1.1 Ethical Rationale

The trial was conducted according to the ethical principles contained in the Declaration of Helsinki (1). Written informed consent was obtained from all subjects before any trial-specific procedures were done. Investigator explained the trial and its procedures to each subject verbally and the subjects received a Subject Information Sheet in order to acquaint themselves with the trial details. Subjects were asked to sign the Informed Consent Form only after they had had sufficient time to consider participation in the trial.

All subjects received active management of air leakage if deemed necessary by the surgeon. Stapling and suturing were not mandatory as primary management. The suturing or stapling method for air leakage management is widely used for control of intra-operative air leakage in lung surgery.

Post-randomisation treatment in the standard surgical treatment group (control group) was left at the surgeon's discretion and could be re-suturing or no treatment. The need for surgical treatment in this group depends on the individual type and site of lung resection. This was according to routine surgical standards.

Persisting air leakage after pulmonary surgery may have untoward consequences for post-operative complications, overall morbidity, hospitalisation costs and health care costs. The use of TachoSil® (hereafter referred to as TachoSil) may have beneficial effects on these variables if air leakage is prevented or reduced by using TachoSil.

The trial was designed to evaluate the efficacy and safety of TachoSil as air leakage treatment in lung surgery. TachoSil was expected not to cause serious adverse reactions as its efficacy and safety have been demonstrated in controlled clinical trials with either TachoSil or its predecessor product TachoComb® H (2,3,4,5). TachoSil was authorised in Europe in Jun 2004 for supportive treatment in surgery for improvement of haemostasis where standard techniques are insufficient.

The immunological safety profile of TachoSil is expected to be improved in comparison with its predecessor products TachoComb® and TachoComb® H since TachoSil is an equine collagen sponge coated with only human components.

Benefits, Risks and Discomfort

The use of TachoSil may reduce the incidence and intensity of air leakage after lung surgery. The benefits of this may be a reduced period of chest tube drainage, fewer post-operative complications and a shortened stay in hospital. Collagen sponge products with similar coagulation factors as TachoSil have been used extensively in the past decade with no untoward consequences for the subjects. The use of TachoSil was therefore expected to be safe and without risks although the possibility of unforeseen AEs could not be ruled out. Subjects in the control group received additional (standard) surgical treatment as a general surgical routine.

Management of air leakage was expected to be achieved with the trial treatments. If this, however, was not the case, the surgeon could use any other method to control air leakage. The risk of participation in the trial was therefore minimal.

1.2 Legal Aspects

The protocol was dated 27 Oct 2005*;* Amendment 1 09 Mar 2006 and Amendment 2 15 Nov 2006 (Appendix 1.1).

The trial was conducted in accordance with the protocol, the Declaration of Helsinki (1), ICH Good Clinical Practice (6), the EU Directive (2001/20/EC) (7), the EU Directive 95/46/EC (8), 21CFR Part 54 (9) and any applicable local regulation.

Approvals

Ethics Committees

The relevant Ethics Committees (ECs) approved the protocol and the Subject Information Sheet/Informed Consent Form before inclusion of the first subjects at the sites. The two amendments were submitted to the ECs as soon as possible after issue. The addresses and compositions of the ECs appear in Appendix 1.3 in which also the dates of notification/ approval by the ECs of the Subject Information Sheet/Informed Consent Form and the two amendments are available.

Competent Authorities

The protocol was submitted to/approved by the National Competent Authorities (CAs). The addresses of the CAs and approval dates by country appear in Appendix 1.3.

Informed consent

Prior to any trial-related activity, the Investigator gave the subject oral and written information about the trial in a form that the subject could understand. Investigator had to ensure that the subject was fully informed about the aims of the trial, procedures, potential risks, any discomforts and expected benefits. The subject should have ample time according to local requirements to consider and to pose questions, before consenting.

The subject agreed that authorised sponsor trial personnel or their representatives, CAs including foreign CAs and ECs could have direct access to the subject's original data/ personal medical records (including photocopying source data in an anonymous form). The subject also agreed that his/her data would be processed and stored in an anonymous form for evaluation of this trial and any later overviews and that his/her data could also be transferred in an anonymous form to third parties, e.g. other companies or authorities, which could be located in other countries with potentially different regulations for data protection. Data will follow the development of the product and be used for documentation of the product’s efficacy and safety. Data would be transferred to involved parties only within the authority given by official agencies.

It had to be emphasised that participation was voluntary and that the subject had the right to withdraw from the trial at any time without prejudice.

A physician had to obtain the subject’s voluntary, personally signed and dated Informed Consent Form before any trial-related procedure. The Informed Consent Form stated that any data obtained would be kept even if the consent was withdrawn but that no new data would be collected from the subject and added to existing data or a database.

The English master text of the Subject Information Sheet and Informed Consent Form is shown in Appendix 1.3.

Amendments

Two amendments to the protocol were issued: a substantial Amendment 1 dated 09 Mar 2006 and a non-substantial Amendment 2 dated 15 Nov 2006 (Appendix 1.1). Relevant changes are implemented in the text of the report.

Substantial changes

- General change: Testing of neo-antigenicity was not to be performed since no standard testing for neo-antigenicity exists
- General change: Standard surgical treatment was changed to: *additional (standard)* surgical treatment since all subjects were already treated with standard surgical treatment
- Summary, Safety (p 5):……*Pulmonary function tests were performed at screening only* (correction of error)
- Section 6.1.3 Descriptive variables:……Emphysema of the lung was changed to: *progression/increase of soft tissue* emphysema *documented by X-ray*, since emphysema of the lung develops over years whereas tissue emphysema is a post-operative complication
- Section 7.3 Exclusion criterion 1: Has the subject had previous lung surgery *on the same side?* since a higher risk of air leakage is only present if surgery takes place on the same side of the lung as the previous surgery
- Section 7.3 Exclusion criterion 15: Was wedge *or sleeve* resection of the lung performed? Sleeve resection was added in order to differentiate standard lobectomy
- Section 8.1.1 Screening:……Laboratory tests include the following ~~if done as a standard at the site~~: haematology……before surgery. ~~A subject must be excluded from the trial if the Investigator considers the coagulation status (INR value) to be clinically significant~~. Screening laboratory tests……These changes were implemented since it is hospital routine that if the coagulation status is clinically significant, an additional assessment by Investigator is mandatory before surgery
- Section 8.1.5 Day of Chest Drain Removal:……Two drainage tubes should be used routinely; removal of the drains can be made on two separated days. *Clamping of drainage tubes is required before disconnection*…...Clamping was added since it is good surgical practice to avoid any back flow to the lung, which could occur without clamping

- Section 8.1.6 Discharge from Hospital:……Laboratory tests: haematology, ~~blood gases~~ and coagulation test. *Blood gases may be assessed if this is hospital routine*. May be done the day before discharge if this is standard procedure at the site……Correction of error since blood gas tests were only mandatory at Screening and if the subject suffered from any problems after surgery.

Non-substantial changes

Amendment 2 described changes to the following functions: Co-ordinating Trial Manager (CTM), Medical Safety Advisor, Trial Managers/Monitors in Austria, Belgium and Switzerland, Clinical Trial Supplies Coordinator and Safety Data Manager.

Further non-substantial changes concerned reference to current versions of the TachoSil Investigator's Brochure and the Summary of Product Characteristics (SmPC) as well as storage and drug accountability of TachoSil.

2 Responsibilities

The trial was conducted at 12 sites in eight European countries: Austria (1), Belgium (1), Denmark (1), Germany (3), Hungary (1), Italy (3), Sweden (1) and Switzerland (1).

The Sponsor co-ordinated the trial, which was monitored by the Nycomed local affiliate Trial Managers at the following sites: Vienna (A); Leuven (B); Odense (DK), Heidelberg (D) and Gothenburg (S). Monitoring of the remaining sites was outsourced.

2.1 Investigators

The name, affiliation and address of the Principal Investigators are listed in Appendix 1.4, which includes the name and affiliation of Co-Investigators and other staff actively involved in the conduct of the trial; the number of subjects by site is also listed. Curricula vitae (CVs) are available in Appendix 1.13.

2.2 Sponsor Personnel

Address: Nycomed, Clinical Trial Operations, Langebjerg 1, DK-4000 Roskilde, Denmark.

Co-ordinating Trial Managers

- Lise Hejl Hyldstrup, BSN, until 15 Apr 2005

- Eva Nobis, MSc, Nycomed office Austria, from 16 Apr 2005 to 23 Jul 2006
- David Becedas, MSc.Pharm., from 24 Jul 2006 to 31 Jul 2007
- Martin Petersen, MSc., Ph.D. from 1 Aug 2007.

Medical Advisers

- Vilhelm Tetens, MSc., PhD.
- Jens Pauli Marstein, MD.

2.3 Contract Research Organisations

The CRO PharmaNet performed project management and monitoring for all sites except the five sites listed in Section 2 and the Swiss site, this site was managed by Cirkel Consulting. Data management was outsourced to NNIT A/S whereas Larix Aps performed part of the statistics. The Interactive Voice Response System (IVRS) was provided by Almac Clinical Technologies. For details of co-operation with the CROs, see Appendix 1.14.

3 Introduction

TachoSil is formulated as a haemostatic and tissue sealant. It consists of an equine collagen sponge coated with two haemostatically active proteins, human fibrinogen and human thrombin. The active side is coloured yellow with riboflavin. Unlike conventional fibrin sealants, the components of TachoSil are activated after application in a fixed combination and in this way adhere to the tissue (resection surface) providing a haemostatic seal, which is resistant to moderate/oozing haemorrhage.

TachoSil, which is a further development of TachoComb® and TachoComb® H, is an equine collagen sponge coated with only human fibrin glue components. More than 800,000 patients have been treated with TachoComb®. TachoSil was authorised in June 2004 by the European Commission for supportive treatment in surgery for improvement of haemostasis where standard techniques are insufficient. Its efficacy and safety have been demonstrated in controlled trials. For further information on efficacy and safety, see the TachoSil Investigator's Brochure (10) and the SmPC (11).

It is acknowledged that TachoSil has good adhesive properties and provides tissue sealing as well. The present trial was conducted in order to evaluate the efficacy and safety of TachoSil as air leakage treatment in lung surgery.

The previous lung trial (TC-013-IN)

TachoSil has previously been tested in pulmonary lobectomy (2) (TC-013-IN), in which 189 subjects scheduled for lobectomy due to lung cancer were included. The design of TC-013-IN was essentially identical to that of the present trial, except for the following: (i) Subjects with absence of persistent air leakage (Grade 0) following lobectomy and primary stapling were included, and (ii) the primary efficacy endpoint was presence of air leakage 48 hours after surgery. Unexpectedly about half of the subjects achieved Grade 0 air leakage following the primary stapling, thus eroding the power of the trial. This caused the outcome of the planned analyses of difference in treatment efficacy to be statistically insignificant.

The intention-to-treat (ITT) analysis of all subjects in TC-013-IN, regardless of the degree of air leakage at randomisation, showed that air leakage 48 (± 6) hours after surgery (primary efficacy endpoint) was present in 34% for TachoSil and 37% for standard treatment (p=0.76). The odds ratio (OR) of presence of air leakage with TachoSil compared to standard treatment was 0.91 (95% confidence interval (CI): 0.48 - 1.72). Assessment of secondary endpoints showed no significant differences between treatment groups. However, ITT analyses of the sub-population with persistent air leakage after primary stapling (Grades 1 - 2; n=89) indicated efficacy of TachoSil (analyses not pre-defined in protocol). In summary, the results were:

- Persisting air leakage at 48 hours was present in 39% and 49% of TachoSil and standard treatment, respectively (p=0.29). The OR of TachoSil compared with standard treatment was 0.61 (95% CI: 0.24 - 1.56). Due to the small number of subjects with air leakage at randomisation, this favourable trend failed to reach statistical significance
- Reduction of intra-operative air leakage intensity after the first application of trial treatment was more pronounced in the TachoSil group than in the standard treatment group (p=0.015)
- The mean area under the curve (AUC) of post-operative air leakage intensity was significantly lower for TachoSil than for the standard treatment (p=0.047)
- While the duration of postoperative air leakage was reduced in TachoSil treated subjects (1.9 vs. 2.7 days, p=0.015), the duration of postoperative chest tube drainage did not differ between the treatment groups.

Based on the findings of this trial, it was decided to conduct a second lung trial, which should include subjects with air leakage Grade 1 and 2, only.

For further information on non-clinical studies and clinical trials, see the TachoSil Investigator's Brochure (10).

4 Trial Objectives

To compare sealing efficacy and safety of TachoSil versus standard surgical treatment as secondary management of intra-operative pulmonary air leakage after lobectomy in subjects with lung malignancies with or without metastases.

5 Investigational Plan

5.1 Design Overview and Rationale

Open, randomised, prospective, multi-centre, parallel-group, phase IIIb trial with two treatment arms to which subjects were evenly distributed. Randomisation to TachoSil or additional (standard) surgical treatment was done after lobectomy with Interactive Voice Response System (IVRS) (see Section 5.5.2) when intra-operative air leakage had been assessed; air leakage Grades 1 and 2 qualified for inclusion. The centralised randomisation system ensured allocation concealment to prevent selection bias as recommended in the CONSORT statement (12). Subjects with air leakage Grade 3 could be reassessed for randomisation after (further) stapling and/or suturing. The trial was open, since the appearance of TachoSil made it impossible to blind the two treatments during surgery.

The prospective and controlled trial design as well as the use of objective endpoints are recommended by authorities along with recommendations to compare efficacy with standard treatment without fibrin sealant (13).

5.2 Trial Design

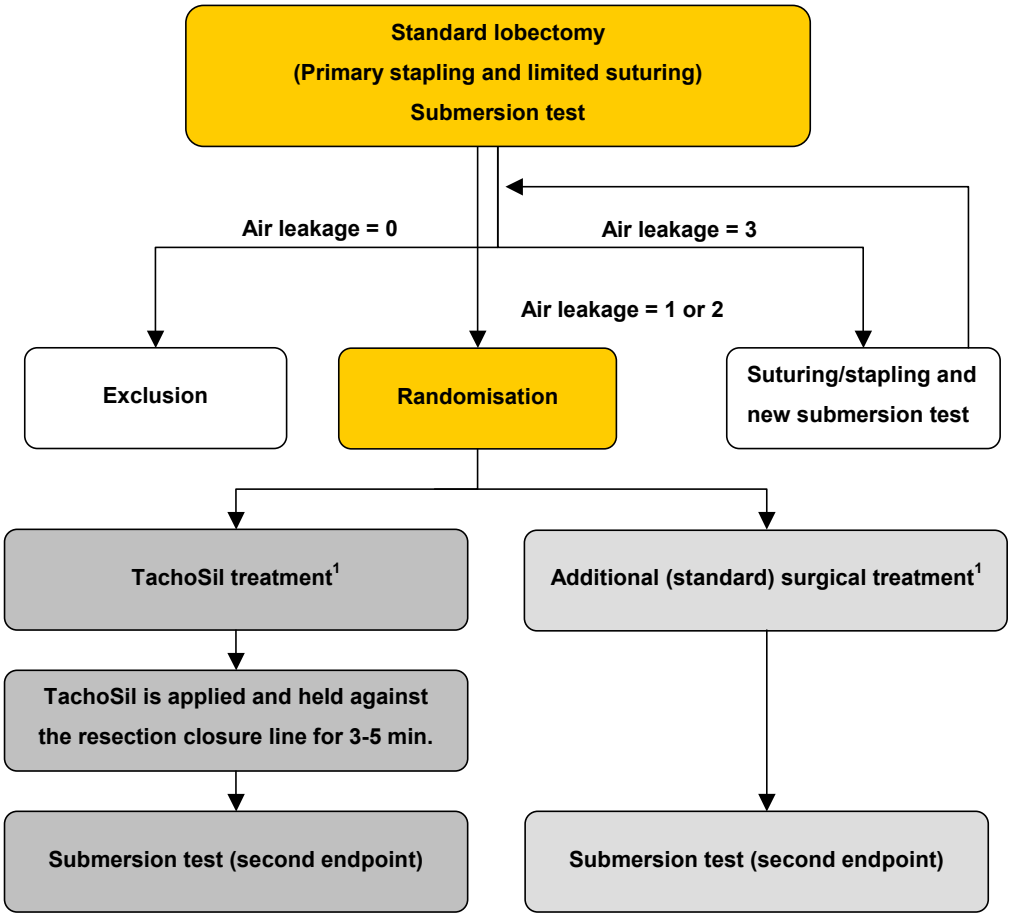
Flow Chart

Day of assessment Activities/ assessments for CRF-entry	Screening (- 7 days)	Surgery Day 0 (*before* surgery)	Surgery Day 0 (*during* and *after* surgery)	Day 1	Day 2 until cessation of air leakage	Day of chest drain removal	Discharge from hospital	Follow-up 1 month (+/- 10 days)
Informed consent	X							
Inclusion/Exclusion criteria	X		X					
Demographic data/ Smoking/Alcohol	X							
Vital signs[1]	X	X		X	X	X	X	
Physical examination	X[3]						X	
Past and concomitant illness	X[3]	X[3]		X	X	X	X	
Concomitant medication	X[3]	X		X	X	X	X	
Pregnancy test	X[4]							
ECG	X							
Laboratory tests (haematology, blood gases[2], INR)	X[4]			(X)[5]			X[11]	
Pulmonary function: FEV-1, TLC, RV	X							
Chest X-ray	(X)[5]			(X)[5]		X[9]	X	(X)[5]
Adverse events	X	X	X	X	X	X	X	X
Pulmonary lobectomy			X					
Primary stapling and suturing			(X)[6]					
Air leakage test(s) by water submersion			X					
IVRS randomisation			X					
Trial treatment of air leakage			X					
Surgery and trial treatment variables			X					
Drug accountability			X					
Drainage volume assessment				X	X	(X)		
Sentinel Seal/Air leakage test (cough)			X[7]	X[8]	X[8]	X		
(Post-operative) complications			X	X	X	X	X	X
Removal of drains						X[10]		
End of trial								X

1: Included body temperature, heart rate, blood pressure and respiratory rate
2: Only mandatory at Screening
3: To be recorded in the CRF only if the subject was randomised
4: Pregnancy test and laboratory tests had to be repeated if done more than 48 hours before surgery

5: If done routinely
6: Not mandatory
7: 3 - 5 hours after surgery
8: Twice a day (day and evening shift) until cessation of air leakage. If drainage was needed, suction had to be maintained for at least three days
9: Chest X-rays had to be performed before removal of drains and on the following day
10: Chest drainage tubes were removed after evaluation of air leakage; date and time of removal were recorded. If removed on separate days, only the day and time of removal of the last chest drainage tube were recorded
11: On the day of discharge or the day before according to hospital standard procedure.

Intra-Operative Flow Chart



1: If air leakage control was considered insufficient after the first application of trial treatment, trial treatment (application of TachoSil or additional (standard) surgical treatment) could be repeated until air leakage was sufficiently controlled.

5.3 Visit Procedures

For an overall view of activities and assessments to be performed see the Flow Chart above. The activities and assessments are listed and described below only for the day when first performed. For full details, see Section 8.1 of the protocol.

5.3.1 Screening (Within 7 Days of Surgery)

- **Informed consent**. Before any trial-related activities, the subject had to personally sign and date the Informed Consent Form, see Section 1.2
- **Inclusion/exclusion criteria at screening,** see Section 5.4.2
- **Demographic data** included date of birth, sex, race, height and weight
- **Smoking and use of alcohol**. Mean weekly consumptions were recorded
- **Vital signs** included body temperature, heart rate, blood pressure and respiratory rate. Temperature could be recorded rectally, orally, axillary or in the ear. The same method had to be used throughout for a subject. Blood pressure and heart rate had to be assessed after the subject had been sitting for five min
- **Physical examination** according to normal pre-operative procedure. Included 1) Ears, eyes, nose, throat, neck; 2) Respiratory system; 3) Cardiovascular system; 4) Gastrointestinal system including mouth; 5) Genito-urinary system, breasts; 6) Musculoskeletal system; 7) Central and peripheral nervous system, 8) Skin and 9) Other
- **Past and concomitant illness**, see Section 5.5.4
- **Concomitant medication**, see Section 5.5.4. Any steroid treatment as well as past and current lung therapy had to be recorded
- **Pregnancy test** was performed in all female subjects of childbearing potential. Childbearing potential was considered present until menopause had lasted for more than 12 months. Surgically hysterectomised and surgically sterile females could be included on the same conditions as male subjects. Pregnancy was an exclusion criterion. The screening pregnancy test had to be done within 48 hours before surgery and was performed with a urine stick
- **ECG (ElectroCardioGram)** was assessed as normal or abnormal (clinically significant (CS) or not clinically significant (NCS))
- **Laboratory tests** included haematology (haemoglobin; haematocrit; erythrocyte, leucocyte, platelet counts), blood gases (pO_2 and pCO_2) and coagulation factor (International normalised ratio (INR)).The laboratory tests at screening had to be done in

accordance with hospital standard procedure and within 48 hours before surgery. Investigator had to comment on all abnormal laboratory test results and indicate if the result was CS, NCS or a sampling or laboratory error (SE). An abnormal test result had a value outside the normal range

- **Pulmonary function tests** included total lung capacity (TLC), residual volume (RV) and forced expiratory volume – 1 second (FEV-1) (all in ml). The variables could be assessed with any test system and were recorded as BTPS (Body temperature (37ºC) and Pressure (P_B) Saturated with water vapour)
- **Chest X-rays** were assessed for inflation of lung (full, incomplete, collapsed) (if done routinely)
- **Adverse events** since the subject signed the Informed Consent Form, see Section 7.

5.3.2 Day 0 - Day of Surgery

Before surgery

- **Vital signs**
- **Concomitant illness.** Any changes since screening were recorded. Worsening should be recorded as an adverse event (AE), see Section 5.5.4
- **Concomitant medication**. Any changes since screening were recorded, see Section 5.5.4
- **Adverse events** since the subject signed the Informed Consent Form.

During and after surgery

- **Pulmonary lobectomy** with either antero- or postero-lateral incision and intra-pulmonary lymphadenectomy
- **Primary stapling and/or limited suturing** if considered necessary by the surgeon
- **Air leakage test by water submersion (eligibility test).** After the above procedures (before randomisation), all parenchymal resection sites were identified and air leakage was assessed by water submersion test under standard airway pressure of 20-25 cm H_2O. (A resection site was defined as any site with potential air leakage including stapling lines, areas of resection a.o.). The submersion test was performed as follows (14): Sterile physiological saline was poured into the chest cavity and the lung submerged and inflated to check for sites and degree of air bubbles. Each surgical site was graded under an inflation pressure of 20 - 25 cm H_2O.

Grade 0/absent:	no apparent leak
Grade 1/mild:	countable bubbles
Grade 2/moderate:	stream of bubbles
Grade 3/severe:	coalesced bubbles

In case of several sites, severity was taken from the site with the highest grade. Any site with air leakage Grade 3 had to have further stapling or limited suturing of the collapsed lung followed by submersion test until Grade 0, 1 or 2 was obtained. See the Intra-Operative Flow Chart, Section 5.2

- **Inclusion/exclusion criteria after lobectomy.** Only subjects with resection site air leakage Grade 1 or 2 were eligible for randomisation, see Section 5.4.2
- **IVRS Randomisation.** IVRS was used to randomise subjects to trial treatment, see Section 5.5.2
- **Trial treatment** was performed with either TachoSil or additional (standard) surgical treatment according to randomisation.

  TachoSil

  TachoSil had to be applied under aseptic conditions. The application of TachoSil should be to all lung resection area(s), specifically the hilar area. Prior to application, the resection site(s) should be cleansed, e.g. from blood, disinfectants and other fluids. After removal of TachoSil from the sterile package, the sponge should be pre-moistened in saline solution and applied immediately. Another way to apply TachoSil was to use it dry and press a moistened pad against it. The yellow, active side of the TachoSil sponge was applied to the resection area and held against it with gentle pressure for 3-5 min. Pressure had to be applied with either a moistened surgical glove or a moist pad. The sponge had to cover the resection site(s) at least 1–2 cm beyond the margins. If more than one sponge was needed, the individual sponges had to overlap. A sponge could be cut with sterile scissors as needed. Any cut-off surplus pieces had to be discarded. Due to strong affinity of collagen to blood, TachoSil may also stick to surgical instruments or gloves covered with blood. This may be avoided by pre-moistening surgical instruments and gloves with physiological saline.

  Additional (standard) surgical treatment

  For subjects randomised to additional (standard) surgical treatment, the resection site(s) were closed at the discretion of the surgeon. This could be re-suturing, stapling or even no treatment.

- **Trial treatment variables**
  For TachoSil subjects, the number of sponges used and the pack number (TC-XXX) on the used cartons of TachoSil were recorded
  For standard surgical treatment, stapling (size used for lung tissue) or suturing method (continuous, singular), suturing thread (polydioxanone (PDS), proline, vicryle, other), size of suture (diameter 3.0, 4.0 etc.) or other methods, if any, had to be recorded. Any treatment other than trial treatment used to close air leakage sites had to be recorded. TachoSil could be used to close air leakage sites in the TachoSil treatment group but not as a haemostatic
- **Surgery variables** included type of thoracic incision (antero-/posterolateral), use of lymphadenectomy (ues/no), type of resection and location of resection site, time of day of incision, surgery ended (skin closed) and last water submersion test
- **Air leakage test by water submersion (treatment test).** Intensity of air leakage after the first application of trial treatment was assessed by water submersion test as above. Trial treatment could be repeated if air leakage control was considered insufficient after the first as well as the second application of trial treatment.
  If the surgeon needed to use other measures than trial treatment, i.e. rescue treatment, to manage air leakage before closing the chest cavity, the subject was considered a treatment failure. Rescue treatment included any available surgical technique or sealant (fibrin or non-fibrin) except TachoSil in subjects randomised to additional (standard) surgical treatment
- **Drug accountability,** see Section 5.5.5
- **Sentinel Seal / air leakage test (cough).** Sentinel Seal Dual Collection Chamber System (Ref. Number: 8888 - 571513 from Tyco) was used at continuous suction of 10 - 15 cm H_2O. The system allowed determination of air leakage by air bubbles appearing in a water reservoir. After closure of the chest cavity, two chest drainage tubes (an upper and a lower chest drainage site) were connected to the Sentinel Seal chest drainage unit (CDU). If drainage was needed, a continuous post-surgical suction of 10 - 15 cm H_2O for at least three days was mandatory. After three days, drainage could be maintained but without suction. Suction should not necessarily be “continuous” but could be stopped for e.g. 30 min to permit mobilisation of the subject. After five post-operative days of air leakage, the Investigator should consider re-operation. An increase of air leakage had to be recorded as an AE. Nycomed provided the necessary number of Sentinel Seal CDUs to the sites. The same system was used by all trial sites.

If there was no apparent air leakage at rest with the Sentinel Seal CDU, **provocation by coughing** was performed under continued suction of 10 - 15 cm H_2O. In this condition with no residual air, the subject was asked to cough and the appearance of air bubbles in the CDU was assessed at the second or third effective coughing. If no air bubbles developed, air leakage was considered absent. Presence of air leakage post-operatively on Day 0 was assessed at rest 3 - 5 hours after completion of surgery

- **Post-operative complications** including pneumonia, pulmonary embolism, atelectasis of the lung, bleeding, surgical wound infection, cardiac arrhythmia and progression/ increase of soft tissue emphysema documented by X-ray of the lung were recorded as AEs. The reason for additional chest drainage, need of re-operation, respiratory assistance and blood transfusion were reported as AEs. The number of units of blood transfusion was recorded (whole blood, packed red blood cells (RBC), fresh frozen plasma or other).

5.3.3 Day 1

- **Laboratory tests** if done routinely (haematology, blood gases and INR)
- **Chest X-ray** if done routinely
- **Volume of drainage** was assessed between 05:00 and 10:00 a.m.
- **Air leakage test / provocation (cough).** Presence of air leakage was assessed twice a day (morning and evening) at rest with the Sentinel Seal CDU, see Section 5.3.2. Time of assessment was recorded. Assessments had to be done until drains were removed. If drainage was needed, a continuous post-surgical suction of 10-15 cm H_2O for at least three days was mandatory.

Vital signs, concomitant illness, concomitant medication, AEs and post-operative complications were assessed as described previously.

5.3.4 Daily from Day 2 until Absence of Air Leakage

Assessments on Day 2 and until absence of air leakage were the same as for Day 1 except that laboratory tests and chest X-rays were not requested. After five post-operative days of air leakage, re-operation should be considered.

5.3.5 Day of Chest Drain Removal

- **Chest X-ray** should be performed on the day of chest drain removal (before removal) and again within 24 hours
- **Removal of chest drainage tubes** was done after the last assessment of air leakage after absence of air leakage. Two drainage tubes should be used routinely; removal of the drains could be done on two separate days. Clamping of drainage tubes was required before disconnection.

  The total threshold volume for removing the drain(s) was left at the physician's discretion but is usually (less than) 200 ml fluid/day. If the drainage tubes were removed on separate days, only the date and time of removal of the last tube should be recorded.

Vital signs, concomitant illness, concomitant medication, AEs, volume of drainage, Sentinel Seal/air leakage test (cough) and post-operative complications were assessed as described previously.

5.3.6 Discharge from Hospital

- **Physical examination** was repeated
- **Laboratory tests: haematology and INR** could be done the day before discharge if this was standard procedure. Blood gases were assessed if this was hospital routine.

Vital signs, concomitant illness, concomitant medication, AEs, chest X-ray and post-operative complications were assessed as described previously.

5.3.7 Follow-Up (1 Month +/- 10 Days after Surgery)

The follow-up visit should be done at site.

- **Chest X-ray** if done routinely
- **End of trial**. If the subject did not complete the trial, the reason was recorded on the "End of trial" page in the CRF.

AEs and post-operative complications were assessed as described previously.

5.3.8 Unscheduled Visits

Any visit that was not planned according to the protocol was recorded including reason(s) for the visit and any actions taken.

5.4 Trial Population

5.4.1 Target Population

The trial population consisted of subjects scheduled for lung lobectomy due to lung malignancies with or without metastases. It was planned that 300 subjects would be randomised. For calculation of sample size, see Section 9.1.

5.4.2 Selection Criteria

Inclusion criteria

All inclusion criteria had to be answered “yes” for a subject to participate in the trial.

At pre-operative screening

1. Has the subject given informed consent according to local requirements before any trial-related activities? (A trial-related activity is any procedure that would not have been performed during the routine management of the subject)
2. Is the subject 18 years of age or above?
3. Is an elective lobectomy for lung malignancy with intrapulmonary lymphadenectomy (with antero- or postero-lateral incision) planned?

For female subjects of childbearing potential

4. Does the subject use adequate contraception (contraceptive pill, contraceptive implants, contraceptive injections or intrauterine device (IUD))?

After pulmonary lobectomy with intrapulmonary lymphadenectomy (and primary stapling and limited suturing if considered necessary by the surgeon):

5. Is the air leakage of Grade 1 or 2?

If more than one resection site was affected after lobectomy, the highest grade applied as grade of entry. Subjects with air leakage Grade 3 could be reassessed for randomisation after further stapling and/or suturing. The air leaks should originate from the pulmonary parenchyma and not from the bronchi.

Exclusion criteria

All exclusion criteria had to be answered “no” for a subject to participate in the trial.

At pre-operative screening

1. Has the subject had previous lung surgery on the same side?
2. Has the subject had previous anti-tumour chemotherapy within the last 3 weeks?
3. Has the subject had radiotherapy for lung malignancy within the last 4 weeks?
4. Does the subject have a history of allergic reactions after application of human fibrinogen, human thrombin and/or collagen of any origin?
5. Is this an emergency surgery?
6. Does the subject have an FEV-1 < 40%?
7. Has the subject previously been exposed to TachoComb, TachoComb H or TachoSil?
8. Does the subject have a present abuse of drugs or alcohol?
9. Has the subject participated in any other trials with an investigational drug or device within 30 days prior to inclusion in this trial?
10. Does the subject participate or plan to participate in another clinical trial during the trial period?

For female subjects of childbearing potential

11. Is the pregnancy test positive before application of trial treatment?
12. Is the subject breast feeding?

After pulmonary lobectomy with intrapulmonary lymphadenectomy (and primary stapling and limited suturing, if considered necessary by the surgeon):

13. Did serious surgical complications occur including need for surgical adhesiolysis of the remaining lung tissue?
14. Was pneumonectomy performed?
15. Was wedge or sleeve resection of the lung performed?
16. Was any fibrin glue sealant (including TachoSil) used before randomisation?

Subjects that were found eligible for participation at screening but did not fulfil the entry criteria at randomisation were not randomised.

5.4.3 Withdrawal of Subjects

For instructions in case of withdrawal/discontinuation of subjects, see Section 7.4 of the protocol.

5.5 Treatments

5.5.1 Investigational Medicinal Product

TachoSil

TachoSil is a sterile, ready-to-use, absorbable sponge for intra-operative topical application. It consists of an equine collagen sponge coated with the fibrin glue components human fibrinogen (5.5 mg/cm^2) and human thrombin (2.0 IU/cm^2). The active side is coloured with riboflavin. TachoSil was manufactured, packed and labelled according to Good Manufacturing Practice (GMP). The sponge size was 9.5 x 4.8 x 0.5 cm.

For management of air leakage sites in TachoSil treated subjects, as many sponges as needed were used. The sponge(s) had to cover the site(s) at least 1 - 2 cm beyond the immediate margins. If more than one sponge was used, the individual sponges had to overlap.

Batch nos. and release certificates are available in Appendix 1.15. Details of packaging and labelling are available in Appendix 1.16.

TachoSil had to be stored at a room temperature not exceeding 25°C and kept in a safe and locked area with limited access during the duration of the trial. TachoSil was delivered in sterile cover and had to be handled accordingly. Later sterilisation was not possible.

Additional (standard) surgical treatment

Additional standard management of air leakage sites in the control group had to be done with sutures, staples or even with no treatment according to the routine at the site.

Rescue treatment

Any surgical sealing technique or sealant (non-fibrin or fibrin, except the application of TachoSil in subjects randomised to additional (standard) surgical treatment) was used according to the routine at the site.

5.5.2 Assignment Procedures

Subjects were randomised to either TachoSil or additional (standard) surgical treatment. When a subject had qualified for participation according to Section 5.4.2, the Investigator called a central IVRS that was used to secure total allocation blinding (12). After having received specific user (site) identification, trial identification and date of birth of the subject to be randomised, the IVRS informed the Investigator of subject number and the trial treatment allocated to the subject, either TachoSil or additional (standard) surgical treatment.

A subject was always given the lowest subject number available at the site. Investigator recorded the subject number and the allocated trial treatment and kept a "Subject Identification Code Log", which connects subjects and randomisation numbers. If a subject was not randomised, Investigator had to state the reason.

Subjects were evenly distributed between TachoSil and additional (standard) surgical treatment. Block randomisation was ordered by the CTM and performed by Clinical Trial Supply, Nycomed. Sealed randomisation lists for all subjects were available at Clinical Trial Supply but not at site. The randomisation list (Appendix 1.7) was stored at Clinical Trial Supply until the database was released. Of the 1,000 randomisation numbers, numbers in the sequence 1-360 were used. Since IVRS allocated sequences of 10 to the individual sites, the last numbers of the last sequences were unused by the sites (except site 7) when inclusion of subjects was completed. Therefore 59 numbers were not used (206-10, 216-20, 238-40, 256-60, 263-70, 295-300, 319-20, 322-30, 336-40, 343-50, 358-60). Of the 310 CRFs numbered 1-310, nine CRFs were not used (nos. 111, 203, 205, 258-9, 265-6, 304-5).

5.5.3 Blinding

The trial was open since the use of TachoSil (and additional (standard) surgical treatment) precluded blinding.

5.5.4 Past and Concomitant Illness and Concomitant Treatment

Definitions

Past illness	any clinically relevant past medical condition or illness
Concomitant illness	any illness present at the start of the trial

Concomitant medication any medication other than the trial product (TachoSil) taken during the trial – from screening to follow up. Air leakage treatment other than trial treatment had to be avoided if at all possible.

A worsening in severity or frequency of a baseline concomitant illness as well as any new illness diagnosed during the trial had to be regarded as AEs whether or not they were considered to be related to the trial product and had to be reported as such, see Section 7.

Any changes in concomitant medication or treatment procedures had to be recorded at each visit. Prophylactic anticoagulation treatment before surgery had to be recorded - also if stopped within two days before surgery.

Concomitant medication excepted from this was medication/treatment in relation to the surgical intervention documented in advance, i.e. medication covering pre-medication (except anticoagulation therapy), anaesthesia and post-operative medication including pain management. If requested by Nycomed, the Investigator had to provide information of any such medication. Any type of steroid treatment (local or systemic) had to be recorded.

5.5.5 Drug Accountability

It was the responsibility of Investigators to keep account of their TachoSil supplies. For further instructions regarding accountability of TachoSil, see Section 9.4 of the protocol.

6 Assessments of Efficacy Variables

A sample of the CRF can be found in Appendix 1.2.

6.1 Efficacy Measurements

Primary efficacy endpoint

- Duration of post-operative air leakage for the ITT-analysis set. Assessment of this endpoint was in accordance with the schedule of air leakage assessments made at the evening of the day of operation (Day 0) and subsequently twice daily (at morning and evening shifts). Assessment of air leakage was done by observing bubbles in a standardised CDU

- Duration of post-operative air leakage for the PP-analysis set (secondary analysis).

Secondary efficacy endpoints

- Reduction of intra-operative air leakage intensity after the first application of trial treatment for the ITT analysis sets.

Descriptive variables

- Total number of days until removal of the (last) chest drain
- Predefined post-operative complications: pneumonia, pulmonary embolism, atelectasis of the lung, surgical wound infection, cardiac arrhythmia, progression/increase of soft tissue emphysema documented by X-ray, need for additional chest drainage, need for re-operation, need for respiratory assistance, bleeding and need for blood transfusion.

6.2 Appropriateness of Measurements

The prospective and controlled trial design as well as the use of objective endpoints are recommended by authorities along with recommendations to compare efficacy with standard surgical treatment without fibrin sealant (13).

7 Safety Assessments

7.1 Adverse Events

7.1.1 Definitions

Adverse event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

The following should not be reported as adverse events

- A pre-planned procedure unless the condition for which the procedure was planned has worsened since baseline. However, complications to pre-planned procedures should be reported as AEs
- A pre-existing condition found as a result of screening procedures (Should be recorded at screening)

- Post-operative nausea, vomiting or pain that Investigator considers common and expectable post-operative findings, treated or untreated, should not be recorded as AEs. Any post-operative event considered by Investigator as either uncommon, unexpected or both must be recorded as an AE
- Air leakage is an efficacy variable and should therefore not be recorded as an AE
- Progression of pre-existing cancer should not be reported as an AE.

Clinical laboratory adverse event

A clinical laboratory adverse event is any clinical laboratory abnormality that suggests a disease and/or organ toxicity and is of a severity, which requires active management, i.e. change of dose, medical treatment, discontinuation of product, more frequent follow-up or diagnostic investigation.

Serious adverse event

A serious adverse event (SAE) is any untoward medical occurrence that at any dose

- results in death
- is life-threatening. Life-threatening in the definition of an SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe
- requires hospitalisation or prolongation of existing hospitalisation. Only inpatient hospitalisation including an over-night admission was regarded as an SAE
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is a medically important AE that is not immediately life-threatening or does not result in death or require hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

Non-serious adverse event

A non-serious adverse event is any AE that does not meet the criteria for an SAE.

7.1.2 Classifications

Severity

Severity is a clinical observation and describes the intensity of the event.

- Mild: Transient symptoms, no interference with the subject's daily activities

- Moderate: Marked symptoms, moderate interference with the subject's daily activities
- Severe: Considerable interference with the subject's daily activities.

Causality

- Probable: Good reasons and sufficient documentation to assume a causal relationship
- Possible: A causal relationship is conceivable and cannot be dismissed
- Unlikely: The event is most likely related to an aetiology other than the trial product
- Not related: An event for which sufficient information exists to conclude that the aetiology is unrelated to the Investigational Medicinal Product.

Outcome categories

- Recovered: Fully recovered or the condition has returned to the level observed at baseline
- Recovered with sequelae: As a result of the AE, the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf or paralysed)
- Not recovered
- Fatal
- Unknown.

7.1.3 Adverse Event Recording

For details regarding recording of AEs, see Section 10.3 of the protocol.

7.1.4 Adverse Event Reporting

For details regarding reporting of AEs, see Section 10.4 of the protocol.

7.1.5 Follow-Up of Adverse Events

For follow-up of AEs, see Section 10.5 of the protocol.

7.2 Pregnancy

For instructions in case of pregnancy, see Section 10.6 of the protocol. No female trial subjects were pregnant at inclusion or became pregnant during the trial period.

7.3 Precautions/Overdose

As with any product, allergic type hypersensitivity reactions to TachoSil are possible. Subjects with a known history of allergic reactions after application of human fibrinogen, human thrombin and/or collagen of any origin had to be excluded from the trial.

Drug interactions may be expected only with drugs interfering with the coagulation system such as heparin, warfarin, streptokinase, urokinase or tissue-type plasminogen activator. Based on preclinical data, reduced efficacy due to interactions was not expected but could not be totally excluded in case of high doses/concentrations of these drugs (15).

The number of TachoSil sponges used for a subject depended on surgical need. Overdoses have not been reported for TachoSil (15).

8 Data Quality

8.1 Monitoring/Audits

Monitoring

Monitoring was performed according to the Monitoring Plan provided by the CTM. During the trial, the Monitor visited the sites before trial initiation and at 4 - 6 weeks intervals or more often depending on recruitment and was available for discussions by phone. The purpose of the monitoring visits was to ensure that the CRFs were completed correctly, the protocol was adhered to and drug accountability monitored. Further details regarding monitoring are available in Section 12.1 of the protocol.

Audits

The headquarter Trial Master File was audited as were the country files in Austria, Belgium, Denmark, Germany, Hungary, Italy and Sweden. Site audits were conducted in Vienna (A), Leuven (B), Odense (DK), Freiburg (D), Budapest (HU), Milano (I) and Gothenburg (S). For audit certificates and a list of auditees, auditors and dates of audits, see Appendix 1.8.

8.2 Data Handling

The CRO, NNIT A/S, performed data management. The Data Handling Plan (DHP) (Appendix 1.19) including a database annotation was finalised before any data were entered

into the database. The annotation describes mapping of CRF fields to the delivered, database fields and the fields in the final statistical data sets. The Trial Data Manager provided a Data Validation Plan (DVP) (Appendix 1.19) before any data cleaning. The DVP describes all logical and qualitative checks used to clean the database and to assure accurate and consistent data in the database. Plans were approved by the CTM, the Trial Statistician and the Trial Data Manager.

Subject were identified in the database only by subject ID number (screening and/or subject number), site name and Trial ID (TC-021-IM).

All subject data were entered into the database either directly from the CRF or (partly) as electronic transfer. Data cleaning, including logical checks and query processes, was handled by NNIT. Data handling is documented in the Data Handling Report (Appendix 1.19). The clean database was transferred from NNIT to the Trial Statistician as either ASCII files or SAS® version 8.2 compatible data sets.

NNIT performed the coding of concomitant illness and AEs according to MedDRA current version and of concomitant medication according to WHO Drug Dictionary, version 3, 2004. Medication related to the surgical intervention, i.e. pre-medication, anaesthesia and post-operative medication, was not to be recorded in the CRF.

Before database lock, Central Pharmacovigilance (CPV), Nycomed approved the coding of concomitant illness and AEs; the CTM approved the coding of concomitant medication.

SAEs were reported to and handled by CPV.

The Interactive Voice Response System (IVRS) was provided by Almac Clinical Technologies.

9 Determination of Sample Size and Statistical Methods Planned in the Protocol

Larix ApS and Nycomed performed the statistics; the responsibilities of Larix ApS are described in Appendix 1.14.

9.1 Determination of Sample Size

The sample size calculation was based on the primary endpoint, duration of post-operative air leakage. The H_0 hypothesis was that the survivor functions in the two treatment groups were equal. The alternative hypothesis H_1 stated that the survivor functions differed between the treatments. The H_0 hypothesis was to be tested with a log-rank test.

The calculation was based on the results from an earlier trial with TachoSil (TC-013-IN) with similar objective and design as the present (2). In the subgroup of subjects in TC-013-IN with intra-operative air leakage grade > 0, the median duration of post-operative air leakage was 1 day for subjects treated with TachoSil and 2 days for subjects allocated to standard treatment; this is the minimal relevant difference between treatments to be identified. A number of trials (10,000) were simulated. Each trial was generated by selecting subjects from the above defined subpopulation in TC-013-IN using random sampling with replacement. Equal number of subjects was chosen from each of the two treatment groups. In each trial the log-rank test was performed to assess the difference between treatments. The percentage of trials with the log-rank test showing statistical significance based on α = 5% was used as power estimate. The results of the simulations are shown below:

Total number of subjects	Power
200	82%
250	90%
300	94%

Given the results of the simulations, a total sample size of 300 subjects, equally allocated to treatment groups, was chosen.

9.2 Statistical and Analytical Plans

A test level of α = 5% was used throughout to determine statistical significance. Numerical data were summarised descriptively by some or all of the following statistics: N, Missing (Number of missing values), Mean, standard deviation (SD), Median, Minimum, Maximum. Categorical data were summarised descriptively by frequency: N (%).

Primary efficacy endpoint

Duration of post-operative air leakage was analysed for the ITT and AT analysis sets using

life table analysis. From the evening on the day of surgery and onwards presence of post-operative air leakage was evaluated using the Sentinel Seal Dual Chamber system and provocation by coughing. Since air leakage was recorded at nominal time points, i.e. the evening on the day of surgery, 1st shift on the day after surgery etc., the actual time points of sealing were not observed, which was attributed to one of the time intervals Day $0_{operation}$- Day $0_{evening}$, Day $0_{evening}$ - Day $1_{morning}$, Day $1_{morning}$ - Day $1_{evening}$, etc. Subjects that did not obtain absence of air leakage were censored at the day of the last assessment. This analysis was repeated for the PP analysis set.

For subjects where duration of post-operative air leakage could not be assessed because the last assessments of air leakage were missing, the duration of post-operative air leakage was censored at the time of the last available assessment. Details of the censored observations are available in Appendix 1.9.

For subjects needing rescue treatment the duration was censored at the maximum duration of post-operative air leakage (whether censored or not) among all other subjects. A sensitivity analysis was performed where missing values in the TachoSil group were assigned the maximum duration of post-operative air leakage in the treatment group, and in the standard treatment group the assigned value was the last measurement. In both treatment groups the values were right censored. The Log-rank test of equality over treatments was performed controlling, i.e. stratifying, for centre, and the survival curves were estimated and presented overall and by centre using the life table method.

In addition to the ITT analysis, incorrect treatment of one subject (TachoSil instead of standard treatment) resulted in analyses of subjects with the actual trial treatment received (AT analysis set). Results from the AT analysis set are presented in Appendix 1.9 as a sensitivity analysis.

An exploratory parametric survival analysis of the primary endpoint, which took account of the interval censoring, was performed using an accelerated failure time model. The distribution of the observed event times was compared with standard distributions within the framework of accelerated failure time models. A Weibull model was subsequently selected on the basis of log-likelihood tests. The model had treatment and centre as effects. In this

analysis the actual time points of air leakage assessment were used. The time to sealing was measured from the time point of the last water submersion test.

The low number of subjects recruited by some sites resulted in estimation difficulties in the parametric analyses of the primary endpoint. For consistency and to avoid giving subjects from small centres undue weight in the non-parametric primary analyses, prior to database lock it was decided to pool subjects from centres with few subjects with subjects from other centres. Consequently, the subjects from the centres in Zurich, Essen and Gothenburg were pooled into one centre while the subjects from the site in Leuven were pooled with the subjects from the site in Vienna due to relatively similar hospital standards at the two centres.

Secondary efficacy endpoint

Reduction in intra-operative air leakage intensity after the first application of trial treatment was analysed for the ITT and AT analysis sets. Subjects were randomised with rating 1 or 2 and had ratings 0, 1, 2 or 3 after the first round of trial treatment. The reduction was tested for equality between treatments by a Wilcoxon test. No imputation of missing values was done.

Descriptive efficacy variables

In addition to the primary and secondary efficacy endpoints, the following descriptive variables were summarised by descriptive statistics and presented by treatment:

- Total number of days until removal of the (last) chest drain (ITT)
- Predefined post-operative complications: pneumonia, pulmonary embolism, atelectasis of the lung, surgical wound infection, cardiac arrhythmia, progression/increase of soft tissue emphysema, need for additional chest drainage, need for re-operation, need for respiratory assistance, bleeding and need for blood transfusion (AT).

For details, see the Statistical Analysis Plan (SAP) (Appendix 1.20) and Documentation of Statistical Methods (Appendix 1.9).

9.3 Handling of Missing Data and Withdrawals

The protocol defined no specific criteria for excluding subjects from the PP analysis set. However, as described in the meeting minutes from the Investigators' meeting held before trial start on 18 January 2006, it was decided to exclude:

- Subjects that needed respiratory assistance post-operatively (indicated by a tick in the post-operative complications form)

In addition the following criterion lead to exclusion of subjects from the PP analysis set:

- Rescue treatment applied.

Any major protocol violation judged to obscure the evaluation of TachoSil efficacy lead to exclusion. The CTM, Statistician and Data Manager decided, in consultation with the Medical Adviser, on exclusion of subjects from the PP analysis set and decisions were documented, see Appendix 1.9. The major protocol deviations leading to exclusion of 26 subjects from the PP analysis set were as follows (for details, see Section 11.2):

- If one or more re-operations were carried out while air leakage was still present - unless the Investigator specifically stated that re-operation had no impact on the assessment of the primary endpoint
- If wedge resection of the lung was performed
- Use of Heimlich valves while air leakage was still present
- Use of rescue treatment
- Use of respiratory assistance
- Failure to report air leakage assessments in the Extra Days pages of the CRF creating uncertainty about time of air leakage stop
- Randomisation error in case the actual treatment applied was different from that assigned to the subject by the IVRS system.

For the parametric analysis, duration of post-operative air leakage is defined using the exact time recordings. Thus, time until air leakage stop is measured from the time of the last water submersion test. The time of the last water submersion test was not available in four of the 299 randomised subjects. To be conservative, time of incision was used instead for the one TachoSil subject in question whereas time when surgery ended was used for the three Standard subjects.

9.4 Baseline Comparability of Treatment Groups

Baseline comparability of the treatment groups was assessed by inspection of summary tables of demography and other variables, see Sections 12.2.11, 12.3.4.

9.5 Safety Analyses

Safety tabulations should include all randomised subjects that received trial treatment, i.e. the AT analysis set. For AEs, only treatment emergent events, i.e. events with onset after application of trial treatment, are included in the summary tables. AEs are tabulated according to the Nycomed Full ICH report guideline.

The number of TachoSil sponges used was summarised by descriptive statistics.

The presentation of clinical laboratory variables follows the Nycomed Full ICH report guideline. Laboratory values from the day after surgery (Day 1) and from discharge were plotted against the values from screening for both treatments. Changes in laboratory values from screening were compared between treatments by means of Mann-Whitney test.

Vital signs were summarised by descriptive statistics by treatment and day. Frequencies of normal/abnormal ECGs at screening were summarised by descriptive statistics.

9.6 Software

The statistical program package SAS® version 9.1.3 was used.

The following SAS 9 syntax was used in the analysis of the primary endpoint to carry out a log rank test of equality in survival times between the two treatments. This syntax employs a ties-handling method recommended for situations where survival times are discrete and heavily tied. The syntax yields log rank test results identical to the global score test of the phreg procedure with the option ties = discrete which is recommended for the discrete time-scale model (see appendix 1.9 for further details).

```
proc lifetest data=some_dataset;
  time Time*Censored(0);
  strata Centre / group=Treatment;
run;
```

Attention is drawn to the fact that the only proc lifetest syntax available in SAS 8 (and earlier versions) for performing a test of treatment while stratifying by centre is as follows:

```
proc lifetest data=some_dataset;
  time Time*Censored(0);
  strata Centre;
  test Treatment;
run;
```

The test statement here computes linear rank tests for the association of survival time with covariates and produces log rank test results identical to the global score test of the phreg procedure when the option ties = breslow suitable for the continuous time-scale model. When there are no tied survival times the two syntaxes produce identical results.

10 Changes in the Planned Analyses

Due to post-operative complications, false-negative assessments of air leakage appeared. This matter was brought to the attention of the co-ordinating investigator Prof. W. Klepetko, who approved of the following clarification in Section 10.2 of the SAP: Due to post-operative complications false-negative assessments of the air leakage can appear. The time point of air leakage stop is defined as the last observed measurement where air leakage is not present. False-negative assessments are assumed to be equally distributed between the two treatments.

Following a meeting on 27 Jun 2007 the definition of the time point of air leakage stop was clarified further to: The time point of air leakage stop was defined as the first observed time point without air leakage after the last time point where air leakage was observed.

To overcome estimation difficulties arising from the inclusion of small centres in the statistical analysis of the primary endpoint, centres contributing with only a few subjects were pooled with other centres. The three smaller centres of Zürich, Essen and Göteborg were consequently pooled into a single centre while Leuven was pooled with Vienna due to relatively similar hospital standards at the two centres.

The parametric survival analysis on the primary endpoint was performed on the ITT analysis set and in addition also presented as an exploratory analysis for the PP analysis set. The PP analysis on the primary endpoint was considered important to the parametric analysis. This was done since the observed survival times on the primary endpoint were not entirely

consistent with the standard distributional assumptions necessary for the type of parametric analysis planned (SAP, Section 10.2) resulting in increased uncertainty in the estimates. As with the non-parametric analysis, the statistical evidence resulting from the PP analysis in favour of a treatment difference is stronger than that of the ITT analysis. In particular, the parametric analysis on the PP analysis set resulted in a significant difference while the ITT analysis set did not.

The use of Heimlich valves in some subjects could obscure assessment of the primary endpoint. However, censoring the event times of such subjects, as was originally proposed in the SAP, constitutes informative censoring and may lead to bias as described in the Documentation of Statistical Methods (Appendix 1.9). Subjects treated with a Heimlich valve were consequently excluded from the PP analysis set but remained in the ITT analysis set with their observed event times.

An exploratory sensitivity analysis investigating the impact resulting from the use of Heimlich Valves in some patients was added to the analyses on the primary endpoint. During the result meeting on 22 Aug 2007, co-ordinating Investigator Prof. W Klepetko proposed that the use of Heimlich Valves could be regarded as an indicator of treatment failure. It was agreed that an exploratory sensitivity analysis was included in which subjects treated with Heimlich Valves were assigned the longest observed post-operative duration of air leakage across all subjects.

Additionally the primary analysis of duration of post-operative air leakage was conducted for each of the following sub-groups: subjects aged 65 or under, subjects aged 66 or above, male subjects and female subjects.

11 Subjects

Individual data for the 486 screened subjects and the 299 subjects that received trial treatment are available in Appendices 2.1-20, 4.1.

11.1 Disposition of Subjects

Of the 486 screened subjects, 301 were randomised and 299 received trial treatment. For the number of subjects by site and trial treatment (ITT), see Table 1. One subject that was

randomised to standard treatment received TachoSil and therefore both an ITT and an "as treated" (AT) analysis set exist, which differ as shown in the table below.

Number of subjects		
Screened	486	
Screening failures	185	
Randomised	301	
Trial treatment	**TachoSil**	**Standard**
Received no trial treatment	2	0
Intention-to-treat (ITT) analysis set	148	151
"As treated" (AT)* and safety analysis sets	149	150
Per-protocol (PP) analysis set	135	138
Discontinued due to adverse events	2	0
Discontinued due to non-compliance / for other reasons	4	2

Data from Table 2

Details of reason for discontinuation are given in Appendix 2.1.

11.2 Protocol Deviations

Two subjects were randomised to TachoSil but received no trial treatment:
No 1101/21: During surgery the site had problems with contacting the Interactive Voice Response System (IVRS) and couldn't get the patient allocated to a treatment. The investigator continued the operation and treated the patient with standard treatment. Afterwards, the site received a fax from the IVRS stating that the patient should have been allocated to TachoSil. The investigator took a decision of withdrawing the patient, and no further information was collected.
Nycomed considered the decision of excluding this patient from the ITT population reasonable and justifiable according to ICH E9 (22). The interpretation was based on an obvious randomisation error, an investigator decision of withdrawing the patient from the trial, and the absence of any efficacy information collected.

This case was reported by a monitor (CRA) and due to the circumstances, Nycomed decided to include one additional patient in the trial. This explains that 301 patients were randomised.

No. 1242/285: An emergency situation occurred during the surgery, which resulted in an investigator decision of not applying the randomised treatment (TachoSil) and, furthermore, immediately to withdraw the patient from the trial. No further efficacy data was collected. The decision of not having this patient in the trial was based on these three factors: No efficacy data, no information about the applied treatment, and the investigators decision of not having this patient in the trial.

One subject (no. 187) was randomised to standard treatment but received TachoSil instead (Appendix 2.2). All other subjects had the trial treatment to which they were randomised.

Twenty-six subjects were excluded from the PP analysis set for one or two violations (Appendix 2.3):

- Documented use of Heimlich valve: nine subjects (TachoSil: nos. 167, 224, 262; standard: nos. 36, 131, 150, 153, 228, 255)
- Need of respiratory assistance: five subjects (TachoSil: nos. 8, 57, 226; standard: nos. 69, 86)
- Re-operation before air leakage stop: four (five) subjects (TachoSil: nos. 11, (167, see above), 291; standard: nos. 54, 157)
- Uncertainty about time of leakage stop: four subjects (TachoSil: nos. 188, 273; standard: nos. 41, 177)
- Use of wedge resection: two subjects (TachoSil: nos. 144, 251)
- Use of rescue treatment: one (two) subject(s): (TachoSil: nos. 27, (144, see above))
- Application of incorrect trial treatment: one subject (standard: no. 187).

12 Results

12.1 Analysis Sets Analysed

Data are presented for the 299 randomised subjects that received trial treatment. They constitute the ITT, the AT and the safety analysis sets. As described above, the ITT and AT

analysis sets differ in the distribution of trial treatments (148/151 vs. 149/150) since one subject received TachoSil instead of standard treatment. In this report, data are presented for the ITT analysis set when planned in the SAP; the remaining variables are presented for the AT analysis set, which is identical to the safety analysis set. Tables not presented for the AT analysis set are available in Appendix 1.9.

The PP analysis set counts 273 subjects as described in Section 11.2. Two analyses were performed for the PP analysis set: parametric and non-parametric analysis of the primary endpoint: post-operative duration of air leakage.

12.2 Demographics and Baseline Characteristics

For individual data, see Appendix 2.4. For distribution of these characteristics by trial treatment, see Section 12.2.11.

12.2.1 Demographics, ITT

Of the 299 subjects, 201 (67%) were male and 98 (33%) were female (Tables 3,4). Mean (range) age was 64 (33 - 83) years; subjects older than 65 years constituted 51% of the male and 43% of the female population. Mean Body Mass Index was 26.0 (15.2 - 38.6) kg/m^2. Data for weight and height are also available. All subjects were Caucasian (Table 5).

12.2.2 Smoking and Use of Alcohol, ITT

Smoking was reported for 94 (31%) and use of alcohol for 84 subjects (28%) (Table 5).

12.2.3 Vital Signs and Electrocardiogram, AT

At screening, the mean (range) systolic and diastolic blood pressure was 134 (90 - 210) and 78 (40 - 105) mmHg, respectively (Table 6). Heart rate was 77 (40 - 128)/min; respiratory rate was 16 (8 - 26)/min. A screening ECG was obtained from all but seven subjects; of the 55 abnormal ECGs from 24 TachoSil and 31 standard treatment subjects, 12 were clinically significant (4 TachoSil/8 standard treatment) (Appendix 4.1).

12.2.4 Physical Examination, AT

For 198 subjects, no abnormal findings were reported at the physical examination (Table 7). Most abnormal findings (clinically or not clinically significant) were seen for the respiratory, cardiovascular and musculoskeletal systems (see Appendix 2.6).

12.2.5 Pulmonary Function, ITT

The mean (range) FEV-1 was 2,486 (103 - 7,200) ml (n=295) (Table 8), TLC was 6,153 (2,300 - 9,780) ml (n=256) and RV was 2,630 (720 - 7,830) ml (n=254).

12.2.6 Chest X-Ray, AT

A chest X-ray taken at screening was available for 238 subjects; full inflation was seen in all subjects (Table 9).

12.2.7 Concomitant Illness, AT

Concomitant illness was recorded for 250 (84%) subjects (Table 10a). Vascular disorders were the most frequent (in 152 subjects) followed by metabolism and nutrition disorders (86 subjects) and respiratory, thoracic and mediastinal disorders (80 subjects). The number of concomitant illnesses per subject varied from 1 (54 subjects) to 14 (1 subject) (Table 10b).

12.2.8 Concomitant Medication, AT

Concomitant medication was taken by 257 subjects (86%) (Table 11, Appendix 2.7).

12.2.9 Laboratory Tests, AT

Normal ranges by sex for the eight laboratory tests are available by site in Table 12. The mean, median, minimum and maximum test results from screening, Day 1 and discharge are presented in Tables 13a,b (Table b gives standardised values using the z-values method). Mean values for the tests were similar for the treatment groups. For changes in test results from screening to Day 1 and discharge, see Table 14, Section 13.4.

12.2.10 Pregnancy Test

No pregnant subject was included in the trial (Appendix 4.1).

12.2.11 Characteristics by Trial Treatment

The table below presents most of the above characteristics by trial treatment and overall.

Variable	Unit	TachoSil	Standard	All subjects
Sex				
Male	%	69	66	67
Female		31	34	33
Age	years	64 (33 - 83)	64 (34 - 82)	64 (33 - 83)
Age > 65 years	%	49	47	48
Height	cm	170 (142 - 192)	169 (144 - 192)	170 (142 - 192)
Weight	kg	75 (42 - 128)	75 (46 - 113)	75 (42 - 128)
Body Mass Index	kg/m^2	25.8 (15.2 - 38.6)	26.1 (17.3 - 38.6)	26.0 (15.2 - 38.6)
Ratio of smokers	%	32	31	31
Users of alcohol	%	30	27	28
Blood pressure*				
Systolic	mmHg	134 (90 - 210)	134 (100 - 210)	134 (90 - 210)
Diastolic		78 (40 - 105)	78 (40 - 100)	78 (40 - 105)
Heart rate*	/min	78 (50 - 110)	77 (40 - 128)	77 (40 - 128)
Respiratory rate*	/min	16 (10 - 26)	16 (8 - 23)	16 (8 -26)
ECG*				
Abnormal (CS)		24 (4)	31 (8)	55 (12)
FEV-1	ml	2,477 (1,050-5,000)	2,495 (103-7,200)	2,486 (103-7,200)
TLC	ml	6,169 (2,300-9,720)	6,138 (2,520-9,780)	6,153 (2,300-9,780)
RV	ml	2,654 (780-7,830)	2,606 (720-7,150)	2,630 (720-7,830)

Variables are presented as percentage or mean (range)
*: Data for the AT analysis set; Data from Tables 3-6,8

For all the above variables, the two trial treatment groups were similar.

12.3 Surgical Variables

For individual data, see Appendix 2.8. For distribution of pre-randomisation surgical variables by treatment, see Section 12.3.4.

12.3.1 Thoracic Incision and Lymph Adenectomy, AT

The type of thoracic incision and use of lymph adenectomy by trial treatment and site are presented in Table 15. Overall, antero- and postero-lateral incisions were used in 164 (55%) and 135 (45%) subjects, respectively; lymph adenectomy was used in 284 (95%) subjects.

12.3.2 Type of Lung Resection, AT

Right upper lobectomy was performed in 105 subjects (35%), left upper lobectomy in 72 subjects (24%), whereas right and left lower lobectomy were performed in 44 (15%) and 49 (16%) subjects, respectively (Table 16). Middle lobe lobectomy, upper and lower bi-lobectomy were performed in 5%, 1% and 3% of the subjects, respectively.

12.3.3 Intra-Operative Intensity of Air Leakage at Randomisation, ITT

Sixteen subjects had Grade 3 air leakage at the first submersion test, after which suturing/ stabling and the submersion test were repeated. Five of these subjects were randomised with Grade 1 and eleven with Grade 2 (Appendix 4.1). At randomisation, Grade 1 air leakage was recorded for a total of 148 subjects (49%) and Grade 2 for 150 subjects (50%); data were missing for 1 subject (Table 17, Appendix 2.10).

12.3.4 Surgical Variables by Trial Treatment

The table below presents the above surgical variables by trial treatment and overall.

Variable	Unit	TachoSil	Standard	All subjects
Thoracic incision*				
Antero-lateral	%	56	54	55
Postero-lateral		44	46	45
Lymph adenectomy*	%	97	93	95
Type of resection*				
Right upper lobectomy	%	37	34	35
Right lower lobectomy		14	16	15
Left upper lobectomy		23	26	24
Left lower lobectomy		17	16	16
Middle lobe lobectomy		5	5	5
Upper bi-lobectomy		0	2	1
Lower bi-lobectomy		4	2	3
Intensity of air leakage*				
Grade 1	%	51	48	50
Grade 2		49	52	50

Intensity of air leakage missing for one standard treatment subject. *: Data for the AT analysis set
Data from Tables 15-17

For all the above variables, the two trial treatment groups were similar.

12.3.5 Trial Treatment, AT

TachoSil treatment. The total number of TachoSil sponges used per subject varied from 1 to 5. One sponge was used in 79 subjects (53%), whereas 42 subjects (28%), 24 (16%), 3 (2%) and 1 (1%) received 2, 3, 4 and 5 sponges, respectively. Twenty subjects had more than one round of TachoSil treatment (Table 18a). The number of TachoSil sponges used by site is shown in Table 18b. Individual data are available in Appendix 2.5.

Standard treatment. Forty-two (28%) of the 150 standard treatment subjects had no additional standard treatment after randomisation (Table 19a). During the first round of trial treatment, suturing was used in 79 subjects (53%), stapler in 23 (15%) and other standard treatment in four subjects (3%). Continuous and singular suturing was used in 65 and 14 subjects, respectively. Proline suturing thread was the most frequently used. The most used diameter was 4.0. Three of the 12 sites used stapler; the sizes are presented in Table 19b. Individual data are available in Appendix 2.9.

12.3.6 Number and Location of Trial Treatments, AT

TachoSil treatment. Twenty subjects had two treatment rounds of TachoSil; six subjects had a further third treatment round (Table 20a).

Standard treatment. Of the 150 subjects randomised to standard treatment, 108 had standard treatment after randomisation, three had two rounds of treatment (Table 19a).

The lobes affected by surgery, i.e. sites 1, 2 and 3, are listed in Table 20b; two and three lobes were involved for 58% and 13% of the subjects, respectively.

12.3.7 Intra-Operative Intensity of Air Leakage after Trial Treatment, ITT

Intra-operative intensity of air leakage after the first application of trial treatment is shown in Table 21. As a secondary efficacy endpoint, see Section 12.4.2.1.

12.3.8 Duration of Surgery, AT

The mean (range) duration of surgery was 144 (65 - 311) min and 142 (50 - 476) min for TachoSil and standard treatment, respectively (Table 22).

12.3.9 Treatment Failures, ITT

Rescue treatment was used in two TachoSil subjects: no. 27 had suturing and “other” (not specified), no. 144 had “other” (sleeve resection) (Table 23, Appendix 2.13).

12.4 Efficacy Evaluation

12.4.1 Primary Efficacy Endpoint

12.4.1.1 Duration of Post-Operative Air Leakage, ITT

The ITT subjects with post-operative air leakage (%) at selected time points are shown in Table 24, Figures 1a-d (by site, overall). 34% (TachoSil) and 29% (standard treatment) had no air leakage in the evening of the day of surgery. The duration of air leakage was shown to be significantly less in the TachoSil group compared to the Standard treatment group (log-rank p-value = 0.030)

An exploratory parametric analysis, based on an accelerated failure time model, resulted in an overall estimated mean effect difference between the two trial treatments of 0.310 units on the log-time scale (p=0.153) (Table 25). This non-significant result corresponds to an estimated 36% increase in the duration of post-operative air leakage for standard treatment compared to TachoSil. The estimated median time until cessation of air leakage was 14.5 h for TachoSil and 19.5 h for standard treatment.

A sensitivity analysis was done in which censored observations in the TachoSil group (n=4) were assigned the longest post-operative duration of air leakage recorded (20 days) (Table 26). This means that a worst case scenario is presented for those TachoSil subjects without a known duration of air leakage. The results of this conservative analysis just failed to reach statistical significance (p=0.051) and thus support the primary analysis consistent with the hypothesis of a treatment difference in the duration of post-operative air leakage.

Table 27 presents the results of an exploratory sensitivity analysis of the impact on the primary endpoint resulting from the use of Heimlich valves. Subjects treated with Heimlich valves (n=9) may be regarded as treatment failures and were consequently assigned the longest observed post-operative duration of air leakage across all subjects (20 days). In line

with the primary analysis, the results demonstrate a statistically significant difference in favour of TachoSil treatment (p=0.032).

A further sensitivity analysis was conducted to evaluate the impact of assigning subjects whose first post-operation assessments were obtained outside the protocol-specified time window of 3-5 hours post-operation, as having air leakage at that time point. This analysis demonstrated the relative robustness of the primary analysis results with respect to this issue (p = 0.056, ITT; p = 0.014, PP). See the statistical methods appendix for details.

12.4.1.2 Duration of Post-Operative Air Leakage, PP

The PP subjects (%) with post-operative air leakage at selected time points are presented in Table 28; 37% (TachoSil) and 32% (standard treatment) had no air leakage in the evening of the day of surgery. As for the ITT analysis set; the percentage of subjects without air leakage was higher in the TachoSil than in the standard treatment group at all selected time points. The log-rank test provided statistical evidence of a shorter duration of post-operative air leakage in the TachoSil group (p=0.006).

As for the ITT analysis set, a supportive parametric analysis was done for the PP analysis set, which resulted in an overall estimated mean effect difference between the two trial treatments of 0.436 units on the log-time scale (p=0.034) (Table 29). This corresponds to an estimated 55% increase in the duration of post-operative air leakage for standard treatment compared to TachoSil. The estimated median time until cessation of air leakage was 11.2 h for TachoSil and 16.8 h for standard treatment.

12.4.2 Secondary Efficacy Endpoint

12.4.2.1 Reduction of Intra-Operative Air Leakage Intensity, ITT

Reduction of intra-operative air leakage from the first (before randomisation) to the second water submersion test (3 - 5 min after the first application of trial treatment) is presented by grade (0 - 3), trial treatment, site and overall in Table 21, Figures 2a-d. The number of subjects (%) without intra-operative air leakage after TachoSil and standard treatment was 88 (60%) and 63 (43%), respectively. 71% of the TachoSil subjects achieved reduction of

one or two grade units compared with 62% of the standard treatment subjects (p=0.042, Wilcoxon's rank sum test) (Table 30).

12.4.3 Descriptive Post-Operative Variables

12.4.3.1 Number of Days Until Removal of Last Chest Drain, ITT

Mean (range) number of days until removal of the (last) chest drain was 4.9 (1 - 25) days for TachoSil and 5.5 (1 - 21) days for standard treatment (Table 31, Figures 3a-d).

12.4.3.2 Post-Operative Complications and Additional Procedures, AT

A survey of post-operative complications and additional procedures is given in the table below; for further details, see the text below the table.

Variable	Unit	TachoSil	Standard
Total volume of chest tube drainage	ml	1,738 (390 - 6,590)	1,656 (190 - 5,745)
Postoperative complications*, e.g.	%	26	33
Cardiac arrhythmia		6.7	8.0
Atelectasis		6.0	7.3
Pneumonia		6.0	6.0
Additional procedures*	%	11	11
Additional chest tube drainage		4.7	4.0
Need of blood transfusion		4.7	6.0
Re-operation		4.0	3.3
Need of respiratory assistance		2.7	2.0
Inflation of the lung*			
Incomplete on e.g. Day 1	%	22	16
Pneumothorax*, e.g.			
Present on Day 1	%	29	24
Before drain removal		25	28

*: Data for the AT analysis set; Data from Tables 9,32,34

Total and daily volume of post-operative chest tube drainage. The mean (range) total volume of chest tube drainage was 1,738 (390 - 6,590) ml for TachoSil and 1,656 (190 - 5,745) ml for standard treatment (Table 32). Daily volumes of chest tube drainage and at drain removal are presented by site and overall in Table 33 (these figures may represent volumes accumulated over several days). Individual data are available in Appendix 2.11.

Post-operative complications were seen in 39 (26%) of the TachoSil and in 50 (33%) of the standard treatment subjects (Table 34, Appendix 2.12). The most frequent complications were cardiac arrhythmia (10/12 subjects), atelectasis of lung (9/11) and pneumonia (9/9).

Additional procedures were performed in 17 (11%) of the TachoSil and in 17 (11%) of the standard treatment subjects (Table 34). Seven (5%) TachoSil and nine (6%) standard treatment subjects had **blood transfusion**, see below for types and units of blood supplied. Seven (5%) TachoSil and six (4%) standard treatment subjects had **additional chest tube drainage** whereas six (4%) and five (3%) subjects needed **re-operation**.

Types and units of blood transfusions. Seven Tachosil and nine standard treatment subjects received blood transfusions, which mostly consisted of packed RBCs or whole blood; fresh frozen plasma was given to only one subject (Table 35). The number of transfusions and units are shown in Table 36.

Inflation of the lung. On Day 1, chest X-rays showed incomplete inflation of the lung in 29% of the TachoSil and in 21% of the standard treatment subjects (percentage of subjects with data available) (Table 9, Appendix 2.11). The percentages of subjects with incomplete inflation were similar in the two treatment groups both before and after drain removal, at discharge and at follow-up.

Pneumothorax on Day 1 was present in 38% of the TachoSil and in 32% of the standard treatment subjects (percentage of subjects with data available) (Table 9, Appendix 2.11). Before and after drain removal, at discharge and at follow-up the percentages of subjects with pneumothorax were similar in the two treatment groups. Data for the apical gap and the gap surrounding the lung (cm) are also available in the table.

12.4.3.3 Days Until Discharge, AT

The TachoSil and standard treatment subjects were discharged 9.3 (1 - 36) and 9.7 (4 - 28) days after surgery, respectively (Table 37).

12.4.3.4 Unscheduled Visits, AT

The number of unscheduled visits was eight: five for TachoSil and three for standard treatment subjects (Table 38). Except for one TachoSil subject, who complained of dyspnoea and thoracic pain, the reasons for these visits were procedural.

12.4.4 Sub-group analyses of the primary endpoint by age and gender

Table 52 and figures 5a–5d present the results of the sub-group analyses by age and gender. The primary analysis of post-operative duration of air leakage was carried out separately in sub-groups defined by age (≤65, >65) and gender. Just over half the subjects were 65 years of age or younger whereas the male population accounted for around two thirds of all subjects.

Although there are some variations in the life table estimates presented in figures 5a-5d, the treatment effect of TachoSil is comparable in males and females and in subjects less than 65 compared to subjects 65 years of age and older..

12.5 Efficacy Conclusions

The statistical analyses demonstrate that TachoSil was superior to standard surgical treatment for the sealing of air leakage following pulmonary lobectomy. TachoSil treatment provided significantly shorter post-operative air leakage (primary endpoint) based on the analysis of both the ITT and PP analysis sets. This was supported by significant results in favour of TachoSil for the secondary endpoint, reduction of intra-operative air leakage intensity.

13 Safety Evaluation

The safety analysis set consists of the 299 subjects that received trial treatment and is equal to the AT analysis set. 149 subjects received TachoSil and 150 subjects received standard treatment. Listings of individual AE are available in Appendices 2.14-19, 4.1.

13.1 Extent of Exposure

The number of TachoSil sponges used is presented in Tables 18a,b, Section 12.3.5.

13.2 Adverse Events

A total of 274 AEs were reported during the trial period: 140 events in 66 (44%) TachoSil subjects and 134 events in 66 (44%) standard treatment subjects (Table 39).

13.2.1 Display of Adverse Events

AEs with an occurrence > 1%, i.e. in at least three subjects, are shown below in descending order by System organ class (SOC) and Preferred term (PT) (Table 40).

N = number of subjects exposed to treatment n = number of subjects with event % = number of subjects having event per subjects exposed (%) E = number of events		Trial treatment						
		TachoSil N = 149			Standard N = 150			All
		n	%	E	n	%	E	
SOC	**PT**							
Respiratory, thoracic and mediastinal disorders	Atelectasis	7	5	7	10	7	10	17
	Bronchopleural fistula	3	2	4	8	5	10	14
	Pneumothorax	4	3	4	5	3	5	9
	Pleural effusion	5	3	5	2	1	2	7
	Lung disorder	3	2	3	4	3	4	7
	Dyspnoea	2	1	2	2	1	2	4
Gastrointestinal disorders	Constipation	5	3	5	9	6	9	14
	Flatulence	2	1	2	7	5	7	9
	Nausea	3	2	4	0	0	0	4
	Diarrhoea	1	1	1	2	1	2	3
Infections and infestations	Pneumonia	8	5	10	9	6	10	20
	Cystitis	2	1	2	1	1	1	3
Cardiac disorders	Atrial fibrillation	11	7	11	5	3	5	16
	Tachyarrhythmia	1	1	1	4	3	4	5
General disorders	Pyrexia	6	4	6	3	2	3	9
	Pain	2	1	2	1	1	1	3
Procedural complications	Anaemia postoperative	2	1	2	1	1	1	3
	Haemothorax	2	1	2	1	1	1	3
	Post procedural haemorrh.	1	1	1	2	1	2	3
Blood and lymphatic system disorders	Anaemia	4	3	4	5	3	5	9
Psychiatric disorders	Sleep disorder	2	1	3	3	2	3	6
Vascular disorders	Hypertension	2	1	2	4	3	4	6
Skin and subcutaneous tissue disorders	Pruritus	4	3	4	0	0	0	4
Nervous system disorders	Vocal cord paralysis	1	1	1	3	2	3	4

Data from Table 40

13.2.2 Analysis of Adverse Events

The AEs have been summary tabulated as planned whereas no statistical analyses were planned. Severity and causality to trial treatment are described below.

Severity. Of the 274 AEs, severity was mild for 202 (94 after TachoSil/108 after standard treatment), moderate for 54 (37/17) and severe for 18 (9/9) of the AEs (Table 41); the mild and the moderate AEs thus comprised the majority of the AEs.
Causality. Causality **possible** was given to six AEs after TachoSil and two AEs after standard treatment. Except for pyrexia reported in two TachoSil subjects and lung disorder reported in one TachoSil and one standard treatment subject, the AEs with causality possible each occurred in one subject. Causality **probable** was given to six AEs after TachoSil and two AEs after standard treatment (Table 42). Except for pleural effusion reported for two TachoSil and one standard treatment subjects, the AEs with causality probable each occurred in one subject. Of these 16 AEs with causality possible/ probable, one event in a TachoSil subject was severe and serious: drug ineffective (causality possible) (Tables 43,44).

The most frequently reported AEs were pneumonia (10 in TachoSil/10 in standard treatment subjects), atelectasis (7/10), atrial fibrillation (11/5), constipation (5/9), bronchopleural fistula (4/10), flatulence (2/7), pyrexia (6/3), pneumothorax (4/5), anaemia (4/5) and pleural effusion (5/2) which are well known complications to the surgical procedure and the underlying cancer disease. There were no major differences in the distribution of these AEs between the two trial treatments. The SAEs are described below.

13.3 Deaths, Other Serious Adverse Events and Other Significant Adverse Events

Thirty-two SAEs were reported: 19 events in 16 TachoSil and 13 events in 12 standard treatment subjects (Table 45). Six events occurred in more than one subject: pneumonia (2 TachoSil/3 standard treatment subjects); pneumothorax (2/1); vocal cord paralysis of laryngeal nerve (1/2); atelectasis (2/0); post-procedural haemorrhage (1/1); bronchopleural fistula (0/2).

Severity. Of the 32 SAEs, the severity was mild for ten (4/6), moderate for seven (6/1) and severe for 15 (9/6) (Table 46).

Causality. Causality **possible** was given to three SAEs in three TachoSil subjects: drug ineffective (severe), pleural effusion and pneumothorax (Table 47).

Deaths

Four subjects died: three TachoSil subjects (due to candida sepsis plus atelectasis; cerebro-vascular accident (this subject died approx. 1 month after the 1-month follow-up); pneumonia aspiration plus bronchial fistula) and one standard treatment subject (due to bronchopleural fistula) (Table 48); for details, see Section 13.3.1, for narratives, see Section 13.3.2.

Withdrawals due to adverse events

Two subjects were withdrawn due to AEs (Table 49).

13.3.1 Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

No statistical analyses of the SAEs were planned. Details of the individual events are given in the CIOMS reports (Appendix 4.2).

Deaths

Three TachoSil subjects (nos. 57, 104, 291) and one standard surgical treatment subject (no. 221) died (Table 48); for narratives, see Section 13.3.2. The time of death varied between 4 and 64 days after surgery. No death was related to trial treatment; all deaths were related to the underlying illness or to complications of surgery.

Other serious adverse events

The three SAEs possibly related to trial treatment occurred in subjects treated with TachoSil; for narratives, see Section 13.3.2. However, in all three subjects, there was an alternative aetiology for development of the event (lung cancer and lobectomy in nos. 24, 262, incorrect application of the TachoSil sponges in no. 156). All three subjects recovered although no. 24 recovered with non-specified sequelae.

Except for the three SAEs possibly related to trial treatment, the remaining 29 SAEs were all related to the underlying medical condition or to complications to surgery; for details see the CIOMS forms (Appendix 4.2).

13.3.2 Narratives of Deaths, Other Serious Adverse Events and Certain Significant Adverse Events

Deaths in the 1-month trial period

TachoSil treatment

Subject no. 57: A 54-year-old female with a medical history of chronic obstructive pulmonary disease underwent lung resection on 1 Dec 2006 due to lung cancer. During surgery, resection of the left upper lobe with mediastinal lymphadenectomy was performed and two TachoSil sponges were applied as secondary management of air leakage. The TachoSil treatment was part of the clinical trial, TC-021-IM. On 4 Dec 2006, the subject developed respiratory decompensation due to atelectasis of the left lower lobe, for which she was re-intubated and started treatment with antibiotics. Cardiac assistance was performed because of low output due to sepsis with candida albicans. Some hours later the subject developed septic-toxic shock followed by multi-organ failure. The subject died on 5 Dec 2006. The Investigator considered the atelectasis to be due to the underlying lung disease.

Subject no. 291: A 69-year-old male underwent left upper lobectomy due to lung cancer on 5 Feb 2007. One TachoSil sponge was applied on lobe hilus as secondary management of Grade 1 air leakage. On 7 Feb 2007, the subject developed pneumonia, which was caused by aspiration. Enterobacter cloacae and enterococcous faecalis were detected. Ventilation was performed and therapy with antibiotics and cortisone was started. The subject developed a bronchial stump fistula on 23 Feb 2007, which required two re-operations. On 2 Mar 2007, the subject developed insufficient respiration and died due to the aspiration pneumonia and the bronchial fistula. The reporting Investigator considered the event to be unrelated to TachoSil treatment but due to the aspiration.

Standard surgical treatment

Subject no. 221: A 64-year-old male underwent unspecified lung surgery on 1 Dec 2006. The subject was randomised to standard surgical treatment. On 3 Dec 2006, the subject developed bronchopleural fistula resulting in broncho-insufficiency with sepsis. Re-operation was performed and the subject was treated with antibiotics and mechanically ventilated.

However, the subject died due to multi-organ failure on 22 Dec 2006. The reporting Investigator considered the event to be due to postoperative complications.

Death after the 1-month trial period

TachoSil

Subject no. 104: A 77-year-old male underwent left upper lobectomy on 29 Aug 2006. One TachoSil sponge was applied as secondary management of air leakage. The subject received anti-coagulation therapy with nadroparina from 1 Sep to 3 Sep 2006. On 17 Sep 2006, the subject developed stroke and was admitted to hospital. Steroid therapy was initiated and neurosurgery was planned. The subject died on 1 Nov 2006, i.e. 64 days after surgery. The reporting Investigator considered the event to be unrelated to TachoSil treatment; intra-lesional haemorrhage due to pecipital brain metastases was reported as the most likely alternative aetiology.

Serious adverse events considered related to trial treatment

TachoSil

Subject no. 24: A 37-year-old female underwent lower lobe resection on 15 Aug 2006. The subject had Grade 1 air leakage before application of one TachoSil sponge applied as secondary management of air leakage. Pleural effusion developed on 5 Sep 2006 and the subject was admitted to hospital. Drainage performed during four days revealed 400 ml pleural exudative effusion. No sign of pneumonia was noted. The subject suffered from atelectasis of the left lower lobe due to retention of secretion in the bronchus. On 8 Sep 2006, the subject recovered with an acceptable residue of the effusion. The subject recovered without sequelae. The reporting Investigator considered the event to be possibly related to TachoSil treatment. However, the Investigator also suspected atelectasis as the most likely alternative aetiology for the pleural effusion.

Subject no. 156: A 60-year-old male with a medical history of peripheral occlusive artery disease, carotid arteries stenosis, chronic obstructive pulmonary disease and arterial hypertension underwent surgery for adenocarcinoma of the left lower lobe on 28 Jun 2006. During surgery, five TachoSil sponges were applied: the first two sponges (TC-026/ 027) did not adhere to the resection site and were removed after which another three sponges (TC-028/029/030) were applied successfully. The subject recovered the same day. The sponges

that did not adhere were discharged. The five sponges were of the same batch (10248609, expiry Jan 2008). The surgeon was experienced in using TachoSil and all sponges were applied with the same technique: dry application with wet towel pressure for two minutes, i.e. that the TachoSil sponges were not moistened in saline solution before application. The subject's temperature was unchanged during the procedure and no other medication was administered between the unsuccessful and successful applications. The TachoSil batch 10248609 was re-analysed; all analytical test results were within the specified limits.

Subject no. 262: A 62-year-old male underwent right lower lobe lobectomy due to lung cancer on 19 Jan 2007. During surgery two TachoSil sponges were applied for secondary management of Grade 2 air leakage. The sponges were applied dry with the yellow side towards the resection area with a pre-moistened pad used for five minutes to press the sponges against the resection area. Afterwards a Grade 1 air leakage was noted. On 23 Jan 2007, the subject developed worsening of air leakage and pneumothorax was diagnosed. The subject had drainage with a Heimlich valve and recovered on 7 Feb 2007. The reporting Investigator considered the event to be possibly related to TachoSil treatment; an alternative aetiology is unknown.

13.4 Display and Analysis of Laboratory Tests

The mean, median, minimum and maximum laboratory test results from Day 1 and discharge appear in Tables 13a,b. Mean changes from screening to Day 1 and discharge are shown in Table 14; scatter plots are presented in Figures 4a-h. No statistically significant differences between TachoSil and standard treatment were seen. Individual test results are available in Appendix 2.20.

13.5 Vital Signs

Blood pressure, heart rate, respiratory rate and temperature were obtained daily until the subjects were discharged (Tables 6, 50).

13.6 Physical Examination

At the physical examination at discharge, a total of 76 clinically significant changes from screening were reported: 39 in the TachoSil and 37 in the standard treatment group of subjects (Table 51). Most of the changes concerned the incision for lung surgery.

13.7 Safety Conclusions

A total of 274 AEs were reported during the trial period: 140 events in 66 (44%) TachoSil subjects and 134 events in 66 (44%) standard treatment subjects. The most frequently reported AEs were pneumonia, atelectasis, atrial fibrillation, constipation, bronchopleural fistula, flatulence, pyrexia, pneumothorax, anaemia and pleural effusion that all are well known complications to the surgical procedure and the underlying cancer disease. Except for atrial fibrillation, AEs in general were equally distributed between the two treatment groups for the total number of AEs, SAEs, the most frequent AEs as well as for causality and severity. Overall, it may be concluded that TachoSil was well tolerated.

14 Discussion

Alveolar air leakage remains a problem related to lung surgery. Persistent leakage may lead to post-surgical morbidity due to insufficient lung dilation, prolonged intercostal drainage and immobility, potentially resulting in prolonged hospitalisation of the patient (16,17).

The present trial demonstrated superiority of TachoSil over standard surgical treatment for the sealing of alveolar air leakage following pulmonary lobectomy. This was shown both intra- and post-operatively by statistically significant results for the secondary and primary endpoints, respectively.

Study design

The surgical indication for this trial was planned pulmonary lobectomy. This procedure is highly standardised and with a high incidence of post-operative air leakage (18,19). Surgery on the lung is furthermore characterised by relatively little bleeding from the lung parenchyma. Pulmonary surgery is however technically challenging due to the respiratory movements of the lung, which complicate any surgical handling of the lung parenchyma including the application of air sealing treatment. Pulmonary lobectomy thus constitutes a suitable and challenging indication for demonstrating the tissue sealing efficacy and safety of fibrin sealant products such as TachoSil.

The inherent potential risk of bias in an open-label trial design was apparently absent since the pre-randomisation subject characteristics were similar for the two treatment groups (see

Sections 12.2.11, 12.3.4). The use of centralised randomisation probably contributed to this by eliminating any potential selection bias (12).

The primary endpoint, duration of postoperative air leakage, has direct clinical relevance for surgeons and hospitals. The secondary endpoint, reduction of intra-operative air leakage, shows the immediate treatment effect, which is important to the surgeon and which also reflects the pharmacodynamic properties of TachoSil. The use of a previously proven scale for clinical grading of intra-operative air leakage intensity (14,20,21) adds to the validity of this endpoint. It may thus be concluded that the efficacy endpoints of this trial provided clinically relevant and robust outcome data.

Trial population

It should be noted that the baseline characteristics of randomised subjects were similar for the treatment groups. Similarity was also present for risk factors for pulmonary surgery and postoperative morbidity, e.g. age, smoking, alcohol consumption and lung function. All subjects had persisting air leakage after lobectomy and primary air sealing by use of stapler (and/or limited suturing). Air leaks after lobectomy needing sealing treatment are present in a large proportion of patients (18,19,20), which makes this trial population clinically relevant.

The age and sex distributions of the trial subjects enable generalisation of the trial conclusions to be valid for all adults, since the age of the subjects was equally distributed below and above 65 years and since females accounted for one third of the trial subjects.

Efficacy

The tissue sealing efficacy of TachoSil was clearly demonstrated in this trial. A previous clinical trial with a similar design but with a population, which included subjects without intra-operative air leakage, showed no statistically significant results for the planned analysis of the primary endpoint. However, supplementary analyses of the sub-population with persistent air leakage following standard lobectomy and primary stapling did show superior results of TachoSil vs. standard surgical treatment of air leaks (2,20). The results of the present trial thus confirm the outcome of the supplementary analyses in the previous trial.

The equal distribution between treatment groups of the type of lung resection performed indicates unbiased randomisation; together with the equal distribution of entry grade air

leakage it furthermore ensured the appropriate background for comparing the two trial treatments. The distribution of the number of TachoSil sponges used per subject was similar to the distribution reported for the previous TachoSil lung trial (2), which indicates similar usage and treatment strategy for TachoSil in the two trials. It appeared that there were fewer treatment rounds used in the standard group compared to the TachoSil group, which can be explained by the surgeon's concern of producing new leakage sites by standard surgical treatment (stapler, sutures). This concern does not apply to the atraumatic application of TachoSil to lung parenchyma.

Rescue treatment following failure to adequately seal alveolar air leaks with trial treatment was used in only two subjects (TachoSil). These subjects were conservatively given the longest recorded air leakage duration (for a standard treatment subject) in the statistical analysis. This approach lowered the overall difference between treatments for the primary endpoint.

There was a noticeable centre effect on the primary endpoint, duration of post-operative air leakage. However, neither differences in the distribution of the type of resection (upper/middle/lower lobe) nor differences in treatment variables (number of TachoSil sponges, use of stapler and type of sutures) could apparently account for the centre effect (Tables 16,18b,19a). Differences in the hospital routines for post-operative patient and drain management as well as subtle differences in surgical techniques for application of intra-operative air sealing treatment might potentially have contributed to the centre effect. However, it should be noted that the trial results showed significant effect despite centre effects.

Air leakage duration was reduced from a median value of 19.5 hours in the standard group to 14.5 hours in the TachoSil group. This non-significant result for the ITT analysis set was found significant (p=0.034) for the exploratory PP analysis, thus indicating a true calculated reduction of leakage duration of approximately 5 hours by use of TachoSil, which is of clear clinical relevance.

The use of Heimlich valve is a standard procedure for prolonged air leakage following lung surgery. However, the use of Heimlich valve precluded assessment of the primary endpoint, which according to the protocol had to be assessed by use of the Sentinel Seal CDU. The

supplementary sensitivity analysis showed that the use of Heimlich valve in nine subjects did not change the trial outcome with respect to the primary endpoint (Table 27).

The results of the additional sub-group analyses are consistent with those of the overall population and demonstrate that TachoSil can be considered efficacious for the sealing of postoperative air leakage in all adult subjects, irrespective of age and gender.

The overall trial results of significantly shorter duration of post-operative air leakage (primary endpoint) and shorter time to chest drain removal (descriptive variable) in TachoSil treated subjects compared to subjects with standard surgical treatment of alveolar air leakage have direct clinical relevance.

Safety

Overall, the frequency, causality and severity of AEs were equally distributed between the two treatment groups and the majority of the events were of mild or moderate severity. The number of non-serious as well as serious AEs considered related to trial treatment was small and equally distributed between the treatments.

Although there were no major differences in the distribution of the most frequent AEs between the two treatment groups, atrial fibrillation was seen with a higher frequency in the TachoSil treated subjects.

Atrial fibrillation (including atrial and supraventricular tachycardia) were seen in 13 TachoSil and five standard treatment subjects. For one standard treatment subject, atrial fibrillation was reported as an SAE of mild severity. Atrial fibrillation is unlisted in the current reference safety information for TachoSil. Cardiac arrhythmia, e.g. atrial fibrillation, premature beats and ventricular arrhythmia, occur in 3.1% to 14.3% of patients after lobectomy. Increased vagal tone, hypoxemia, intra-operative fluid administration of more than 2 litres and intra-operative hypotension are often mentioned as causes of postoperative arrhythmia. Atrial arrhythmia is the most common; 96% occur during the first postoperative week whereas ventricular arrhythmia is rare. The likelihood of arrhythmia increases with advancing age and previous cardiac history. No atrial fibrillation was considered related to trial treatment; all cases of atrial fibrillation were considered related to the underlying disease or to

complications of surgery. The slightly higher incidence of atrial fibrillation in the TachoSil group seems incidental.

15 Overall Conclusion

The primary efficacy endpoint showed TachoSil to be significantly superior to standard surgical treatment in the reduction of postoperative air leakage duration in patients undergoing elective lobectomy of the lung. This result is supported by a significant reduction of intra-operative air leakage intensity in TachoSil compared to standard treatment patients. TachoSil was well tolerated and safe as treatment for reduction of postoperative air leakage in patients undergoing elective lobectomy of the lung.

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Table of Contents

Table 01: Number of Subjects by Centre and Treatment, ITT

Site Name	TachoSil	Standard	Total
Vienna	21	21	42
Leuven	5	6	11
Zürich	3	2	5
Heidelberg	17	17	34
Essen	7	7	14
Freiburg	13	14	27
Odense	18	17	35
Budapest	15	15	30
Milano	13	12	25
Padova	13	15	28
Rome	17	19	36
Göteborg	6	6	12

Program:Table_Subjects_Treatment_Centre.sas, Output:Table_Subjects_Treatment_Centre_ITT.lst, 02MAR09

Table 02: Disposition of Subjects

Number of patients screened: 486

	TACHOSIL		STANDARD		All	
	N	%	N	%	N	%
Randomised	150	100.0	151	100.0	301	100.0
Completed Surgery	148	98.7	151	100.0	299	99.3
Completed Day1 after Surgery	147	98.0	150	99.3	297	98.7
Completed Day2 after Surgery	143	95.3	148	98.0	291	96.7
Completed Day of Drain Removal	146	97.3	149	98.7	295	98.0
Completed Discharge from Hospital	146	97.3	149	98.7	295	98.0
Completed Follow-Up Visit	142	94.7	149	98.7	291	96.7
Discontinued	6	4.0	2	1.3	8	2.7
- Due to Adverse Events	2	1.3	0	0.0	2	0.7
- Due to Non-Compliance	0	0.0	2	1.3	2	0.7
- Due to Other Reasons	4	2.7	0	0.0	4	1.3
ITT	148	98.7	151	100.0	299	99.3
AT	149	99.3	150	99.3	299	99.3
PP	135	90.0	138	91.4	273	90.7

AT = As Treated -Subjects in this analysis set figure under the actual treatment received
which may differ from the IVRS randomised treatment
Only 2 of the 4 subjects that discontinued due to other reasons form part of the AT / ITT analysis sets
Program:Table_disposition.sas, Output:Table_disposition.lst, 02MAR09

Table 03: Demographics and Baseline Characteristics, ITT

	TACHOSIL						STANDARD						All					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
MALE																		
Age (years)	102	64.3	10.0	66.0	33.0	83.0	99	64.8	8.2	65.0	34.0	82.0	201	64.5	9.1	66.0	33.0	83.0
Age > 65	53	71.8	4.6	71.0	66.0	83.0	49	71.2	4.4	70.0	66.0	82.0	102	71.5	4.5	70.0	66.0	83.0
Age <= 65	49	56.1	7.3	57.0	33.0	65.0	50	58.6	6.0	60.0	34.0	65.0	99	57.3	6.8	59.0	33.0	65.0
Weight (kg)	102	80.2	14.3	77.0	52.0	128.0	99	78.2	12.3	77.0	55.0	113.0	201	79.2	13.4	77.0	52.0	128.0
Height (cm)	102	174.0	7.0	175.0	154.0	192.0	99	172.2	6.6	172.0	156.0	192.0	201	173.1	6.8	173.0	154.0	192.0
BMI (kg/m^2)	102	26.5	4.4	26.3	16.8	38.6	99	26.4	4.0	25.9	19.0	38.6	201	26.4	4.2	26.0	16.8	38.6
FEMALE																		
Age (years)	46	62.8	10.3	64.5	36.0	81.0	52	61.8	8.7	64.0	40.0	76.0	98	62.3	9.4	64.5	36.0	81.0
Age > 65	20	71.8	4.8	70.0	66.0	81.0	22	69.7	3.4	69.0	66.0	76.0	42	70.7	4.2	69.5	66.0	81.0
Age <= 65	26	56.0	7.7	57.5	36.0	65.0	30	55.9	6.4	56.5	40.0	65.0	56	55.9	7.0	56.5	36.0	65.0
Weight (kg)	46	63.6	13.0	62.0	42.0	94.0	52	68.0	13.4	67.0	46.0	102.0	98	65.9	13.3	66.0	42.0	102.0
Height (cm)	46	161.5	7.3	162.5	142.0	176.0	52	162.9	7.7	163.0	144.0	178.0	98	162.2	7.5	163.0	142.0	178.0
BMI (kg/m^2)	46	24.3	4.4	23.9	15.2	34.9	52	25.6	4.7	24.6	17.3	37.0	98	25.0	4.6	24.4	15.2	37.0
All																		
Age (years)	148	63.8	10.1	65.0	33.0	83.0	151	63.8	8.5	65.0	34.0	82.0	299	63.8	9.3	65.0	33.0	83.0
Age > 65	73	71.8	4.7	70.0	66.0	83.0	71	70.7	4.2	70.0	66.0	82.0	144	71.3	4.4	70.0	66.0	83.0
Age <= 65	75	56.0	7.4	57.0	33.0	65.0	80	57.6	6.2	59.0	34.0	65.0	155	56.8	6.9	58.0	33.0	65.0
Weight (kg)	148	75.0	15.9	74.0	42.0	128.0	151	74.7	13.6	75.0	46.0	113.0	299	74.9	14.7	74.0	42.0	128.0
Height (cm)	148	170.1	9.1	170.0	142.0	192.0	151	169.0	8.2	170.0	144.0	192.0	299	169.5	8.7	170.0	142.0	192.0
BMI (kg/m^2)	148	25.8	4.5	25.5	15.2	38.6	151	26.1	4.3	25.5	17.3	38.6	299	26.0	4.4	25.5	15.2	38.6

Program:Table_demographics_baseline.sas, Output:Table_demographics_baseline_ITT.lst, 02MAR09

Table 04: Sex Distribution, ITT

	TACHOSIL		STANDARD		All	
	N	%	N	%	N	%
MALE	102	68.9	99	65.6	201	67.2
FEMALE	46	31.1	52	34.4	98	32.8
All	148	100.0	151	100.0	299	100.0

Program:Table_Sexdistribution.sas, Output:Table_Sexdistribution_ITT.lst, 02MAR09

Table 05: Distribution of Race, Smoking and Use of Alcohol, ITT

	TACHOSIL		STANDARD		All	
	N	%	N	%	N	%
Race						
- CAUCASIAN	148	100.0	151	100.0	299	100.0
Smoking						
- YES	47	31.8	47	31.1	94	31.4
- NO	101	68.2	103	68.2	204	68.2
- Missing	-	-	1	0.7	1	0.3
Use of alcohol						
- YES	44	29.7	40	26.5	84	28.1
- NO	101	68.2	108	71.5	209	69.9
- Missing	3	2.0	3	2.0	6	2.0

Program:Table_race_smoke_alcohol.sas, Output:Table_race_smoke_alcohol_ITT.lst, 02MAR09

Table 06: Vital Signs - Blood Pressure, Heart Rate and Respiratory Rate, AT

	TACHOSIL						STANDARD						All					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
SCREENING																		
BP - Systolic	148	134.2	19.3	130	90	210	148	133.5	18.2	130	100	210	296	133.9	18.7	130	90	210
BP - Diastolic	148	77.8	10.2	80	40	105	148	77.8	10.6	80	40	100	296	77.8	10.3	80	40	105
Heart rate	148	77.5	9.1	78	50	110	148	77.0	10.7	77	40	128	296	77.3	9.9	78	40	128
Respiratory rate	122	16.2	2.6	16	10	26	126	15.7	2.2	16	8	23	248	15.9	2.4	16	8	26
DAY 0 PRE-RANDOM																		
BP - Systolic	147	129.5	18.0	130	90	194	149	129.2	15.7	130	90	180	296	129.3	16.9	130	90	194
BP - Diastolic	147	75.6	10.7	80	43	100	149	75.8	11.2	80	50	100	296	75.7	10.9	80	43	100
Heart rate	146	77.3	9.2	78	52	110	145	76.1	9.8	78	50	100	291	76.7	9.5	78	50	110
Respiratory rate	121	17.0	3.3	17	12	40	124	16.1	2.4	16	11	24	245	16.5	2.9	16	11	40
DAY 1																		
BP - Systolic	148	123.3	18.5	120	85	180	149	123.2	17.5	122	72	180	297	123.3	18.0	120	72	180
BP - Diastolic	148	68.4	12.0	70	40	100	149	70.5	11.2	70	45	110	297	69.4	11.6	70	40	110
Heart rate	148	78.2	12.4	80	55	111	148	78.7	10.7	80	50	115	296	78.4	11.6	80	50	115
Respiratory rate	124	17.1	2.9	17	11	32	126	16.8	2.8	16	11	24	250	17.0	2.8	17	11	32
DAY 2																		
BP - Systolic	144	126.0	17.5	120	89	170	147	127.3	18.5	130	90	191	291	126.6	18.0	125	89	191
BP - Diastolic	144	72.7	11.8	70	30	105	147	72.4	11.6	70	44	101	291	72.6	11.7	70	30	105
Heart rate	144	80.5	13.6	79	56	146	147	82.1	12.5	80	55	130	291	81.3	13.1	80	55	146
Respiratory rate	120	17.8	7.8	17	12	96	121	17.0	3.3	16	8	28	241	17.4	6.0	16	8	96
DAY 3																		
BP - Systolic	123	129.9	19.3	130	85	190	134	129.0	18.7	130	95	200	257	129.4	19.0	130	85	200
BP - Diastolic	123	74.3	12.3	71	46	115	134	74.6	11.7	77	40	105	257	74.4	12.0	75	40	115
Heart rate	123	85.8	58.7	80	48	721	134	82.1	11.7	80	55	120	257	83.9	41.4	80	48	721
Respiratory rate	106	17.1	3.7	16	12	30	109	16.7	3.0	16	11	25	215	16.9	3.3	16	11	30
DAY 4																		
BP - Systolic	50	128.9	16.2	129	90	170	57	132.5	20.2	130	90	180	107	130.8	18.5	130	90	180
BP - Diastolic	50	76.1	10.6	80	50	100	57	75.7	10.2	77	55	100	107	75.9	10.4	80	50	100
Heart rate	50	80.6	14.2	80	56	140	57	81.4	10.2	80	60	128	107	81.0	12.2	80	56	140
Respiratory rate	34	16.3	3.8	16	10	30	47	16.5	2.6	16	12	22	81	16.4	3.1	16	10	30

(Continued)

Program:Table_vitalsigns_bp_hr_rr_AT.sas, Output:Table_vitalsigns_bp_hr_rr_AT_AT.lst, 02MAR09

Table 06: Vital Signs - Blood Pressure, Heart Rate and Respiratory Rate, AT

	TACHOSIL						STANDARD						All					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
DAY 5																		
BP - Systolic	36	131.8	19.0	130	95	180	44	129.6	19.2	128	100	180	80	130.6	19.0	130	95	180
BP - Diastolic	36	74.3	10.5	75	50	90	44	75.0	11.1	76	45	90	80	74.7	10.8	75	45	90
Heart rate	36	79.2	9.6	80	56	97	44	82.9	13.9	80	60	132	80	81.2	12.3	80	56	132
Respiratory rate	25	16.4	3.2	16	13	28	35	16.2	2.7	16	12	22	60	16.3	2.9	16	12	28
DAY 6																		
BP - Systolic	21	129.3	16.8	130	100	150	35	129.7	17.1	125	100	180	56	129.5	16.9	125	100	180
BP - Diastolic	21	73.8	12.0	75	50	90	35	76.4	14.1	75	50	130	56	75.4	13.3	75	50	130
Heart rate	21	80.6	11.8	80	64	106	35	82.5	13.9	80	60	129	56	81.8	13.1	80	60	129
Respiratory rate	15	15.6	2.5	16	11	22	29	16.4	3.1	16	12	24	44	16.1	2.9	16	11	24
DAY 7																		
BP - Systolic	13	127.3	19.9	130	90	160	21	135.6	12.4	135	110	160	34	132.4	15.9	130	90	160
BP - Diastolic	13	70.5	12.5	70	50	95	21	78.1	8.3	80	60	90	34	75.2	10.6	76	50	95
Heart rate	13	81.0	12.2	80	66	110	21	80.4	11.8	80	60	100	34	80.6	11.8	80	60	110
Respiratory rate	10	16.1	3.2	16	12	23	17	16.4	3.1	16	12	22	27	16.3	3.1	16	12	23
DAY 8																		
BP - Systolic	8	126.9	15.3	125	110	160	17	136.2	14.3	140	110	160	25	133.2	15.0	130	110	160
BP - Diastolic	8	68.6	11.6	70	50	90	17	79.7	4.1	80	70	90	25	76.2	8.8	80	50	90
Heart rate	8	89.8	12.9	91	70	110	17	78.6	9.5	80	62	96	25	82.2	11.7	80	62	110
Respiratory rate	7	15.9	2.6	16	12	20	14	16.4	2.8	16	12	22	21	16.2	2.7	16	12	22
DAY 9																		
BP - Systolic	8	127.5	10.4	130	110	140	13	129.0	17.4	130	100	162	21	128.4	14.8	130	100	162
BP - Diastolic	8	71.9	7.5	70	60	80	13	75.0	10.0	80	60	90	21	73.8	9.1	70	60	90
Heart rate	8	86.8	15.0	86	70	110	13	78.5	8.6	78	62	92	21	81.6	11.8	78	62	110
Respiratory rate	7	16.6	3.0	18	11	19	11	16.5	3.3	16	12	22	18	16.5	3.1	17	11	22
DAY 10																		
BP - Systolic	6	131.2	13.0	139	110	140	10	130.8	11.8	134	110	140	16	130.9	11.8	138	110	140
BP - Diastolic	6	71.0	6.6	71	60	80	10	75.3	6.2	80	65	80	16	73.7	6.5	73	60	80
Heart rate	7	90.0	14.5	91	70	115	10	77.4	7.1	78	65	88	17	82.6	12.2	80	65	115
Respiratory rate	6	16.3	3.4	17	11	20	9	17.2	3.7	16	12	24	15	16.9	3.5	16	11	24

(Continued)

Program:Table_vitalsigns_bp_hr_rr_AT.sas, Output:Table_vitalsigns_bp_hr_rr_AT_AT.lst, 02MAR09

Table 06: Vital Signs - Blood Pressure, Heart Rate and Respiratory Rate, AT

	TACHOSIL						STANDARD						All					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
DAY 11																		
BP - Systolic	4	142.5	12.6	140	130	160	7	131.4	15.7	120	120	160	11	135.5	15.1	140	120	160
BP - Diastolic	4	75.0	5.8	75	70	80	7	75.7	12.4	70	65	100	11	75.5	10.1	70	65	100
Heart rate	4	80.5	6.6	81	72	88	7	80.3	11.0	80	67	100	11	80.4	9.2	80	67	100
Respiratory rate	4	15.0	3.6	16	11	18	7	15.4	2.5	16	12	20	11	15.3	2.8	16	11	20
DAY 12																		
BP - Systolic	3	138.3	7.6	140	130	145	5	133.6	23.8	140	100	160	8	135.4	18.6	140	100	160
BP - Diastolic	3	76.7	5.8	80	70	80	5	77.0	14.0	70	65	100	8	76.9	11.0	75	65	100
Heart rate	3	89.0	11.3	95	76	96	5	81.4	7.7	80	70	90	8	84.3	9.3	84	70	96
Respiratory rate	3	15.3	3.1	16	12	18	5	15.8	1.5	16	14	18	8	15.6	2.0	16	12	18
DAY 13																		
BP - Systolic	2	130.0	14.1	130	120	140	4	129.5	17.9	129	110	150	6	129.7	15.3	129	110	150
BP - Diastolic	2	70.0	0.0	70	70	70	4	76.3	14.9	75	60	95	6	74.2	12.0	70	60	95
Heart rate	2	79.0	12.7	79	70	88	4	82.3	4.8	82	77	88	6	81.2	7.0	82	70	88
Respiratory rate	2	14.0	0.0	14	14	14	4	15.8	4.5	15	12	22	6	15.2	3.6	14	12	22
DAY 14																		
BP - Systolic	1	130.0	-	130	130	130	5	136.0	16.7	140	110	150	6	135.0	15.2	135	110	150
BP - Diastolic	1	70.0	-	70	70	70	5	76.0	5.5	80	70	80	6	75.0	5.5	75	70	80
Heart rate	1	84.0	-	84	84	84	5	78.0	7.2	80	70	88	6	79.0	6.9	80	70	88
Respiratory rate	1	19.0	-	19	19	19	5	17.2	2.3	18	14	20	6	17.5	2.2	18	14	20
DAY 15																		
BP - Systolic	1	115.0	-	115	115	115	4	127.5	5.0	130	120	130	5	125.0	7.1	130	115	130
BP - Diastolic	1	66.0	-	66	66	66	4	76.3	7.5	75	70	85	5	74.2	7.9	70	66	85
Heart rate	1	96.0	-	96	96	96	4	89.0	8.9	88	80	100	5	90.4	8.3	92	80	100
Respiratory rate	1	18.0	-	18	18	18	4	18.0	2.8	19	14	20	5	18.0	2.4	18	14	20
DAY 16																		
BP - Systolic	1	100.0	-	100	100	100	2	135.0	7.1	135	130	140	3	123.3	20.8	130	100	140
BP - Diastolic	1	50.0	-	50	50	50	2	72.5	3.5	73	70	75	3	65.0	13.2	70	50	75
Heart rate	1	60.0	-	60	60	60	2	80.0	0.0	80	80	80	3	73.3	11.5	80	60	80
Respiratory rate	0	-	-	-	-	-	2	16.0	2.8	16	14	18	2	16.0	2.8	16	14	18

(Continued)

Program:Table_vitalsigns_bp_hr_rr_AT.sas, Output:Table_vitalsigns_bp_hr_rr_AT_AT.lst, 02MAR09

Table 06: Vital Signs - Blood Pressure, Heart Rate and Respiratory Rate, AT

	TACHOSIL						STANDARD						All					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
DAY 17																		
BP - Systolic	-	-	-	-	-	-	2	120.0	0.0	120	120	120	2	120.0	0.0	120	120	120
BP - Diastolic	-	-	-	-	-	-	2	72.5	3.5	73	70	75	2	72.5	3.5	73	70	75
Heart rate	-	-	-	-	-	-	2	86.5	2.1	87	85	88	2	86.5	2.1	87	85	88
Respiratory rate	-	-	-	-	-	-	2	16.5	2.1	17	15	18	2	16.5	2.1	17	15	18
DAY 18																		
BP - Systolic	-	-	-	-	-	-	2	115.0	7.1	115	110	120	2	115.0	7.1	115	110	120
BP - Diastolic	-	-	-	-	-	-	2	70.0	0.0	70	70	70	2	70.0	0.0	70	70	70
Heart rate	-	-	-	-	-	-	2	80.0	0.0	80	80	80	2	80.0	0.0	80	80	80
Respiratory rate	-	-	-	-	-	-	2	17.0	4.2	17	14	20	2	17.0	4.2	17	14	20
DAY 19																		
BP - Systolic	-	-	-	-	-	-	2	115.0	21.2	115	100	130	2	115.0	21.2	115	100	130
BP - Diastolic	-	-	-	-	-	-	2	70.0	14.1	70	60	80	2	70.0	14.1	70	60	80
Heart rate	-	-	-	-	-	-	2	77.5	3.5	78	75	80	2	77.5	3.5	78	75	80
Respiratory rate	-	-	-	-	-	-	2	16.0	2.8	16	14	18	2	16.0	2.8	16	14	18
DAY 20																		
BP - Systolic	-	-	-	-	-	-	2	130.0	0.0	130	130	130	2	130.0	0.0	130	130	130
BP - Diastolic	-	-	-	-	-	-	2	80.0	0.0	80	80	80	2	80.0	0.0	80	80	80
Heart rate	-	-	-	-	-	-	2	87.0	12.7	87	78	96	2	87.0	12.7	87	78	96
Respiratory rate	-	-	-	-	-	-	2	16.0	2.8	16	14	18	2	16.0	2.8	16	14	18
DAY 21																		
BP - Systolic	-	-	-	-	-	-	1	110.0	-	110	110	110	1	110.0	-	110	110	110
BP - Diastolic	-	-	-	-	-	-	1	70.0	-	70	70	70	1	70.0	-	70	70	70
Heart rate	-	-	-	-	-	-	1	90.0	-	90	90	90	1	90.0	-	90	90	90
Respiratory rate	-	-	-	-	-	-	1	20.0	-	20	20	20	1	20.0	-	20	20	20
DRAIN REMOVAL																		
BP - Systolic	142	130.9	19.8	130	89	200	137	127.6	17.6	127	95	180	279	129.3	18.8	130	89	200
BP - Diastolic	142	75.0	11.1	75	46	115	137	74.4	11.0	73	44	110	279	74.7	11.0	74	44	115
Heart rate	142	80.1	12.3	80	55	125	137	80.2	10.9	80	55	116	279	80.1	11.6	80	55	125
Respiratory rate	119	17.7	7.8	16	12	96	113	16.4	2.8	16	11	24	232	17.0	5.9	16	11	96

(Continued)

Program:Table_vitalsigns_bp_hr_rr_AT.sas, Output:Table_vitalsigns_bp_hr_rr_AT_AT.lst, 02MAR09

Table 06: Vital Signs - Blood Pressure, Heart Rate and Respiratory Rate, AT

	TACHOSIL						STANDARD						All					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
DISCHARGE																		
BP - Systolic	135	131.6	17.9	130	90	190	138	129.7	16.1	130	92	188	273	130.6	17.0	130	90	190
BP - Diastolic	135	76.0	10.2	80	42	100	138	74.7	10.0	75	50	110	273	75.4	10.1	80	42	110
Heart rate	135	78.8	9.8	80	53	114	137	80.5	9.3	80	56	115	272	79.7	9.6	80	53	115
Respiratory rate	109	16.3	2.6	16	12	28	107	16.1	2.6	16	10	22	216	16.2	2.6	16	10	28

Program:Table_vitalsigns_bp_hr_rr_AT.sas, Output:Table_vitalsigns_bp_hr_rr_AT_AT.lst, 02MAR09

Table 07: Baseline Physical Examination, AT

	TACHOSIL								STANDARD								All							
	Normal		NCS Abnormal		CS Abnormal		All		Normal		NCS Abnormal		CS Abnormal		All		Normal		NCS Abnormal		CS Abnormal		All	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
EARS, EYES, NOSE, THROAT, NECK	136	92	7	5	5	3	148	100	140	94	7	5	2	1	149	100	276	93	14	5	7	2	297	100
RESPIRATORY SYSTEM	136	91	4	3	9	6	149	100	133	89	4	3	12	8	149	100	269	90	8	3	21	7	298	100
CARDIOVASCULAR SYSTEM	132	89	4	3	13	9	149	100	136	91	2	1	11	7	149	100	268	90	6	2	24	8	298	100
GASTROINTESTINAL SYSTEM INCL. MOUTH	142	96	4	3	2	1	148	100	140	94	2	1	7	5	149	100	282	95	6	2	9	3	297	100
GENITO-URINARY SYSTEM, BREASTS	136	93	8	5	3	2	147	100	140	95	5	3	3	2	148	100	276	94	13	4	6	2	295	100
MUSCULOSKELETAL SYSTEM	132	89	10	7	7	5	149	100	137	92	8	5	4	3	149	100	269	90	18	6	11	4	298	100
CENTRAL AND PERIPHERAL NERVOURS SYSTEM	144	97	4	3	1	1	149	100	148	99	-	-	1	1	149	100	292	98	4	1	2	1	298	100
SKIN	137	93	5	3	6	4	148	100	136	91	4	3	9	6	149	100	273	92	9	3	15	5	297	100
OTHER	138	94	8	5	1	1	147	100	147	99	2	1	-	-	149	100	285	96	10	3	1	0	296	100
All	95	100	-	-	-	-	95	100	103	100	-	-	-	-	103	100	198	100	-	-	-	-	198	100

NCS = Not Clinically Significant CS = Clinically Significant
Program:Table_baseline_physicalexam_AT.sas, Output:Table_baseline_physicalexam_AT.lst, 02MAR09

Table 08: Pulmonary Function before Lobectomy, ITT

	TACHOSIL							STANDARD							All						
	N	NMiss	Mean	Std	Median	Min	Max	N	NMiss	Mean	Std	Median	Min	Max	N	NMiss	Mean	Std	Median	Min	Max
Forced Expiratory Volume - 1 second (ml)	146	2	2477	706.2	2380.0	1050	5000	149	2	2495	765.9	2390.0	103.0	7200	295	4	2486	735.7	2390.0	103.0	7200
Total Lung Capacity (ml)	127	21	6169	1334	6120.0	2300	9720	129	22	6138	1294	6150.0	2520	9780	256	43	6153	1312	6135.0	2300	9780
Residual Volume (ml)	127	21	2654	989.2	2540.0	780.0	7830	127	24	2606	854.4	2470.0	720.0	7150	254	45	2630	922.8	2505.0	720.0	7830

NMISS = Number of missing observations
Program:Table_pulmonary_function_before_lobectomy.sas, Output:Table_pulmonary_function_before_lobectomy_ITT.lst, 02MAR09

Table 09: Chest X-ray- Inflation of the Lung and Presence of Pneumothorax, AT

Inflation of the lung	TACHOSIL		STANDARD		All	
	N	%	N	%	N	%
SCREENING						
FULL	119	79.9	119	79.3	238	79.6
INCOMPLETE	-	0.0	-	-	-	0.0
MISSING	30	20.1	31	20.7	61	20.4
All	149	100.0	150	100.0	299	100.0
DAY 1						
FULL	82	55.4	90	60.4	172	57.9
INCOMPLETE	33	22.3	24	16.1	57	19.2
MISSING	33	22.3	35	23.5	68	22.9
All	148	100.0	149	100.0	297	100.0
DRAIN REMOVAL						
FULL	96	65.3	102	68.9	198	67.1
INCOMPLETE	27	18.4	27	18.2	54	18.3
MISSING	24	16.3	19	12.8	43	14.6
All	147	100.0	148	100.0	295	100.0
AFTER REMOVAL						
FULL	111	77.6	112	77.8	223	77.7
INCOMPLETE	29	20.3	27	18.8	56	19.5
MISSING	3	2.1	5	3.5	8	2.8
All	143	100.0	144	100.0	287	100.0
DISCHARGE						
FULL	89	60.5	90	60.8	179	60.7
INCOMPLETE	23	15.6	22	14.9	45	15.3
MISSING	35	23.8	36	24.3	71	24.1
All	147	100.0	148	100.0	295	100.0
FOLLOW-UP						
FULL	70	49.0	74	50.0	144	49.5
INCOMPLETE	8	5.6	6	4.1	14	4.8
MISSING	65	45.5	68	45.9	133	45.7
All	143	100.0	148	100.0	291	100.0

(continued)

Table 09 (continued)

Presence of pneumothorax	TACHOSIL		STANDARD		All	
	N	%	N	%	N	%
DAY 1						
YES	43	29.1	35	23.5	78	26.3
NO	70	47.3	75	50.3	145	48.8
MISSING	35	23.6	39	26.2	74	24.9
All	148	100.0	149	100.0	297	100.0
DRAIN REMOVAL						
YES	36	24.5	42	28.4	78	26.4
NO	86	58.5	84	56.8	170	57.6
MISSING	25	17.0	22	14.9	47	15.9
All	147	100.0	148	100.0	295	100.0
AFTER REMOVAL						
YES	40	28.0	47	32.6	87	30.3
NO	96	67.1	89	61.8	185	64.5
MISSING	7	4.9	8	5.6	15	5.2
All	143	100.0	144	100.0	287	100.0
DISCHARGE						
YES	27	18.4	31	20.9	58	19.7
NO	82	55.8	81	54.7	163	55.3
MISSING	38	25.9	36	24.3	74	25.1
All	147	100.0	148	100.0	295	100.0
FOLLOW-UP						
YES	9	6.3	8	5.4	17	5.8
NO	67	46.9	70	47.3	137	47.1
MISSING	67	46.9	70	47.3	137	47.1
All	143	100.0	148	100.0	291	100.0

(continued)

Table 09 (continued)

Pneumothorax, details	TACHOSIL				STANDARD				All			
	N	Mean	Min	Max	N	Mean	Min	Max	N	Mean	Min	Max
DAY 1												
Apical gap (cm)	38	2.4	0.0	6.0	31	2.7	0.2	10.0	69	2.6	0.0	10.0
Gap surrounding the lung (cm)	22	0.9	0.0	6.0	10	0.7	0.0	3.0	32	0.9	0.0	6.0
DRAIN REMOVAL												
Apical gap (cm)	32	1.7	0.0	5.0	36	1.8	0.0	5.0	68	1.8	0.0	5.0
Gap surrounding the lung (cm)	14	0.6	0.0	5.0	13	1.3	0.0	9.0	27	1.0	0.0	9.0
AFTER REMOVAL												
Apical gap (cm)	38	1.7	0.0	5.0	40	1.7	0.0	5.0	78	1.7	0.0	5.0
Gap surrounding the lung (cm)	17	0.9	0.0	5.0	16	0.6	0.0	2.0	33	0.8	0.0	5.0
DISCHARGE												
Apical gap (cm)	24	1.6	0.0	5.0	28	1.9	0.1	5.7	52	1.8	0.0	5.7
Gap surrounding the lung (cm)	9	1.7	0.0	5.0	11	0.6	0.0	2.0	20	1.1	0.0	5.0
FOLLOW-UP												
Apical gap (cm)	9	2.5	0.5	5.0	7	2.3	1.0	5.0	16	2.4	0.5	5.0
Gap surrounding the lung (cm)	5	1.0	0.0	4.0	5	0.2	0.0	1.0	10	0.6	0.0	4.0

Program:Table_chestxray_inflation_of_lung_AT.sas, Output:Table_chestxray_inflation_of_lung_AT.lst, 02MAR09

Table 10a: Past and Concomitant Illnesses by System Organ Class, AT

System Organ Class	Tachosil n	Tachosil %	Tachosil E	Standard n	Standard %	Standard E	Total n	Total %	Total E
Past illnesses									
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	132	88.6	152	133	88.7	164	265	88.6	316
Surgical and medical procedures	46	30.9	52	47	31.3	66	93	31.1	118
Infections and infestations	8	5.4	10	12	8.0	16	20	6.7	26
Cardiac disorders	6	4.0	6	8	5.3	9	14	4.7	15
Gastrointestinal disorders	5	3.4	6	8	5.3	8	13	4.3	14
Vascular disorders	3	2.0	3	10	6.7	12	13	4.3	15
Hepatobiliary disorders	4	2.7	5	4	2.7	5	8	2.7	10
Respiratory, thoracic and mediastinal disorders	4	2.7	4	4	2.7	4	8	2.7	8
Nervous system disorders	5	3.4	5	2	1.3	2	7	2.3	7
Renal and urinary disorders	1	0.7	1	4	2.7	4	5	1.7	5
General disorders and administration site conditions	3	2.0	3	1	0.7	2	4	1.3	5
Musculoskeletal and connective tissue disorders	1	0.7	1	2	1.3	2	3	1.0	3
Psychiatric disorders	2	1.3	2	1	0.7	1	3	1.0	3
Reproductive system and breast disorders	3	2.0	3	.	.	.	3	1.0	3
Eye disorders	2	1.3	3	.	.	.	2	0.7	3
Injury, poisoning and procedural complications	.	.	.	2	1.3	2	2	0.7	2
Endocrine disorders	1	0.7	1	.	.	.	1	0.3	1
Investigations	1	0.7	1	.	.	.	1	0.3	1
Metabolism and nutrition disorders	.	.	.	1	0.7	1	1	0.3	1
Pregnancy, puerperium and perinatal conditions	1	0.7	1	.	.	.	1	0.3	1
Total	139	93.3	259	136	90.7	298	275	92.0	557

n = number of subjects with the event, % = number with event as % of all, E = number of events
Program:Table_concomitant_illness_AT.sas, Output:Table_concomitant_illness_AT_a.lst, 02MAR09

Table 10a: Past and Concomitant Illnesses by System Organ Class, AT

System Organ Class	Tachosil			Standard			Total		
	n	%	E	n	%	E	n	%	E
Concomitant illnesses									
Vascular disorders	76	51.0	92	76	50.7	90	152	50.8	182
Metabolism and nutrition disorders	43	28.9	59	43	28.7	46	86	28.8	105
Respiratory, thoracic and mediastinal disorders	39	26.2	43	41	27.3	45	80	26.8	88
Cardiac disorders	29	19.5	35	30	20.0	39	59	19.7	74
Gastrointestinal disorders	17	11.4	20	27	18.0	32	44	14.7	52
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	18	12.1	26	25	16.7	31	43	14.4	57
Musculoskeletal and connective tissue disorders	21	14.1	23	13	8.7	20	34	11.4	43
Reproductive system and breast disorders	17	11.4	17	14	9.3	14	31	10.4	31
Psychiatric disorders	16	10.7	17	13	8.7	13	29	9.7	30
Immune system disorders	7	4.7	9	15	10.0	19	22	7.4	28
Infections and infestations	12	8.1	12	10	6.7	10	22	7.4	22
Renal and urinary disorders	15	10.1	17	7	4.7	8	22	7.4	25
Endocrine disorders	10	6.7	11	11	7.3	11	21	7.0	22
Nervous system disorders	8	5.4	9	9	6.0	11	17	5.7	20
Hepatobiliary disorders	5	3.4	5	7	4.7	8	12	4.0	13
Investigations	9	6.0	9	.	.	.	9	3.0	9
Surgical and medical procedures	4	2.7	4	5	3.3	5	9	3.0	9
Eye disorders	4	2.7	4	4	2.7	4	8	2.7	8
Injury, poisoning and procedural complications	4	2.7	4	2	1.3	2	6	2.0	6
Blood and lymphatic system disorders	1	0.7	1	4	2.7	4	5	1.7	5
Skin and subcutaneous tissue disorders	3	2.0	3	2	1.3	2	5	1.7	5
Ear and labyrinth disorders	1	0.7	1	3	2.0	3	4	1.3	4
General disorders and administration site conditions	1	0.7	1	1	0.7	2	2	0.7	3
Congenital, familial and genetic disorders	.	.	.	1	0.7	1	1	0.3	1
Total	121	81.2	422	129	86.0	420	250	83.6	842

n = number of subjects with the event, % = number with event as % of all, E = number of events
Program:Table_concomitant_illness_AT.sas, Output:Table_concomitant_illness_AT_a.lst, 02MAR09

Table 10b: Number of Concomitant Illnesses by Treatment, AT

	Number of concomitant illnesses													
	1	2	3	4	5	6	7	8	9	10	11	13	14	All
-														
TACHOSIL	24	27	19	17	16	6	4	3	2	2	-	1	-	121
STANDARD	30	32	22	17	9	6	5	4	1	1	1	-	1	129
All	54	59	41	34	25	12	9	7	3	3	1	1	1	250

Program:Table_concomitant_illness_AT.sas, Output:Table_concomitant_illness_AT_b.lst, 02MAR09

Table 11: Number of Patients with Concomitant Medication, AT

	Tachosil			Standard			Total		
	n	%	E	n	%	E	n	%	E
Number of patients receiving concomitant medication	121	81.2	535	136	90.7	559	257	86.0	1094

n = number of subjects with the event, % = number with event as % of all, E = number of events
Program:Tab_concmed_AT.sas, Output:Tab_concmed_AT.lst, 02MAR09

Table 12: Laboratory Test Parameters- Normal Ranges

			Erythrocyte Count (10^12/L)			Haematocrit result (ratio)			Haemoglobin result (g/dl)			Leukocyte Count (10^9/L)		
Laboratory	Centre	Gender	Age range	Lower	Upper	Age range	Lower	Upper	Age range	Lower	Upper	Age range	Lower	Upper
AUT004	Vienna	Female	18-100	3.80	5.20	18-100	0.35	0.47	18-100	12.00	16.00	18-100	4.00	10.00
		Male		4.40	5.80		0.40	0.52		13.50	18.00		4.00	10.00
BEL002	Leuven	Female	18-100	3.90	6.00	18-100	0.37	0.47	18-100	12.00	16.00	18-100	4.00	10.00
		Male		3.90	6.00		0.40	0.54		14.00	18.00		4.00	10.00
CHE001	Zürich	Female	18-100	3.90	5.20	18-100	0.35	0.46	18-100	11.70	15.30	18-100	3.00	9.60
		Male		4.20	5.70		0.40	0.50		13.40	17.00		3.00	9.60
DEU015	Heidelberg	Female	18-100	4.40	6.00	18-100	0.37	0.46	18-100	12.00	16.00	18-100	4.30	10.90
		Male		4.40	6.00		0.38	0.57		14.00	18.00		4.30	10.90
DEU016	Essen	Female	18-100	3.90	5.40	18-100	0.36	0.47	18-100	12.00	16.00	18-100	4.00	9.00
		Male		4.50	6.20		0.40	0.54		14.00	18.00		4.00	9.00
DEU017	Freiburg	Female	18-100	4.20	6.30	18-100	0.37	0.52	18-100	12.00	18.00	18-100	4.30	10.00
		Male		4.20	6.30		0.37	0.52		12.00	18.00		4.30	10.00
DNK001	Odense	Female	18-100	3.60	5.10	18-100	0.34	0.44	18-100	11.29	16.13	15-100	3.00	10.00
		Male		4.20	5.50		0.38	0.48		12.90	17.74		3.00	10.00
HUN001	Budapest	Female	18-100	4.04	5.48	18-100	0.38	0.48	18-100	12.20	16.20	18-100	4.60	10.20
		Male		4.69	6.13		0.44	0.54		14.10	18.10		4.60	10.20
ITA001	Milano	Female	19-100	4.00	5.20	18-100	0.35	0.47	18-100	12.00	16.00	18-100	4.00	11.00
		Male		4.50	5.90		0.40	0.54	19-100	13.50	17.50	18-100	4.00	11.00
ITA002	Padova	Female	18-100	4.31	5.10	18-100	0.36	0.45	18-100	12.30	15.30	18-100	4.40	11.00
		Male		4.50	5.90		0.41	0.50		14.00	17.50		4.40	11.00
ITA003	Rome	Female	18-100	4.50	5.90	18-100	0.41	0.50	18-100	14.00	17.50	18-100	4.00	10.00
		Male		4.50	5.90		0.41	0.50		14.00	17.50		4.00	10.00
SWE001	Göteborg	Female	18-100	3.94	5.16	18-100	0.35	0.46	18-100	11.70	15.30	18-100	3.50	8.80
		Male		4.25	5.71		0.40	0.50		13.40	17.00		3.50	8.80

(continued)

Program:Table_laboratory_normal_ranges.sas, Output:Table_laboratory_normal_ranges.lst, 02MAR09

Table 12 (continued)

Laboratory	Centre	Gender	Platelet Count (10^9/L) Age range	Platelet Count (10^9/L) Lower	Platelet Count (10^9/L) Upper	INR result (INR) Age range	INR result (INR) Lower	INR result (INR) Upper	pCO2 result (mm HG) Age range	pCO2 result (mm HG) Lower	pCO2 result (mm HG) Upper
AUT004	Vienna	Female	18-100	150.0	350.0	18-100	1.00	4.50	18-100	32.00	46.00
		Male		150.0	350.0		1.00	4.50		32.00	46.00
BEL002	Leuven	Female	18-100	150.0	450.0	18-100	0.88	1.18	18-100	32.00	45.00
		Male		150.0	450.0		0.88	1.18		35.00	48.00
CHE001	Zürich	Female	18-100	143.0	400.0	18-100	0.00	1.19	18-100	35.03	45.00
		Male		143.0	400.0		0.00	1.19		35.03	45.00
DEU015	Heidelberg	Female	18-100	140.0	440.0	18-100	0.80	1.20	18-100	32.00	45.00
		Male		140.0	440.0		0.80	1.20		35.00	48.00
DEU016	Essen	Female	18-100	150.0	450.0	18-100	0.85	1.15	18-100	36.00	44.00
		Male		150.0	450.0		0.85	1.15		36.00	44.00
DEU017	Freiburg	Female	18-100	140.0	400.0	18-100	0.85	1.15	18-100	35.00	45.00
		Male		140.0	400.0		0.85	1.15		35.00	45.00
DNK001	Odense	Female	18-100	120.0	400.0	18-100	0.70	1.30	18-100	32.25	42.75
		Male		120.0	400.0		0.70	1.30		35.25	45.00
HUN001	Budapest	Female	18-100	142.0	424.0	18-100	1.00	1.16	18-100	31.95	41.93
		Male		142.0	424.0		1.00	1.16		34.95	44.85
ITA001	Milano	Female	18-100	140.0	450.0	18-100	0.80	1.20	18-100	35.00	45.00
		Male		140.0	450.0		0.80	1.20		35.00	45.00
ITA002	Padova	Female	18-100	150.0	450.0	18-100	0.88	1.13	18-100	35.00	45.00
		Male		150.0	450.0		0.88	1.13		35.00	45.00
ITA003	Rome	Female	18-100	130.0	400.0	18-100	0.90	1.20	18-100	35.00	45.00
		Male		130.0	400.0		0.90	1.20		35.00	45.00
SWE001	Göteborg	Female	18-100	165.0	387.0	18-100	0.00	1.19	18-100	33.00	45.00
		Male		145.0	348.0		0.00	1.19		33.00	45.00

Program:Table_laboratory_normal_ranges.sas, Output:Table_laboratory_normal_ranges.lst, 02MAR09

Table 12 (continued)

Laboratory	Centre	Gender	pO2 result (mm HG) Age range	Lower	Upper
AUT004	Vienna	Female	18-100	71.00	104.0
		Male		71.00	104.0
BEL002	Leuven	Female	18- 70	80.00	108.0
		Male		80.00	108.0
		Female	71- 80	70.00	108.0
		Male		70.00	108.0
		Female	81-100	60.00	108.0
		Male		60.00	108.0
CHE001	Zürich	Female	18-100	90.01	99.76
		Male		90.01	99.76
DEU015	Heidelberg	Female	18-100	83.00	108.0
		Male		83.00	108.0
DEU016	Essen	Female	18-100	67.00	95.00
		Male		67.00	95.00
DEU017	Freiburg	Female	18-100	80.00	100.0
		Male		80.00	100.0
DNK001	Odense	Female	0- 40	83.26	108.0
		Male		83.26	108.0
		Female	41-100	72.01	102.8
		Male		72.01	102.8
HUN001	Budapest	Female	18-100	74.86	99.76
		Male		74.86	99.76
ITA001	Milano	Female	18-100	80.00	100.0
		Male		80.00	100.0
ITA002	Padova	Female	18-100	80.00	100.0
		Male		80.00	100.0
ITA003	Rome	Female	18-100	80.00	100.0
		Male		80.00	100.0
SWE001	Göteborg	Female	18-100	79.51	103.5
		Male		79.51	103.5

Program:Table_laboratory_normal_ranges.sas, Output:Table_laboratory_normal_ranges.lst, 02MAR09

Table 13a: Laboratory Tests - Descriptive Statistics, AT

	TACHOSIL						STANDARD					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Haemoglobin (g/dl)												
SCREENING	145	13.6	1.6	13.6	8.8	18.6	146	13.7	1.4	13.7	9.7	17.0
DAY 1	138	12.2	1.6	12.3	7.9	16.5	138	12.2	1.4	12.2	8.9	16.1
DISCHARGE	112	12.0	1.7	12.0	8.4	16.6	111	11.8	1.5	11.6	8.0	15.7
Haemotocrit (ratio)												
SCREENING	136	0.4	0.1	0.4	0.3	0.9	131	0.4	0.0	0.4	0.3	0.5
DAY 1	123	0.4	0.0	0.4	0.2	0.5	123	0.4	0.0	0.4	0.3	0.5
DISCHARGE	103	0.4	0.0	0.4	0.3	0.5	103	0.4	0.0	0.4	0.3	0.5
Erythrocyte count (10^12/L)												
SCREENING	128	4.5	0.5	4.5	3.4	6.0	128	4.5	0.4	4.6	3.1	5.6
DAY 1	122	4.0	0.5	4.1	2.4	5.3	123	4.0	0.5	4.0	3.0	5.1
DISCHARGE	103	4.0	0.5	4.0	2.7	5.2	101	3.9	0.5	4.0	2.8	5.3
Platelet count (10^9/L)												
SCREENING	144	278.3	95.9	262.5	147.0	910.0	144	265.6	73.9	256.5	99.0	478.0
DAY 1	127	235.3	73.7	228.0	117.0	509.0	128	228.1	62.1	230.5	67.0	392.0
DISCHARGE	105	326.0	101.4	312.0	70.0	626.0	103	326.5	116.0	306.0	70.0	674.0
Leukocyte count (10^9/L)												
SCREENING	145	8.0	2.7	7.4	2.6	19.4	147	8.1	2.5	7.8	3.7	21.1
DAY 1	129	11.2	3.0	11.1	5.3	20.2	128	12.2	4.2	11.2	4.0	29.3
DISCHARGE	115	8.9	2.6	8.5	4.6	17.8	109	8.8	2.7	8.3	4.6	21.0
pO2 (mm HG)												
SCREENING	122	83.6	38.5	77.1	54.8	425.3	116	82.4	24.1	78.0	36.0	249.0
DAY 1	58	89.3	26.5	89.3	11.3	188.0	63	87.2	28.5	82.0	11.5	169.0
DISCHARGE	40	77.8	11.4	78.7	39.6	106.0	41	77.2	17.1	77.2	32.2	115.0
pCO2 (mm HG)												
SCREENING	122	39.0	6.8	38.8	31.4	91.0	116	38.4	4.2	38.0	29.2	54.0
DAY 1	57	38.6	5.1	38.8	29.7	62.0	63	40.4	6.8	39.0	30.0	76.1
DISCHARGE	40	38.2	7.1	37.7	31.0	77.5	42	39.9	9.5	38.2	29.6	87.4
INR												
SCREENING	137	1.0	0.1	1.0	0.8	1.3	128	1.0	0.1	1.0	0.4	1.8
DAY 1	70	1.1	0.1	1.1	0.9	1.4	77	1.1	0.1	1.1	0.9	1.4

(Continued)

Program:Table_laboratory_tests_descriptive_AT.sas, Output:Table_laboratory_tests_descriptive_AT_a.lst, 02MAR09

Table 13a: Laboratory Tests - Descriptive Statistics, AT

	TACHOSIL						STANDARD					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
INR												
DISCHARGE	55	1.1	0.5	1.0	0.9	4.4	58	1.1	0.2	1.0	0.8	2.4

Program:Table_laboratory_tests_descriptive_AT.sas, Output:Table_laboratory_tests_descriptive_AT_a.lst, 02MAR09

Table 13b: Standardised Laboratory Tests - Descriptive Statistics , AT

Laboratory values standardised using the z-values method

	TACHOSIL						STANDARD					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Haemoglobin												
SCREENING	145	0.1	0.4	0.1	-1.5	1.3	146	0.1	0.4	0.2	-1.2	0.9
DAY 1	138	-0.2	0.4	-0.2	-1.4	0.7	138	-0.2	0.4	-0.2	-1.3	0.6
DISCHARGE	112	-0.3	0.4	-0.3	-1.6	0.8	111	-0.4	0.5	-0.3	-1.6	0.7
Haemotocrit												
SCREENING	136	0.2	0.6	0.2	-1.4	4.2	131	0.2	0.4	0.2	-1.2	1.0
DAY 1	123	-0.2	0.4	-0.2	-2.5	0.8	123	-0.2	0.4	-0.1	-1.4	0.7
DISCHARGE	103	-0.3	0.5	-0.3	-1.5	0.7	103	-0.3	0.5	-0.3	-1.6	0.7
Erythrocyte count												
SCREENING	128	0.1	0.3	0.1	-0.8	1.1	128	0.2	0.3	0.2	-1.0	1.1
DAY 1	122	-0.2	0.3	-0.2	-1.2	0.6	123	-0.2	0.3	-0.2	-1.0	0.8
DISCHARGE	103	-0.2	0.3	-0.2	-1.3	0.7	101	-0.3	0.4	-0.2	-1.3	0.6
Platelet count												
SCREENING	144	0.5	0.4	0.4	-0.0	2.8	144	0.5	0.3	0.4	-0.3	1.3
DAY 1	127	0.4	0.3	0.3	-0.2	1.4	128	0.3	0.2	0.3	-0.4	0.9
DISCHARGE	105	0.7	0.4	0.7	-0.3	1.6	103	0.7	0.4	0.6	-0.4	1.7
Leukocyte count												
SCREENING	145	0.7	0.5	0.6	-0.3	3.1	147	0.7	0.4	0.6	-0.1	2.9
DAY 1	129	1.2	0.5	1.2	0.1	3.1	128	1.3	0.7	1.2	-0.0	4.2
DISCHARGE	115	0.8	0.5	0.7	0.1	2.6	109	0.8	0.5	0.7	0.1	3.3
pO2												
SCREENING	122	0.2	1.4	-0.1	-3.6	11.5	116	0.2	1.1	0.0	-2.2	7.4
DAY 1	58	0.4	0.9	0.5	-2.0	3.1	63	0.2	1.1	0.1	-3.4	3.2
DISCHARGE	40	-0.1	0.5	-0.0	-2.0	1.3	41	-0.1	0.8	-0.2	-2.4	1.6
pCO2												
SCREENING	122	0.4	0.7	0.4	-0.4	5.6	116	0.4	0.4	0.3	-0.5	1.9
DAY 1	57	0.4	0.5	0.3	-0.6	2.7	63	0.5	0.6	0.4	-0.6	3.2
DISCHARGE	40	0.3	0.7	0.3	-0.4	4.3	42	0.5	0.9	0.3	-0.5	5.2
INR												
SCREENING	137	0.4	0.3	0.5	0.0	2.1	128	0.4	0.4	0.4	-2.0	1.5

(Continued)

Program:Table_laboratory_tests_descriptive_AT.sas, Output:Table_laboratory_tests_descriptive_AT_b.lst, 02MAR09

Table 13b: Standardised Laboratory Tests - Descriptive Statistics , AT
Laboratory values standardised using the z-values method

	TACHOSIL						STANDARD					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
INR												
DAY 1	70	0.6	0.4	0.6	0.0	1.7	77	0.5	0.4	0.6	-0.0	1.8
DISCHARGE	55	0.6	0.5	0.5	0.0	3.7	58	0.5	0.4	0.4	0.0	2.8

Program:Table_laboratory_tests_descriptive_AT.sas, Output:Table_laboratory_tests_descriptive_AT_b.lst, 02MAR09

Table 14: Laboratory Tests - Change from Baseline, AT

	TACHOSIL			STANDARD			
	N	Mean change	StdErr	N	Mean change	StdErr	P-value*
Erythrocyte count (10^12/L)							
Day 1- Baseline	119	-0.48	0.03	120	-0.52	0.04	0.5041
Discharge - Baseline	100	-0.57	0.04	98	-0.60	0.04	0.7218
Haemoglobin (g/dl)							
Day 1- Baseline	135	-1.49	0.11	134	-1.51	0.10	0.7120
Discharge - Baseline	109	-1.73	0.15	107	-1.87	0.12	0.6950
Haemotocrit (ratio)							
Day 1- Baseline	120	-0.05	0.01	119	-0.04	0.00	0.9724
Discharge - Baseline	100	-0.06	0.01	98	-0.05	0.00	0.9565
INR							
Day 1- Baseline	69	0.08	0.01	70	0.05	0.02	0.1690
Discharge - Baseline	53	0.09	0.07	53	0.02	0.03	0.1816
Leukocyte count (10^9/L)							
Day 1- Baseline	126	3.34	0.27	125	4.10	0.34	0.0910
Discharge - Baseline	112	0.73	0.24	106	0.94	0.25	0.4431
Platelet count (10^9/L)							
Day 1- Baseline	124	-34.98	3.58	124	-31.85	3.22	0.6529
Discharge - Baseline	102	60.52	7.82	99	73.07	9.41	0.6908
pCO2 (mm HG)							
Day 1- Baseline	56	0.70	0.77	60	2.69	0.89	0.2009
Discharge - Baseline	40	-0.00	1.08	41	-0.06	0.96	0.6985
pO2 (mm HG)							
Day 1- Baseline	57	10.93	4.15	60	4.80	4.02	0.1702
Discharge - Baseline	40	-3.55	3.45	40	-8.19	4.40	0.4443

*: Mann-Whitney's rank sum test for differences between treatments
Program:Table_laboratory_change_from_baseline_AT.sas, Output:Table_laboratory_change_from_baseline_AT.lst, 02MAR09

Table 15: Operation variables: Thoracic Incision and Lymph Adenectomy, AT

Centre	Treatment Group	Thoracic Incision: Anterolateral	Thoracic Incision: Posterolateral	Lymph Adenectomy: Yes	Lymph Adenectomy: No
Vienna	Standard	21 (100%)	0 (0%)	21 (100%)	0 (0%)
	Tachosil	21 (100%)	0 (0%)	21 (100%)	0 (0%)
Leuven	Standard	1 (17%)	5 (83%)	6 (100%)	0 (0%)
	Tachosil	0 (0%)	5 (100%)	5 (100%)	0 (0%)
Zürich	Standard	2 (100%)	0 (0%)	2 (100%)	0 (0%)
	Tachosil	3 (100%)	0 (0%)	3 (100%)	0 (0%)
Heidelberg	Standard	17 (100%)	0 (0%)	17 (100%)	0 (0%)
	Tachosil	17 (100%)	0 (0%)	17 (100%)	0 (0%)
Essen	Standard	7 (100%)	0 (0%)	7 (100%)	0 (0%)
	Tachosil	7 (100%)	0 (0%)	7 (100%)	0 (0%)
Freiburg	Standard	14 (100%)	0 (0%)	14 (100%)	0 (0%)
	Tachosil	13 (100%)	0 (0%)	13 (100%)	0 (0%)
Odense	Standard	0 (0%)	17 (100%)	17 (100%)	0 (0%)
	Tachosil	0 (0%)	18 (100%)	18 (100%)	0 (0%)
Budapest	Standard	1 (7%)	14 (93%)	10 (67%)	5 (33%)
	Tachosil	3 (20%)	12 (80%)	13 (87%)	2 (13%)
Milano	Standard	12 (100%)	0 (0%)	11 (92%)	1 (8%)
	Tachosil	13 (100%)	0 (0%)	13 (100%)	0 (0%)
Padova	Standard	0 (0%)	14 (100%)	14 (100%)	0 (0%)
	Tachosil	0 (0%)	14 (100%)	14 (100%)	0 (0%)
Rome	Standard	0 (0%)	19 (100%)	19 (100%)	0 (0%)
	Tachosil	0 (0%)	17 (100%)	16 (94%)	1 (6%)
Göteborg	Standard	6 (100%)	0 (0%)	2 (33%)	4 (67%)
	Tachosil	6 (100%)	0 (0%)	4 (67%)	2 (33%)

Program:Table_operation_ThoracicIncision_LymphAdenectomy_AT.sas, Output:Table_operation_ThoracicIncision_LymphAdenectomy_AT.lst, 02MAR09

Table 15: Operation variables: Thoracic Incision and Lymph Adenectomy, AT

Centre	Treatment Group	Thoracic Incision		Lymph Adenectomy	
		Anterolateral	Posterolateral	Yes	No
Total	Standard	81 (54%)	69 (46%)	140 (93%)	10 (7%)
	Tachosil	83 (56%)	66 (44%)	144 (97%)	5 (3%)

Program:Table_operation_ThoracicIncision_LymphAdenectomy_AT.sas, Output:Table_operation_ThoracicIncision_LymphAdenectomy_AT.lst, 02MAR09

Table 16: Operation of the Lung - Type of Resection, AT

		RIGHT UPPER LOBECTOMY		RIGHT LOWER LOBECTOMY		LEFT UPPER LOBECTOMY		LEFT LOWER LOBECTOMY		MIDDLE LOBE LOBECTOMY		UPPER BILOBECTOMY		LOWER BILOBECTOMY		All	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Vienna	TACHOSIL	8	38.1	2	9.5	6	28.6	4	19.0	-	-	-	-	1	4.8	21	100.0
	STANDARD	12	57.1	3	14.3	3	14.3	2	9.5	1	4.8	-	-	-	-	21	100.0
Leuven	TACHOSIL	1	20.0	2	40.0	-	-	1	20.0	-	-	-	-	1	20.0	5	100.0
	STANDARD	1	16.7	1	16.7	1	16.7	2	33.3	1	16.7	-	-	-	-	6	100.0
Zürich	TACHOSIL	1	33.3	-	-	1	33.3	-	-	1	33.3	-	-	-	-	3	100.0
	STANDARD	-	-	1	50.0	-	-	1	50.0	-	-	-	-	-	-	2	100.0
Heidelberg	TACHOSIL	3	17.6	3	17.6	6	35.3	3	17.6	2	11.8	-	-	-	-	17	100.0
	STANDARD	8	47.1	2	11.8	5	29.4	-	-	2	11.8	-	-	-	-	17	100.0
Essen	TACHOSIL	1	14.3	-	-	1	14.3	4	57.1	-	-	-	-	1	14.3	7	100.0
	STANDARD	1	14.3	-	-	5	71.4	1	14.3	-	-	-	-	-	-	7	100.0
Freiburg	TACHOSIL	4	30.8	4	30.8	3	23.1	1	7.7	-	-	-	-	1	7.7	13	100.0
	STANDARD	4	28.6	4	28.6	2	14.3	3	21.4	-	-	-	-	1	7.1	14	100.0
Odense	TACHOSIL	10	55.6	3	16.7	1	5.6	2	11.1	-	-	-	-	2	11.1	18	100.0
	STANDARD	7	41.2	2	11.8	2	11.8	2	11.8	1	5.9	2	11.8	1	5.9	17	100.0
Budapest	TACHOSIL	9	60.0	-	-	3	20.0	2	13.3	1	6.7	-	-	-	-	15	100.0
	STANDARD	5	33.3	2	13.3	4	26.7	4	26.7	-	-	-	-	-	-	15	100.0
Milano	TACHOSIL	5	38.5	1	7.7	3	23.1	2	15.4	2	15.4	-	-	-	-	13	100.0
	STANDARD	4	33.3	3	25.0	3	25.0	1	8.3	1	8.3	-	-	-	-	12	100.0
Padova	TACHOSIL	5	35.7	1	7.1	6	42.9	2	14.3	-	-	-	-	-	-	14	100.0
	STANDARD	3	21.4	2	14.3	5	35.7	2	14.3	1	7.1	-	-	1	7.1	14	100.0
Rome	TACHOSIL	4	23.5	4	23.5	4	23.5	5	29.4	-	-	-	-	-	-	17	100.0
	STANDARD	4	21.1	3	15.8	6	31.6	5	26.3	-	-	1	5.3	-	-	19	100.0
Göteborg	TACHOSIL	4	66.7	1	16.7	-	-	-	-	1	16.7	-	-	-	-	6	100.0
	STANDARD	1	25.0	-	-	2	50.0	-	-	1	25.0	-	-	-	-	4	100.0
All	TACHOSIL	55	36.9	21	14.1	34	22.8	26	17.4	7	4.7	-	-	6	4.0	149	100.0
	STANDARD	50	33.8	23	15.5	38	25.7	23	15.5	8	5.4	3	2.0	3	2.0	148	100.0

Program:Table_type_of_resection_AT.sas, Output:Table_type_of_resection_AT.lst, 02MAR09

Table 17: Intensity of Air Leakage at Randomisation, ITT

	TACHOSIL		STANDARD		All	
	N	%	N	%	N	%
GRADE 1	76	51.4	72	47.7	148	49.5
GRADE 2	72	48.6	78	51.7	150	50.2
Missing	-	-	1	0.7	1	0.3
All	148	100.0	151	100.0	299	100.0

Program:Table_intensity_of_air_leakage.sas, Output:Table_intensity_of_air_leakage_ITT.lst, 02MAR09

Table 18a: Drug Accountability: Number of TachoSil Sponges Used, by Number of Treatment Rounds, AT

	Total number of TachoSil sponges used											
	1		2		3		4		5		All	
	N	%	N	%	N	%	N	%	N	%	N	%
Number of treatment rounds												
1 only	79	53.0	32	21.5	16	10.7	1	0.7	1	0.7	129	86.6
More than 1	-	-	10	6.7	8	5.4	2	1.3	-	-	20	13.4
Total	79	53.0	42	28.2	24	16.1	3	2.0	1	0.7	149	100

Program:Table_drug_accountibility_AT.sas, Output:Table_drug_accountibility_AT_a.lst, 02MAR09

Table 18b: Drug Accountability: Number of TachoSil Sponges Used, by Centre, AT

Centre	Total no. of sponges used	N	Mean	Std	Min	Max
Vienna	51	21	2.4	0.93	1	5
Leuven	12	5	2.4	0.89	1	3
Zürich	4	3	1.3	0.58	1	2
Heidelberg	19	17	1.1	0.49	1	3
Essen	9	7	1.3	0.49	1	2
Freiburg	36	13	2.8	0.44	2	3
Odense	23	18	1.3	0.57	1	3
Budapest	19	15	1.3	0.46	1	2
Milano	21	13	1.6	0.65	1	3
Padova	20	14	1.4	0.76	1	3
Rome	24	17	1.4	0.51	1	2
Göteborg	14	6	2.3	1.37	1	4
Total	252	149	1.7	0.86	1	5

Program:Table_drug_accountibility_AT.sas, Output:Table_drug_accountibility_AT_b.lst, 02MAR09

Table 19a: Type of Standard Surgical Treatment, AT

1st Treatment

Centre	N	No additional treatment	Suturing method		Suturing thread				Diameter of suture			Stapler	Other
			Singular	Continuous	PDS	Proline	Vicryle	Other	3.0	4.0	5.0		
Vienna	21	3 (14%)	-	18 (86%)	17	-	1	-	1	17	-	-	-
Leuven	6	5 (83%)	1 (17%)	-	1	-	-	-	1	-	-	-	-
Zürich	2	2 (100%)	-	-	-	-	-	-	-	-	-	-	-
Heidelberg	17	-	2 (12%)	13 (76%)	-	17	-	-	1	17	-	-	1 (6%)
Essen	7	-	1 (14%)	6 (86%)	-	5	2	-	5	2	-	-	-
Freiburg	14	8 (57%)	-	6 (43%)	6	-	-	-	-	6	-	-	-
Odense	17	11 (65%)	3 (18%)	2 (12%)	-	6	-	-	-	5	-	2 (12%)	-
Budapest	15	2 (13%)	6 (40%)	4 (27%)	-	11	1	2	1	7	6	2 (13%)	1 (7%)
Milano	12	7 (58%)	-	4 (33%)	-	4	-	-	4	-	-	-	1 (8%)
Padova	14	2 (14%)	-	12 (86%)	-	12	-	-	5	7	-	-	-
Rome	19	-	-	-	-	-	-	-	-	-	-	19 (100%)	-
Göteborg	6	2 (33%)	1 (17%)	-	1	-	-	-	1	-	-	-	1 (17%)
Total	150	42 (28%)	14 (9%)	65 (43%)	25	55	4	2	19	61	6	23 (15%)	4 (3%)

(continued)

Table 19a (continued)

2nd Treatment

Centre	N	No additional treatment	Suturing method		Suturing thread				Diameter of suture			Stapler	Other
			Singular	Continuous	PDS	Proline	Vicryle	Other	3.0	4.0	5.0		
Heidelberg	1	-	-	1 (100%)	-	1	-	-	-	1	-	-	-
Odense	1	-	-	1 (100%)	-	1	-	-	-	1	-	-	-
Rome	1	-	-	-	-	-	-	-	-	-	-	1 (100%)	-
Total	3	-	-	2 (67%)	-	2	-	-	-	2	-	1 (33%)	-

Program:Table_standard_type_of_surgery_AT.sas, Output:Table_standard_type_of_surgery_AT_a.lst, 02MAR09

Table 19b: Type of Standard Surgical Treatment - Stapler Size, AT

Stapler size used for lung tissue by treatment

	Treatment #											
	1ST STANDARD						2ND STANDARD					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Odense	2	9.5	0.7	9.5	9.0	10.0	-	-	-	-	-	-
Budapest	2	3.3	0.4	3.3	3.0	3.5	-	-	-	-	-	-
Rome	19	7.5	0.1	7.5	7.0	7.5	1	7.5	-	7.5	7.5	7.5
All	23	7.3	1.4	7.5	3.0	10.0	1	7.5	-	7.5	7.5	7.5

Program:Table_standard_type_of_surgery_AT.sas, Output:Table_standard_type_of_surgery_AT_b.lst, 02MAR09

Table 20a: Number of Test Treatments, AT

	TachoSil		Standard		Total	
Number of test treatments	N	%	N	%	N	%
1ST	149	100.0	150	100.0	299	100.0
2ND	20	13.4	3	2.0	23	7.7
3RD	6	4.0	.	.	6	2.0

Program:Table_number_of_test_treatments_AT.sas, Output:Table_number_of_test_treatments_AT_a.lst, 02MAR09

Table 20b: Location of Resection by Treatment and Site, AT

Site = 1

Treatment	Resection location	Tachosil	Standard	Total
1ST	RIGHT LUNG: UPPER	37 (24.8%)	35 (23.3%)	72 (24.1%)
	RIGHT LUNG: MIDDLE	27 (18.1%)	25 (16.7%)	52 (17.4%)
	RIGHT LUNG: LOWER	22 (14.8%)	27 (18.0%)	49 (16.4%)
	LEFT LUNG: UPPER	29 (19.5%)	32 (21.3%)	61 (20.4%)
	LEFT LUNG: LOWER	29 (19.5%)	29 (19.3%)	58 (19.4%)
	LOBAR HILUS	42 (28.2%)	38 (25.3%)	80 (26.8%)
	Total	148 (99.3%)	147 (98.0%)	295 (98.7%)
2ND	RIGHT LUNG: UPPER	5 (3.4%)	1 (0.7%)	6 (2.0%)
	RIGHT LUNG: MIDDLE	1 (0.7%)	1 (0.7%)	2 (0.7%)
	RIGHT LUNG: LOWER	1 (0.7%)	-	1 (0.3%)
	LEFT LUNG: UPPER	2 (1.3%)	-	2 (0.7%)
	LEFT LUNG: LOWER	2 (1.3%)	-	2 (0.7%)
	LOBAR HILUS	4 (2.7%)	1 (0.7%)	5 (1.7%)
	Total	12 (8.1%)	2 (1.3%)	14 (4.7%)
3RD	RIGHT LUNG: UPPER	4 (2.7%)	-	4 (1.3%)
	RIGHT LUNG: MIDDLE	1 (0.7%)	-	1 (0.3%)
	LEFT LUNG: UPPER	1 (0.7%)	-	1 (0.3%)
	LOBAR HILUS	3 (2.0%)	-	3 (1.0%)
	Total	6 (4.0%)	-	6 (2.0%)

(continued)

Table 20b (continued)

Site = 2

Treatment	Resection location	Tachosil	Standard	Total
1ST	RIGHT LUNG: UPPER	5 (3.4%)	3 (2.0%)	8 (2.7%)
	RIGHT LUNG: MIDDLE	5 (3.4%)	9 (6.0%)	14 (4.7%)
	RIGHT LUNG: LOWER	16 (10.7%)	19 (12.7%)	35 (11.7%)
	LEFT LUNG: UPPER	1 (0.7%)	-	1 (0.3%)
	LEFT LUNG: LOWER	-	1 (0.7%)	1 (0.3%)
	LOBAR HILUS	61 (40.9%)	55 (36.7%)	116 (38.8%)
	Total	86 (57.7%)	87 (58.0%)	173 (57.9%)
2ND	RIGHT LUNG: UPPER	1 (0.7%)	-	1 (0.3%)
	RIGHT LUNG: LOWER	2 (1.3%)	1 (0.7%)	3 (1.0%)
	LEFT LUNG: UPPER	1 (0.7%)	-	1 (0.3%)
	LOBAR HILUS	3 (2.0%)	-	3 (1.0%)
	Total	7 (4.7%)	1 (0.7%)	8 (2.7%)
3RD	LOBAR HILUS	1 (0.7%)	-	1 (0.3%)
	Total	1 (0.7%)	-	1 (0.3%)

(continued)

Table 20b (continued)

Site = 3

Treatment	Resection location	Tachosil	Standard	Total
1ST	RIGHT LUNG: MIDDLE	1 (0.7%)	-	1 (0.3%)
	RIGHT LUNG: LOWER	2 (1.3%)	-	2 (0.7%)
	LOBAR HILUS	15 (10.1%)	21 (14.0%)	36 (12.0%)
	Total	18 (12.1%)	21 (14.0%)	39 (13.0%)
2ND	LOBAR HILUS	1 (0.7%)	-	1 (0.3%)
	Total	1 (0.7%)	-	1 (0.3%)

Program:Table_number_of_test_treatments_AT.sas, Output:Table_number_of_test_treatments_AT_b.lst, 02MAR09

Table 21: Intra-operative Intensity of Air Leakage Assessed before Randomisation and after Trial Treatment, ITT

Centre	Treatment Group	Before randomisation Grade 0	Grade 1	Grade 2	Grade 3	After trial treatment Grade 0	Grade 1	Grade 2	Grade 3
Vienna	Tachosil	0 (0%)	16 (76%)	5 (24%)	0 (0%)	18 (86%)	3 (14%)	0 (0%)	0 (0%)
	Standard	0 (0%)	12 (57%)	9 (43%)	0 (0%)	11 (55%)	9 (45%)	0 (0%)	0 (0%)
Leuven	Tachosil	0 (0%)	3 (60%)	2 (40%)	0 (0%)	3 (60%)	1 (20%)	1 (20%)	0 (0%)
	Standard	0 (0%)	5 (83%)	1 (17%)	0 (0%)	5 (83%)	1 (17%)	0 (0%)	0 (0%)
Zürich	Tachosil	0 (0%)	2 (67%)	1 (33%)	0 (0%)	2 (67%)	0 (0%)	1 (33%)	0 (0%)
	Standard	0 (0%)	1 (50%)	1 (50%)	0 (0%)	0 (0%)	1 (50%)	1 (50%)	0 (0%)
Heidelberg	Tachosil	0 (0%)	8 (47%)	9 (53%)	0 (0%)	12 (75%)	4 (25%)	0 (0%)	0 (0%)
	Standard	0 (0%)	7 (41%)	10 (59%)	0 (0%)	11 (65%)	5 (29%)	1 (6%)	0 (0%)
Essen	Tachosil	0 (0%)	3 (43%)	4 (57%)	0 (0%)	4 (57%)	2 (29%)	1 (14%)	0 (0%)
	Standard	0 (0%)	4 (57%)	3 (43%)	0 (0%)	4 (57%)	3 (43%)	0 (0%)	0 (0%)
Freiburg	Tachosil	0 (0%)	6 (46%)	7 (54%)	0 (0%)	1 (8%)	8 (62%)	4 (31%)	0 (0%)
	Standard	0 (0%)	6 (46%)	7 (54%)	0 (0%)	0 (0%)	7 (54%)	6 (46%)	0 (0%)
Odense	Tachosil	0 (0%)	7 (39%)	11 (61%)	0 (0%)	11 (61%)	4 (22%)	3 (17%)	0 (0%)
	Standard	0 (0%)	7 (41%)	10 (59%)	0 (0%)	2 (12%)	7 (41%)	8 (47%)	0 (0%)
Budapest	Tachosil	0 (0%)	10 (67%)	5 (33%)	0 (0%)	14 (93%)	1 (7%)	0 (0%)	0 (0%)
	Standard	0 (0%)	14 (93%)	1 (7%)	0 (0%)	12 (80%)	2 (13%)	1 (7%)	0 (0%)
Milano	Tachosil	0 (0%)	12 (92%)	1 (8%)	0 (0%)	2 (15%)	10 (77%)	1 (8%)	0 (0%)
	Standard	0 (0%)	12 (100%)	0 (0%)	0 (0%)	0 (0%)	12 (100%)	0 (0%)	0 (0%)
Padova	Tachosil	0 (0%)	5 (38%)	8 (62%)	0 (0%)	7 (54%)	4 (31%)	2 (15%)	0 (0%)
	Standard	0 (0%)	2 (13%)	13 (87%)	0 (0%)	3 (20%)	10 (67%)	2 (13%)	0 (0%)
Rome	Tachosil	0 (0%)	1 (6%)	16 (94%)	0 (0%)	11 (65%)	1 (6%)	5 (29%)	0 (0%)
	Standard	0 (0%)	0 (0%)	19 (100%)	0 (0%)	15 (79%)	0 (0%)	4 (21%)	0 (0%)
Göteborg	Tachosil	0 (0%)	3 (50%)	3 (50%)	0 (0%)	3 (50%)	3 (50%)	0 (0%)	0 (0%)
	Standard	0 (0%)	2 (33%)	4 (67%)	0 (0%)	0 (0%)	1 (50%)	1 (50%)	0 (0%)

Program:Table_intensity_of_air_leakage_2.sas, Output:Table_intensity_of_air_leakage_2_ITT.lst, 02MAR09

Table 21: Intra-operative Intensity of Air Leakage Assessed before Randomisation and after Trial Treatment, ITT

Centre	Treatment Group	Before randomisation Grade 0	Grade 1	Grade 2	Grade 3	After trial treatment Grade 0	Grade 1	Grade 2	Grade 3
Total	Tachosil	0 (0%)	76 (51%)	72 (49%)	0 (0%)	88 (60%)	41 (28%)	18 (12%)	0 (0%)
	Standard	0 (0%)	72 (48%)	78 (52%)	0 (0%)	63 (43%)	58 (40%)	24 (17%)	0 (0%)

Program:Table_intensity_of_air_leakage_2.sas, Output:Table_intensity_of_air_leakage_2_ITT.lst, 02MAR09

Table 22: Surgery Time, AT

	TACHOSIL							STANDARD						
	N	NMiss	Mean	Std	Median	Min	Max	N	NMiss	Mean	Std	Median	Min	Max
Surgery time (minutes)	148	1	143.5	48.9	135	65	311	150	0	141.6	60.5	128	50	476

NMISS = Number of missing observations
Program:Table_surgery_minutes_AT.sas, Output:Table_surgery_minutes_AT_AT.lst, 02MAR09

Table 23: Treatment Failure, ITT

Surgical method		Tachosil	Standard
Rescue treatment	YES	2 (1%)	0 (0%)
	NO	146 (99%)	151 (100%)
Use of suturing		1 (50%)	-
Use of stapling		-	-
Use of surgical sealant		-	-
Other		2 (100%)	-

Program:Table_treatment_failure.sas, Output:Table_treatment_failure_ITT.lst, 02MAR09

Table 24: Duration of Post-Operative Air Leakage: Life Table Estimates, ITT

% of patients with post-opearative air leakage at selected assessments by centre and treatment

	Tachosil (N=148)							Standard (N=151)						
Centre	Day0 E	Day1 M	Day1 E	Day2 E	Day5 M	Day10 M	Day20 M	Day0 E	Day1 M	Day1 E	Day2 E	Day5 M	Day10 M	Day20 M
Vienna	67	33	29	10	5	5	0	86	67	48	24	10	0	0
Leuven	40	40	40	20	0	0	0	67	67	67	33	0	0	0
Zürich	67	33	33	C	C	C	C	50	0	0	0	0	0	0
Heidelberg	53	35	35	18	6	6	6	35	29	24	18	6	0	0
Essen	43	43	43	43	29	14	0	57	57	57	43	14	14	14
Freiburg	69	69	46	31	23	15	8	71	43	43	29	7	7	0
Odense	83	78	72	67	22	6	0	100	88	59	47	35	12	0
Budapest	40	33	13	7	0	0	0	60	53	47	13	7	0	0
Milano	100	100	100	38	0	0	0	100	100	92	58	33	33	0
Padova	77	46	46	31	8	0	0	73	60	53	40	33	13	0
Rome	59	53	41	12	0	0	0	53	53	47	32	21	16	5
Göteborg	67	67	67	33	0	0	0	82	20	20	0	0	0	0
All	66	53	47	27	8	4	2	71	59	49	31	17	8	2

Log-Rank test of equality over treatments stratified by centre:
N=299, Chi-Square=4.7387, df= 1, p=0.0295

E = Evening assessment
M = Morning assessment
C = Last observation censored
Centres contributing with only a few patients were pooled with other centres for purposes of the analysis:
thus centres Zürich, Essen and Göteborg were pooled into a single centre
and centres Leuven and Vienna were likewise pooled into a single centre
Program:Tab_pe.sas, Output:Tab_pe_ITT.lst, 02MAR09

Table 25: Duration of Post-Operative Air Leakage: Parametric Analysis, ITT

Assumed distribution: weibull

N=299

Scale	Effect	Estimate (se)	95% CI Lower	95% CI Upper	Chi-Sq	df	P-value
Log-time	Standard-Tachosil	0.3101 (0.217)	-0.12	0.74	2.038	1	0.1534

Estimated time to event is exp(0.31) = 1.36 times higher in the standard treatment group compared to Tachosil
Estimated relative hazard = 0.84
Estimated median time to event on the Tachosil arm: 14.45 hours
Estimated median time to event on the Standard arm: 19.50 hours
Program:Tab_pe_param2.sas, Output:Tab_pe_param2_ITT.lst, 02MAR09

Table 26: Sentitivity Analysis. Duration of Post-Operative Air Leakage: Life Table Estimates, ITT

% of patients with post-opearative air leakage at selected assessments by centre and treatment
Censored observations in the Tachosil group are assigned the largest time observed (whether censored or not) across all subjects in the Tachosil arm
The analysis then presents a worst-case scenario whereby TachoSil patients for whom time of air leakage stop is unknown are assumed to have had air leakage up until and including at least Day 20

	Tachosil (N=148)						Standard (N=151)					
Centre	Day0 E	Day1 M	Day1 E	Day2 E	Day5 M	Day10 M	Day0 E	Day1 M	Day1 E	Day2 E	Day5 M	Day10 M
Vienna	67	33	29	10	5	5	86	67	48	24	10	0
Leuven	40	40	40	20	0	0	67	67	67	33	0	0
Zürich	67	33	33	33	33	33	50	0	0	0	0	0
Heidelberg	53	35	35	18	6	6	35	29	24	18	6	0
Essen	43	43	43	43	29	14	57	57	57	43	14	14
Freiburg	69	69	46	31	23	15	71	43	43	29	7	7
Odense	83	78	72	67	22	6	100	88	59	47	35	12
Budapest	40	33	13	7	0	0	60	53	47	13	7	0
Milano	100	100	100	38	0	0	100	100	92	58	33	33
Padova	77	46	46	31	8	0	73	60	53	40	33	13
Rome	59	53	41	12	0	0	53	53	47	32	21	16
Göteborg	67	67	67	33	0	0	82	20	20	0	0	0
All	66	53	47	27	9	5	71	59	49	31	17	8

Log-Rank test of equality over treatments stratified by centre:
N=299, Chi-Square=3.8038, df= 1, p=0.0511

E = Evening assessment
M = Morning assessment
C = Last observation censored
Centres contributing with only a few patients were pooled with other centres for purposes of the analysis:
thus centres Zürich, Essen and Göteborg were pooled into a single centre
and centres Leuven and Vienna were likewise pooled into a single centre
Program:Tab_pe_sens.sas, Output:Tab_pe_sens_ITT.lst, 02MAR09

Table 27: Duration of Post-Operative Air Leakage: Life Table Estimates, Exploratory Analysis, ITT

% of patients with post-opearative air leakage at selected assessments by centre and treatment

Exploratory Analysis. Primary Endpoint, ITT
Patients treated with a Heimlich valve are assigned the longest duration of post-operative air leakage observed across all subjects (20 days)

	Tachosil (N=148)							Standard (N=151)						
Centre	Day0 E	Day1 M	Day1 E	Day2 E	Day5 M	Day10 M	Day20 M	Day0 E	Day1 M	Day1 E	Day2 E	Day5 M	Day10 M	Day20 M
Vienna	67	33	29	10	5	5	5	86	67	48	24	10	5	5
Leuven	40	40	40	20	0	0	0	67	67	67	33	0	0	0
Zürich	67	33	33	C	C	C	C	50	0	0	0	0	0	0
Heidelberg	53	35	35	18	6	6	6	35	29	24	18	6	0	0
Essen	43	43	43	43	29	14	14	57	57	57	43	14	14	14
Freiburg	69	69	46	31	23	23	15	71	43	43	29	7	7	0
Odense	83	78	72	67	22	6	0	100	88	59	47	35	12	6
Budapest	40	33	13	7	0	0	0	60	53	47	13	7	0	0
Milano	100	100	100	38	0	0	0	100	100	92	58	33	33	22
Padova	77	46	46	31	8	0	0	73	60	53	40	33	13	7
Rome	59	53	41	12	0	0	0	53	53	47	32	21	16	5
Göteborg	67	67	67	33	0	0	0	82	20	20	0	0	0	0
All	66	53	47	27	8	5	4	71	59	49	31	17	10	5

Log-Rank test of equality over treatments stratified by centre:
N=299, Chi-Square=4.6015, df= 1, p=0.0319

E = Evening assessment
M = Morning assessment
C = Last observation censored
Centres contributing with only a few patients were pooled with other centres for purposes of the analysis:
thus centres Zürich, Essen and Göteborg were pooled into a single centre
and centres Leuven and Vienna were likewise pooled into a single centre
Program:Tab_pe_extra2.sas, Output:Tab_pe_extra2_ITT.lst, 02MAR09

Table 28: Duration of Post-Operative Air Leakage: Life Table Estimates, PP

% of patients with post-opearative air leakage at selected assessments by centre and treatment

	Tachosil (N=135)							Standard (N=138)						
Centre	Day0 E	Day1 M	Day1 E	Day2 E	Day5 M	Day10 M	Day20 M	Day0 E	Day1 M	Day1 E	Day2 E	Day5 M	Day10 M	Day20 M
Vienna	65	30	25	5	0	0	0	84	63	47	21	5	0	0
Leuven	25	25	25	25	0	0	0	60	60	60	20	0	0	0
Zürich	50	0	0	0	0	0	0	50	0	0	0	0	0	0
Heidelberg	47	27	27	13	0	0	0	35	29	24	18	6	0	0
Essen	40	40	40	40	20	0	0	50	50	50	33	0	0	0
Freiburg	64	64	36	18	9	9	0	69	38	38	23	0	0	0
Odense	80	73	67	60	7	0	0	100	87	53	40	27	0	0
Budapest	40	33	13	7	0	0	0	60	53	47	13	7	0	0
Milano	100	100	100	38	0	0	0	100	100	90	50	20	20	0
Padova	75	42	42	25	0	0	0	67	50	42	25	25	8	0
Rome	59	53	41	12	0	0	0	53	53	47	32	21	16	5
Göteborg	67	67	67	33	0	0	0	80	20	20	0	0	0	0
All	63	50	42	22	2	1	0	68	55	46	25	12	4	1

Log-Rank test of equality over treatments stratified by centre:
N=273, Chi-Square=7.4779, df= 1, p=0.0062

E = Evening assessment
M = Morning assessment
C = Last observation censored
Centres contributing with only a few patients were pooled with other centres for purposes of the analysis:
thus centres Zürich, Essen and Göteborg were pooled into a single centre
and centres Leuven and Vienna were likewise pooled into a single centre
Program:Tab_pe.sas, Output:Tab_pe_PP.lst, 02MAR09

Table 29: Duration of Post-Operative Air Leakage: Parametric Analysis, PP

Assumed distribution: weibull

N=273

Scale	Effect	Estimate (se)	95% CI Lower	95% CI Upper	Chi-Sq	df	P-value
Log-time	Standard-Tachosil	0.4356 (0.205)	0.03	0.84	4.493	1	0.0340

Estimated time to event is exp(0.44) = 1.55 times higher in the standard treatment group compared to Tachosil
Estimated relative hazard = 0.77
Estimated median time to event on the Tachosil arm: 11.20 hours
Estimated median time to event on the Standard arm: 16.84 hours
Program:Tab_pe_param2.sas, Output:Tab_pe_param2_PP.lst, 02MAR09

Table 30: Reduction in intraoperative air leakage intensity, ITT

Wilcoxon's rank sum test (using Normal approximation):

STANDARD: Score= 19885 n=145
TACHOSIL: Score= 22893 n=147 z-value=-2.0333 p-value=0.0420

Air Grade Reduction	TACHOSIL		STANDARD		All	
	N	%	N	%	N	%
0	42	28.6	55	37.9	97	33.2
1	69	46.9	66	45.5	135	46.2
2	36	24.5	24	16.6	60	20.5
All	147	100.0	145	100.0	292	100.0

Program:Tab_se.sas, Output:Tab_se_ITT.lst, 02MAR09

Table 31: Total Number of Days until Removal of the Last Chest Drain, ITT

	TACHOSIL						STANDARD						All					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Vienna	21	3.2	3.7	2	1	19	21	3.8	2.5	3	1	10	42	3.5	3.2	2	1	19
Leuven	5	4.8	0.8	5	4	6	6	4.7	1.0	5	3	6	11	4.7	0.9	5	3	6
Zürich	2	3.5	0.7	4	3	4	2	4.5	2.1	5	3	6	4	4.0	1.4	4	3	6
Heidelberg	16	6.2	1.3	6	4	8	17	6.2	1.8	6	4	10	33	6.2	1.6	6	4	10
Essen	7	6.9	3.6	5	4	13	7	5.6	3.0	5	3	12	14	6.2	3.3	5	3	13
Freiburg	13	7.5	4.5	6	3	16	13	6.6	3.9	5	3	16	26	7.1	4.2	6	3	16
Odense	18	5.7	5.3	5	2	25	17	5.9	4.3	4	2	19	35	5.8	4.8	4	2	25
Budapest	15	2.5	0.9	2	2	5	15	2.9	1.2	3	2	6	30	2.7	1.1	2	2	6
Milano	13	4.6	0.7	5	3	5	11	6.7	4.5	5	4	18	24	5.6	3.2	5	3	18
Padova	13	4.7	1.2	4	3	7	15	6.7	4.2	5	4	17	28	5.8	3.3	5	3	17
Rome	17	5.2	1.4	5	4	8	19	6.9	4.2	5	4	21	36	6.1	3.3	5	4	21
Göteborg	6	3.3	1.9	3	2	7	5	2.2	0.8	2	1	3	11	2.8	1.5	3	1	7
All	146	4.9	3.2	4	1	25	148	5.5	3.5	5	1	21	294	5.2	3.4	4	1	25

NOTE: <Days until drain removal> = <date of drain removal> - <date of surgery>
Program:Table_number_of_days_until_drain_removal.sas, Output:Table_number_of_days_until_drain_removal_ITT.lst, 02MAR09

Table 32:Total Volume of Post-operative Chest Tube Drainage (ml), ITT

	TACHOSIL						STANDARD						All					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Budapest	15	1301.7	382.1	1210	650	2030	15	1366.0	355.7	1340	790	2070	30	1333.9	364.2	1305	650	2070
Essen	7	1971.4	1412.9	1350	800	4580	7	1606.4	1791.5	1100	495	5570	14	1788.9	1561.6	1273	495	5570
Freiburg	13	2988.1	1978.9	2460	850	6590	14	2672.1	1635.4	1935	920	5745	27	2824.3	1780.6	2080	850	6590
Göteborg	6	2418.3	1768.1	1983	480	5060	5	736.0	399.7	705	190	1160	11	1653.6	1548.8	1085	190	5060
Heidelberg	16	2525.9	1184.3	2358	580	5580	17	2537.6	1107.9	2180	1200	4905	33	2532.0	1127.5	2235	580	5580
Leuven	5	1465.0	654.4	1070	880	2205	6	1364.2	423.1	1300	820	2070	11	1410.0	513.4	1270	820	2205
Milano	13	1074.7	436.3	970	585	2380	12	1196.0	621.6	960	652	2730	25	1132.9	525.4	970	585	2730
Odense	18	1556.8	785.2	1388	390	3190	17	1176.2	533.6	1050	560	2650	35	1371.9	692.4	1230	390	3190
Padova	13	1487.7	460.7	1300	1100	2830	15	1782.7	630.6	1500	950	3080	28	1645.7	568.3	1460	950	3080
Rome	17	1489.8	660.1	1320	592	2865	19	1594.4	995.9	1335	660	4675	36	1545.0	843.8	1328	592	4675
Vienna	21	1427.3	806.6	1145	540	3700	21	1443.5	941.7	1090	320	3760	42	1435.4	866.1	1145	320	3760
Zürich	3	1488.3	726.2	1165	980	2320	2	1295.0	657.6	1295	830	1760	5	1411.0	618.9	1165	830	2320
All	147	1738.2	1118.8	1350	390	6590	150	1656.2	1065.1	1360	190	5745	297	1696.8	1091.0	1350	190	6590

Program:Table_total_volume_chest_drainage.sas, Output:Table_total_volume_chest_drainage_ITT.lst, 02MAR09

Table 33: Volume of Daily Post-operative Chest Tube Drainage (ml), ITT

Site=Vienna

	Vienna											
	TACHOSIL						STANDARD					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
DAY 1	21	489.6	238.9	450	103	1005	21	470.0	251.8	390	85	1020
DAY 2	19	448.4	292.5	385	140	1500	18	342.1	180.5	313	100	930
DAY 3	5	356.0	146.0	305	225	600	12	307.6	212.3	295	0	640
DAY 4	2	257.5	74.2	258	205	310	6	305.8	148.7	323	75	490
DAY 5	2	260.0	141.4	260	160	360	6	295.0	124.1	240	200	500
DAY 6	1	150.0	-	150	150	150	5	230.0	105.8	200	120	400
DAY 7	1	300.0	-	300	300	300	2	180.0	155.6	180	70	290
DAY 8	1	10.0	-	10	10	10	1	100.0	-	100	100	100
DAY 9	1	60.0	-	60	60	60	-	-	-	-	-	-
DAY 10	0	-	-	-	-	-	-	-	-	-	-	-
DAY 14	0	-	-	-	-	-	-	-	-	-	-	-
DAY 17	0	-	-	-	-	-	-	-	-	-	-	-
DRAIN REMOVAL	20	392.0	282.2	328	140	1500	20	269.1	149.7	275	0	617

Program:Table_volume_chest_drainage.sas, Output:Table_volume_chest_drainage_ITT.lst, 02MAR09

Table 33: Volume of Daily Post-operative Chest Tube Drainage (ml), ITT

Site=Leuven

	Leuven											
	TACHOSIL						STANDARD					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
DAY 1	5	534.0	397.8	300	220	1070	6	678.3	212.0	705	410	1020
DAY 2	5	360.0	160.3	280	230	610	6	385.8	190.1	325	250	755
DAY 3	5	266.0	77.7	290	140	340	6	180.0	107.4	173	30	360
DAY 4	2	280.0	155.6	280	170	390	3	140.0	36.1	150	100	170
DAY 5	1	120.0	-	120	120	120	-	-	-	-	-	-
DRAIN REMOVAL	5	169.0	94.9	185	50	300	6	50.0	63.2	25	0	150

Program:Table_volume_chest_drainage.sas, Output:Table_volume_chest_drainage_ITT.lst, 02MAR09

Table 33: Volume of Daily Post-operative Chest Tube Drainage (ml), ITT

Site=Zürich

	Zürich											
	TACHOSIL						STANDARD					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
DAY 1	3	665.0	352.7	500	425	1070	2	410.0	198.0	410	270	550
DAY 2	3	616.7	549.3	330	270	1250	2	340.0	56.6	340	300	380
DAY 3	1	300.0	-	300	300	300	1	380.0	-	380	380	380
DRAIN REMOVAL	2	160.0	14.1	160	150	170	2	355.0	134.4	355	260	450

Program:Table_volume_chest_drainage.sas, Output:Table_volume_chest_drainage_ITT.lst, 02MAR09

Table 33: Volume of Daily Post-operative Chest Tube Drainage (ml), ITT

Site=Heidelberg

	Heidelberg											
	TACHOSIL						STANDARD					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
DAY 1	16	715.0	364.4	640	300	1570	17	767.4	416.1	650	425	2270
DAY 2	16	581.3	232.6	540	160	1250	17	689.1	314.5	560	325	1350
DAY 3	15	374.3	332.4	350	0	1390	17	407.9	222.8	360	50	980
DAY 4	14	360.4	215.4	320	80	750	12	260.0	150.2	225	0	450
DAY 5	12	315.8	120.2	280	125	525	9	353.3	118.8	350	120	520
DAY 6	6	291.7	147.2	263	100	500	6	266.7	147.2	250	50	450
DAY 7	3	226.7	110.2	280	100	300	3	223.3	68.1	200	170	300
DAY 8	-	-	-	-	-	-	2	240.0	14.1	240	230	250
DAY 9	-	-	-	-	-	-	1	225.0	-	225	225	225
DRAIN REMOVAL	16	174.7	87.4	168	50	400	17	127.6	61.4	120	30	250

Program:Table_volume_chest_drainage.sas, Output:Table_volume_chest_drainage_ITT.lst, 02MAR09

Table 33: Volume of Daily Post-operative Chest Tube Drainage (ml), ITT

Site=Essen

	Essen											
	TACHOSIL						STANDARD					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
DAY 1	7	439.3	133.4	400	300	670	7	247.9	137.3	235	0	400
DAY 2	7	403.6	131.5	460	200	550	7	291.4	132.5	300	120	500
DAY 3	7	293.6	164.2	250	110	525	7	328.6	218.6	240	90	610
DAY 4	5	178.0	72.6	150	100	260	4	185.0	171.4	170	0	400
DAY 5	3	201.7	212.9	110	50	445	2	250.0	70.7	250	200	300
DAY 6	2	447.5	307.6	448	230	665	1	250.0	-	250	250	250
DAY 7	2	415.0	190.9	415	280	550	1	400.0	-	400	400	400
DAY 8	2	565.0	431.3	565	260	870	1	420.0	-	420	420	420
DAY 9	2	175.0	77.8	175	120	230	1	440.0	-	440	440	440
DAY 10	2	152.5	137.9	153	55	250	1	260.0	-	260	260	260
DAY 11	1	70.0	-	70	70	70	1	140.0	-	140	140	140
DAY 12	1	130.0	-	130	130	130	-	-	-	-	-	-
DAY 14	-	-	-	-	-	-	1	0.0	-	0	0	0
DAY 15	-	-	-	-	-	-	1	200.0	-	200	200	200
DAY 16	-	-	-	-	-	-	1	200.0	-	200	200	200
DAY 17	-	-	-	-	-	-	1	250.0	-	250	250	250
DAY 18	-	-	-	-	-	-	1	350.0	-	350	350	350
DAY 19	-	-	-	-	-	-	1	50.0	-	50	50	50
DAY 20	-	-	-	-	-	-	1	330.0	-	330	330	330
DAY 21	-	-	-	-	-	-	1	100.0	-	100	100	100
DRAIN REMOVAL	7	91.4	67.7	80	0	200	6	90.0	89.0	55	0	200

Program:Table_volume_chest_drainage.sas, Output:Table_volume_chest_drainage_ITT.lst, 02MAR09

Table 33: Volume of Daily Post-operative Chest Tube Drainage (ml), ITT

Site=Freiburg

	Freiburg											
	TACHOSIL						STANDARD					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
DAY 1	13	752.3	272.4	700	380	1220	14	797.1	285.0	800	280	1300
DAY 2	13	606.2	351.1	610	200	1530	14	452.1	163.1	410	200	770
DAY 3	13	461.9	485.5	430	40	1930	14	381.1	217.8	360	30	950
DAY 4	6	410.0	78.0	395	300	500	8	399.4	142.9	390	135	600
DAY 5	6	346.7	124.5	300	240	560	7	381.4	242.7	300	170	900
DAY 6	5	249.0	229.2	180	75	640	4	437.5	137.7	425	300	600
DAY 7	4	515.0	169.0	500	350	710	4	362.5	131.5	325	250	550
DAY 8	4	241.3	99.0	245	125	350	3	333.3	175.6	350	150	500
DAY 9	4	330.0	349.7	250	0	820	3	316.7	57.7	350	250	350
DAY 10	3	216.7	40.4	210	180	260	2	225.0	35.4	225	200	250
DAY 11	3	156.7	142.9	190	0	280	2	300.0	70.7	300	250	350
DAY 12	2	250.0	0.0	250	250	250	1	250.0	-	250	250	250
DAY 13	2	75.0	35.4	75	50	100	1	250.0	-	250	250	250
DAY 14	1	50.0	-	50	50	50	1	200.0	-	200	200	200
DAY 15	1	0.0	-	0	0	0	1	250.0	-	250	250	250
DRAIN REMOVAL	13	248.5	629.2	75	0	2330	13	120.8	72.3	140	0	220

Program:Table_volume_chest_drainage.sas, Output:Table_volume_chest_drainage_ITT.lst, 02MAR09

Table 33: Volume of Daily Post-operative Chest Tube Drainage (ml), ITT

Site=Odense

	Odense											
	TACHOSIL						STANDARD					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
DAY 1	18	530.3	332.5	495	100	1600	17	384.7	198.4	340	130	1010
DAY 2	16	406.6	133.9	395	180	750	17	335.9	221.3	270	50	975
DAY 3	14	278.3	130.3	235	125	600	11	206.4	88.6	200	90	400
DAY 4	7	319.3	153.0	300	120	500	7	201.4	102.5	200	30	350
DAY 5	4	205.0	172.5	150	70	450	6	210.0	89.9	210	100	300
DAY 6	3	113.3	58.6	90	70	180	4	212.5	55.0	225	140	260
DAY 7	1	220.0	-	220	220	220	2	230.0	99.0	230	160	300
DAY 8	1	200.0	-	200	200	200	0	-	-	-	-	-
DAY 9	1	200.0	-	200	200	200	0	-	-	-	-	-
DAY 10	1	180.0	-	180	180	180	0	-	-	-	-	-
DAY 11	-	-	-	-	-	-	0	-	-	-	-	-
DAY 12	-	-	-	-	-	-	0	-	-	-	-	-
DAY 16	1	420.0	-	420	420	420	-	-	-	-	-	-
DRAIN REMOVAL	16	216.3	115.8	210	50	500	11	135.9	82.5	105	0	300

Program:Table_volume_chest_drainage.sas, Output:Table_volume_chest_drainage_ITT.lst, 02MAR09

Table 33: Volume of Daily Post-operative Chest Tube Drainage (ml), ITT

Site=Budapest

	Budapest											
	TACHOSIL						STANDARD					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
DAY 1	15	528.1	203.4	500	210	1030	15	582.0	210.4	600	260	980
DAY 2	15	374.0	127.3	370	190	640	15	359.3	116.8	360	150	600
DAY 3	4	227.5	68.5	225	150	310	9	245.6	109.1	200	150	500
DAY 4	1	200.0	-	200	200	200	2	150.0	70.7	150	100	200
DAY 5	-	-	-	-	-	-	1	90.0	-	90	90	90
DRAIN REMOVAL	15	325.7	130.7	335	100	640	15	251.3	109.3	220	120	500

Program:Table_volume_chest_drainage.sas, Output:Table_volume_chest_drainage_ITT.lst, 02MAR09

Table 33: Volume of Daily Post-operative Chest Tube Drainage (ml), ITT

Site=Milano

	Milano											
	TACHOSIL						STANDARD					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
DAY 1	13	336.2	148.4	300	40	700	12	376.4	205.3	340	180	880
DAY 2	13	373.5	163.6	350	180	820	12	334.0	179.6	255	100	690
DAY 3	13	283.5	200.8	200	80	710	12	256.4	120.0	290	100	510
DAY 4	-	-	-	-	-	-	3	186.7	204.3	100	40	420
DAY 5	-	-	-	-	-	-	3	166.7	152.8	200	0	300
DAY 6	-	-	-	-	-	-	2	50.0	70.7	50	0	100
DAY 7	-	-	-	-	-	-	2	100.0	141.4	100	0	200
DAY 8	-	-	-	-	-	-	2	75.0	106.1	75	0	150
DAY 9	-	-	-	-	-	-	2	85.0	120.2	85	0	170
DAY 10	-	-	-	-	-	-	1	0.0	-	0	0	0
DAY 11	-	-	-	-	-	-	1	0.0	-	0	0	0
DAY 12	-	-	-	-	-	-	1	0.0	-	0	0	0
DAY 13	-	-	-	-	-	-	1	0.0	-	0	0	0
DAY 14	-	-	-	-	-	-	1	0.0	-	0	0	0
DRAIN REMOVAL	13	81.5	69.6	80	0	250	9	118.9	108.2	100	20	300

Program:Table_volume_chest_drainage.sas, Output:Table_volume_chest_drainage_ITT.lst, 02MAR09

Table 33: Volume of Daily Post-operative Chest Tube Drainage (ml), ITT

Site=Padova

	Padova											
	TACHOSIL						STANDARD					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
DAY 1	13	548.5	207.1	500	180	850	15	607.3	171.4	600	300	1000
DAY 2	13	407.7	129.4	370	250	700	15	419.3	170.4	360	200	800
DAY 3	13	287.7	129.7	300	100	510	15	302.7	94.9	300	170	500
DAY 4	3	216.7	175.6	200	50	400	6	188.3	111.4	165	100	400
DAY 5	2	250.0	141.4	250	150	350	5	200.0	50.0	200	150	250
DAY 6	-	-	-	-	-	-	3	166.7	76.4	150	100	250
DAY 7	-	-	-	-	-	-	3	150.0	132.3	100	50	300
DAY 8	-	-	-	-	-	-	3	116.7	28.9	100	100	150
DAY 9	-	-	-	-	-	-	2	125.0	35.4	125	100	150
DAY 10	-	-	-	-	-	-	2	115.0	120.2	115	30	200
DAY 11	-	-	-	-	-	-	1	150.0	-	150	150	150
DAY 12	-	-	-	-	-	-	1	100.0	-	100	100	100
DAY 13	-	-	-	-	-	-	1	100.0	-	100	100	100
DAY 14	-	-	-	-	-	-	1	100.0	-	100	100	100
DAY 15	-	-	-	-	-	-	1	100.0	-	100	100	100
DRAIN REMOVAL	13	155.4	56.1	150	100	260	13	180.0	64.9	170	100	300

Program:Table_volume_chest_drainage.sas, Output:Table_volume_chest_drainage_ITT.lst, 02MAR09

Table 33: Volume of Daily Post-operative Chest Tube Drainage (ml), ITT

Site=Rome

	Rome											
	TACHOSIL						STANDARD					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
DAY 1	17	439.7	145.8	440	230	730	19	350.5	129.2	330	60	599
DAY 2	17	388.8	218.6	370	135	1085	19	330.5	100.8	330	210	570
DAY 3	17	248.4	88.8	250	97	420	19	244.5	98.1	240	50	450
DAY 4	8	233.1	44.1	230	190	325	9	267.8	57.7	270	190	365
DAY 5	5	264.0	74.4	240	200	370	8	236.3	70.1	210	160	370
DAY 6	4	272.5	64.6	255	215	365	8	224.4	100.4	193	115	360
DAY 7	2	200.0	113.1	200	120	280	3	215.0	18.0	210	200	235
DAY 8	-	-	-	-	-	-	3	163.3	85.0	160	80	250
DAY 9	-	-	-	-	-	-	3	196.7	46.2	170	170	250
DAY 10	-	-	-	-	-	-	3	190.0	40.0	190	150	230
DAY 11	-	-	-	-	-	-	2	165.0	21.2	165	150	180
DAY 12	-	-	-	-	-	-	2	200.0	28.3	200	180	220
DAY 13	-	-	-	-	-	-	1	275.0	-	275	275	275
DAY 14	-	-	-	-	-	-	1	240.0	-	240	240	240
DAY 15	-	-	-	-	-	-	1	80.0	-	80	80	80
DAY 16	-	-	-	-	-	-	1	70.0	-	70	70	70
DAY 17	-	-	-	-	-	-	1	50.0	-	50	50	50
DAY 18	-	-	-	-	-	-	1	250.0	-	250	250	250
DAY 19	-	-	-	-	-	-	1	70.0	-	70	70	70
DAY 20	-	-	-	-	-	-	1	170.0	-	170	170	170
DRAIN REMOVAL	17	137.9	62.7	150	0	260	19	125.5	55.6	140	30	210

Program:Table_volume_chest_drainage.sas, Output:Table_volume_chest_drainage_ITT.lst, 02MAR09

Table 33: Volume of Daily Post-operative Chest Tube Drainage (ml), ITT

Site=Göteborg

	Göteborg											
	TACHOSIL						STANDARD					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
DAY 1	6	577.5	231.9	560	320	975	5	301.0	190.1	225	130	580
DAY 2	6	732.5	532.3	658	80	1510	4	181.3	185.4	133	30	430
DAY 3	4	560.0	741.3	265	60	1650	2	102.5	88.4	103	40	165
DAY 4	1	300.0	-	300	300	300	-	-	-	-	-	-
DAY 5	1	220.0	-	220	220	220	-	-	-	-	-	-
DAY 6	1	90.0	-	90	90	90	-	-	-	-	-	-
DRAIN REMOVAL	6	633.3	745.7	265	30	1650	5	249.0	245.5	165	30	580

Program:Table_volume_chest_drainage.sas, Output:Table_volume_chest_drainage_ITT.lst, 02MAR09

Table 33: Volume of Daily Post-operative Chest Tube Drainage (ml), ITT

Site = Total

	TACHOSIL						STANDARD					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
DAY 1	147	538.4	272.4	500	40	1600	150	518.4	288.7	480	0	2270
DAY 2	143	457.7	256.2	400	80	1530	146	394.8	217.1	358	30	1350
DAY 3	111	322.3	271.0	265	0	1930	125	293.3	169.4	260	0	980
DAY 4	49	300.4	156.3	260	50	750	60	252.0	140.1	220	0	600
DAY 5	36	277.1	130.3	260	50	560	47	273.6	143.9	260	0	900
DAY 6	22	252.7	171.0	223	70	665	33	242.3	132.3	220	0	600
DAY 7	13	345.4	179.4	300	100	710	20	231.8	127.5	223	0	550
DAY 8	8	288.1	257.1	230	10	870	15	199.3	136.4	150	0	500
DAY 9	8	241.3	252.9	200	0	820	12	218.8	120.3	198	0	440
DAY 10	6	189.2	73.9	195	55	260	9	167.8	93.0	200	0	260
DAY 11	4	135.0	124.5	130	0	280	7	174.3	107.5	150	0	350
DAY 12	3	210.0	69.3	250	130	250	5	150.0	101.0	180	0	250
DAY 13	2	75.0	35.4	75	50	100	4	156.3	129.7	175	0	275
DAY 14	1	50.0	-	50	50	50	5	108.0	111.0	100	0	240
DAY 15	1	0.0	-	0	0	0	4	157.5	81.0	150	80	250
DAY 16	1	420.0	-	420	420	420	2	135.0	91.9	135	70	200
DAY 17	0	-	-	-	-	-	2	150.0	141.4	150	50	250
DAY 18	-	-	-	-	-	-	2	300.0	70.7	300	250	350
DAY 19	-	-	-	-	-	-	2	60.0	14.1	60	50	70
DAY 20	-	-	-	-	-	-	2	250.0	113.1	250	170	330
DAY 21	-	-	-	-	-	-	1	100.0	-	100	100	100
DRAIN REMOVAL	143	232.4	292.9	170	0	2330	136	168.9	120.5	150	0	617

Program:Table_volume_chest_drainage.sas, Output:Table_volume_chest_drainage_ITT.lst, 02MAR09

Table 34: Post-operative Complications or Additional Procedures, AT

	TachoSil N=149		Standard N=150	
	n	%	n	%
Atelectasis_of_lung	9	6.0	11	7.3
Bleeding	2	1.3	4	2.7
Cardiac_arrhythmia	10	6.7	12	8.0
Complication_other	19	13	24	16
Pneumonia	9	6.0	9	6.0
Progression/increase of soft tissue emphysema	1	0.7	2	1.3
Pulmonary_embolism	.	.	1	0.7
Surgical_wound_infection	1	0.7	1	0.7
Total	39	26	50	33
Need for additional chest drainage	7	4.7	6	4.0
Need_for_blood_transfusion	7	4.7	9	6.0
Need_for_re_operation	6	4.0	5	3.3
Need_for_respiratory_assistance	4	2.7	3	2.0
Total	17	11	17	11

N = number of exposed, n = number with the event, % = number with event as % of exposed
Program:Table_postoperative_complications_AT.sas, Output:Table_postoperative_complications_AT.lst, 02MAR09

Table 35: Blood Transfusions by Type, AT

	Number of Patients	Number of Transfusions	Patients receiving Whole blood	Patients receiving Packed RBC	Patients receiving Fresh frozen plasma	Patients receiving Other blood
TACHOSIL	7	9	3	6	0	0
STANDARD	9	9	5	4	1	0

Some patients received two types of blood
Program:Table_type_and_unit_of_blood_transfusion_AT.sas, Output:Table_type_and_unit_of_blood_transfusion_AT_TYPE.lst, 02MAR09

Table 36: Units of transfused blood, AT

	TachoSil N=7						Standard N=9						All					
	n	Mean	Std	Median	Min	Max	n	Mean	Std	Median	Min	Max	n	Mean	Std	Median	Min	Max
Whole blood	3	2.3	0.6	2	2	3	5	2.0	1.2	2	1	4	8	2.1	1.0	2	1	4
Packed RBC	6	1.7	0.8	2	1	3	4	1.5	0.6	2	1	2	10	1.6	0.7	2	1	3
Fresh frozen plasma	0	-	-	-	-	-	1	3.0	-	3	3	3	1	3.0	-	3	3	3
Other	0	-	-	-	-	-	0	-	-	-	-	-	0	-	-	-	-	-

Some patients received two types of blood
Program:Table_type_and_unit_of_blood_transfusion_AT.sas, Output:Table_type_and_unit_of_blood_transfusion_AT_UNITS.lst, 02MAR09

Table 37: Number of Days Spent at Hospital, AT

Difference between Day 0 and Discharge (both days included)

	TACHOSIL							STANDARD						
	Total	N	Mean	Std	Median	Min	Max	Total	N	Mean	Std	Median	Min	Max
Number of days	1367	147	9.3	4.6	8.0	1.0	36.0	1436	148	9.7	4.3	9.0	4.0	28.0

Program:Table_number_of_hospitaldays_AT.sas, Output:Table_number_of_hospitaldays_AT.lst, 02MAR09

Table 38: Number of Unscheduled Visits and Reason, AT

	TACHOSIL	STANDARD
	Number of visits	Number of visits
SMALL APICAL PNEUMOTHORAX CHEST X-RAY: RESOLVED	1	-
REMOVAL OF STITCHES	-	1
REMOVAL OF DRAINAGE TOGETHER WITH HEIMLICH VENTIL	1	-
DYSPNOE, THORACIC PAIN	1	-
DRAINAGE REMOVAL X-RAY PERFORMED AND NORMAL	-	1
CHEST DRAIN REMOVAL	-	1
CHECK-UP HEIMLICH VENTIL	2	-

Program:Table_number_of_unsch_visits_AT.sas, Output:Table_number_of_unsch_visits_AT.lst, 02MAR09

Table 39: All Adverse Events by System Organ Class, AT

		TachoSil N=149			Standard N=150			Total N=299		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
TOTAL	TOTAL	66	44	140	66	44	134	132	44	274
BLOOD AND LYMPHATIC SYSTEM DISORDERS	TOTAL	4	3	4	5	3	5	9	3	9
	Anaemia	4	3	4	5	3	5	9	3	9
CARDIAC DISORDERS	TOTAL	16	11	17	11	7	11	27	9	28
	Arrhythmia	-	-	-	1	1	1	1	0	1
	Atrial fibrillation	11	7	11	5	3	5	16	5	16
	Atrial tachycardia	1	1	1	-	-	-	1	0	1
	Bradycardia	-	-	-	1	1	1	1	0	1
	Supraventricular tachycardia	1	1	1	-	-	-	1	0	1
	Tachyarrhythmia	1	1	1	4	3	4	5	2	5
	Tachycardia	2	1	2	-	-	-	2	1	2
	Ventricular arrhythmia	1	1	1	-	-	-	1	0	1
EAR AND LABYRINTH DISORDERS	TOTAL	1	1	1	-	-	-	1	0	1
	Vertigo	1	1	1	-	-	-	1	0	1
GASTROINTESTINAL DISORDERS	TOTAL	11	7	14	11	7	19	22	7	33
	Constipation	5	3	5	9	6	9	14	5	14
	Diarrhoea	1	1	1	2	1	2	3	1	3
	Flatulence	2	1	2	7	5	7	9	3	9
	Ileus	1	1	1	-	-	-	1	0	1
	Nausea	3	2	4	-	-	-	3	1	4
	Oesophagitis	-	-	-	1	1	1	1	0	1
	Vomiting	1	1	1	-	-	-	1	0	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	10	7	12	6	4	6	16	5	18
	Drug ineffective	1	1	1	-	-	-	1	0	1
	Fatigue	1	1	1	-	-	-	1	0	1
	Localised oedema	-	-	-	1	1	1	1	0	1
	Malaise	1	1	1	-	-	-	1	0	1
	Oedema	1	1	1	-	-	-	1	0	1
	Oedema peripheral	-	-	-	1	1	1	1	0	1

(Continued)

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events
Program:Table_ae_all_AT.sas, Output:Table_ae_all_AT.lst, 02MAR09

Table 39: All Adverse Events by System Organ Class, AT

		TachoSil N=149			Standard N=150			Total N=299		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
GENERAL DISORDERS AND ADMINISTRATION SITE	Pain	2	1	2	1	1	1	3	1	3
CONDITIONS	Pyrexia	6	4	6	3	2	3	9	3	9
HEPATOBILIARY DISORDERS	TOTAL	-	-	-	1	1	1	1	0	1
	Jaundice	-	-	-	1	1	1	1	0	1
IMMUNE SYSTEM DISORDERS	TOTAL	-	-	-	2	1	2	2	1	2
	Drug hypersensitivity	-	-	-	1	1	1	1	0	1
	Hypersensitivity	-	-	-	1	1	1	1	0	1
INFECTIONS AND INFESTATIONS	TOTAL	15	10	20	13	9	14	28	9	34
	Bronchitis	-	-	-	1	1	1	1	0	1
	Bronchitis acute	1	1	1	-	-	-	1	0	1
	Bronchitis bacterial	1	1	1	-	-	-	1	0	1
	Candida sepsis	1	1	1	-	-	-	1	0	1
	Cystitis	2	1	2	1	1	1	3	1	3
	Gastroenteritis	1	1	1	-	-	-	1	0	1
	Infection	1	1	1	-	-	-	1	0	1
	Oesophageal candidiasis	1	1	1	-	-	-	1	0	1
	Pneumonia	8	5	10	9	6	10	17	6	20
	Post procedural pneumonia	1	1	1	-	-	-	1	0	1
	Urinary tract infection	-	-	-	1	1	1	1	0	1
	Wound infection	1	1	1	1	1	1	2	1	2
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	TOTAL	7	5	7	7	5	10	14	5	17
	Anaemia postoperative	2	1	2	1	1	1	3	1	3
	Haemothorax	2	1	2	1	1	1	3	1	3
	Nerve injury	1	1	1	-	-	-	1	0	1
	Post procedural haematoma	-	-	-	2	1	2	2	1	2
	Post procedural haemorrhage	1	1	1	2	1	2	3	1	3
	Postoperative fever	-	-	-	1	1	1	1	0	1
	Procedural pain	-	-	-	2	1	3	2	1	3
	Psychosis postoperative	1	1	1	-	-	-	1	0	1

(Continued)

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events
Program:Table_ae_all_AT.sas, Output:Table_ae_all_AT.lst, 02MAR09

Table 39: All Adverse Events by System Organ Class, AT

		TachoSil N=149			Standard N=150			Total N=299		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
INVESTIGATIONS	TOTAL	4	3	4	3	2	3	7	2	7
	Blood electrolytes decreased	1	1	1	-	-	-	1	0	1
	Blood pH decreased	1	1	1	-	-	-	1	0	1
	C-reactive protein increased	-	-	-	1	1	1	1	0	1
	Electrocardiogram ST segment elevation	1	1	1	-	-	-	1	0	1
	Haemoglobin decreased	-	-	-	1	1	1	1	0	1
	Respiratory rate increased	1	1	1	-	-	-	1	0	1
	Weight increased	-	-	-	1	1	1	1	0	1
METABOLISM AND NUTRITION DISORDERS	TOTAL	3	2	3	1	1	1	4	1	4
	Dehydration	1	1	1	-	-	-	1	0	1
	Diabetes mellitus	2	1	2	-	-	-	2	1	2
	Hypokalaemia	-	-	-	1	1	1	1	0	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE	TOTAL	-	-	-	2	1	2	2	1	2
DISORDERS	Back pain	-	-	-	1	1	1	1	0	1
	Musculoskeletal pain	-	-	-	1	1	1	1	0	1
NERVOUS SYSTEM DISORDERS	TOTAL	5	3	5	5	3	5	10	3	10
	Cerebral haemorrhage	-	-	-	1	1	1	1	0	1
	Cerebrovascular accident	1	1	1	-	-	-	1	0	1
	Headache	1	1	1	-	-	-	1	0	1
	Nervous system disorder	1	1	1	-	-	-	1	0	1
	Paresis	-	-	-	1	1	1	1	0	1
	Syncope vasovagal	1	1	1	-	-	-	1	0	1
	Vocal cord paralysis	1	1	1	3	2	3	4	1	4
PSYCHIATRIC DISORDERS	TOTAL	3	2	4	3	2	3	6	2	7
	Delirium	1	1	1	-	-	-	1	0	1
	Sleep disorder	2	1	3	3	2	3	5	2	6
RENAL AND URINARY DISORDERS	TOTAL	3	2	3	1	1	1	4	1	4
	Haematuria	1	1	1	-	-	-	1	0	1
	Renal failure	-	-	-	1	1	1	1	0	1

(Continued)

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events
Program:Table_ae_all_AT.sas, Output:Table_ae_all_AT.lst, 02MAR09

Table 39: All Adverse Events by System Organ Class, AT

		TachoSil N=149			Standard N=150			Total N=299		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
RENAL AND URINARY DISORDERS	Renal failure chronic	1	1	1	-	-	-	1	0	1
	Urinary retention	1	1	1	-	-	-	1	0	1
RESPIRATORY, THORACIC AND MEDIASTINAL	TOTAL	29	19	37	32	21	41	61	20	78
DISORDERS	Atelectasis	7	5	7	10	7	10	17	6	17
	Bronchial fistula	1	1	1	-	-	-	1	0	1
	Bronchopleural fistula	3	2	4	8	5	10	11	4	14
	Chronic obstructive pulmonary disease	-	-	-	1	1	1	1	0	1
	Chylothorax	2	1	2	-	-	-	2	1	2
	Cough	1	1	1	1	1	1	2	1	2
	Dyspnoea	2	1	2	2	1	2	4	1	4
	Emphysema	1	1	1	1	1	1	2	1	2
	Hydropneumothorax	-	-	-	1	1	1	1	0	1
	Hydrothorax	1	1	1	-	-	-	1	0	1
	Hypoxia	1	1	1	-	-	-	1	0	1
	Increased bronchial secretion	1	1	1	1	1	1	2	1	2
	Lung disorder	3	2	3	4	3	4	7	2	7
	Lung infiltration	-	-	-	1	1	1	1	0	1
	Pharyngolaryngeal pain	-	-	-	1	1	1	1	0	1
	Pleural effusion	5	3	5	2	1	2	7	2	7
	Pneumonia aspiration	1	1	1	-	-	-	1	0	1
	Pneumothorax	4	3	4	5	3	5	9	3	9
	Pulmonary embolism	-	-	-	1	1	1	1	0	1
	Pulmonary infarction	1	1	1	-	-	-	1	0	1
	Respiratory failure	1	1	1	-	-	-	1	0	1
	Sputum retention	1	1	1	-	-	-	1	0	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	TOTAL	5	3	5	2	1	3	7	2	8
	Dermatitis allergic	-	-	-	1	1	1	1	0	1
	Eczema	-	-	-	1	1	1	1	0	1
	Erythema	-	-	-	1	1	1	1	0	1

(Continued)

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events
Program:Table_ae_all_AT.sas, Output:Table_ae_all_AT.lst, 02MAR09

Table 39: All Adverse Events by System Organ Class, AT

		TachoSil N=149			Standard N=150			Total N=299		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Pruritus	4	3	4	-	-	-	4	1	4
	Subcutaneous emphysema	1	1	1	-	-	-	1	0	1
SURGICAL AND MEDICAL PROCEDURES	TOTAL	-	-	-	1	1	1	1	0	1
	Medical device removal	-	-	-	1	1	1	1	0	1
VASCULAR DISORDERS	TOTAL	3	2	4	6	4	6	9	3	10
	Haemorrhage	-	-	-	1	1	1	1	0	1
	Hypertension	2	1	2	4	3	4	6	2	6
	Hypotension	2	1	2	-	-	-	2	1	2
	Phlebitis	-	-	-	1	1	1	1	0	1

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events
Program:Table_ae_all_AT.sas, Output:Table_ae_all_AT.lst, 02MAR09

Table 40: Adverse Events with Incidence > 1% by System Organ Class, AT

		TachoSil N=149			Standard N=150			Total N=299		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
Blood and lymphatic system disorders	TOTAL	4	3	4	5	3	5	9	3	9
	Anaemia	4	3	4	5	3	5	9	3	9
Cardiac disorders	TOTAL	12	8	12	9	6	9	21	7	21
	Atrial fibrillation	11	7	11	5	3	5	16	5	16
	Tachyarrhythmia	1	1	1	4	3	4	5	2	5
Gastrointestinal disorders	TOTAL	9	6	12	10	7	18	19	6	30
	Constipation	5	3	5	9	6	9	14	5	14
	Diarrhoea	1	1	1	2	1	2	3	1	3
	Flatulence	2	1	2	7	5	7	9	3	9
	Nausea	3	2	4	-	-	-	3	1	4
General disorders and administration site conditions	TOTAL	7	5	8	4	3	4	11	4	12
	Pain	2	1	2	1	1	1	3	1	3
	Pyrexia	6	4	6	3	2	3	9	3	9
Infections and infestations	TOTAL	10	7	12	10	7	11	20	7	23
	Cystitis	2	1	2	1	1	1	3	1	3
	Pneumonia	8	5	10	9	6	10	17	6	20
Injury, poisoning and procedural complications	TOTAL	5	3	5	4	3	4	9	3	9
	Anaemia postoperative	2	1	2	1	1	1	3	1	3
	Haemothorax	2	1	2	1	1	1	3	1	3
	Post procedural haemorrhage	1	1	1	2	1	2	3	1	3
Nervous system disorders	TOTAL	1	1	1	3	2	3	4	1	4
	Vocal cord paralysis	1	1	1	3	2	3	4	1	4
Psychiatric disorders	TOTAL	2	1	3	3	2	3	5	2	6
	Sleep disorder	2	1	3	3	2	3	5	2	6
Respiratory, thoracic and mediastinal disorders	TOTAL	23	15	25	28	19	33	51	17	58
	Atelectasis	7	5	7	10	7	10	17	6	17
	Bronchopleural fistula	3	2	4	8	5	10	11	4	14
	Dyspnoea	2	1	2	2	1	2	4	1	4
	Lung disorder	3	2	3	4	3	4	7	2	7

(Continued)

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events
Program:Table_ae_incidence_1percent_AT.sas, Output:Table_ae_incidence_1percent_AT.lst, 02MAR09

Table 40: Adverse Events with Incidence > 1% by System Organ Class, AT

		TachoSil N=149			Standard N=150			Total N=299		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
Respiratory, thoracic and mediastinal	Pleural effusion	5	3	5	2	1	2	7	2	7
disorders	Pneumothorax	4	3	4	5	3	5	9	3	9
Vascular disorders	TOTAL	2	1	2	4	3	4	6	2	6
	Hypertension	2	1	2	4	3	4	6	2	6
Skin and subcutaneous tissue disorders	TOTAL	4	3	4	-	-	-	4	1	4
	Pruritus	4	3	4	-	-	-	4	1	4

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events
Program:Table_ae_incidence_1percent_AT.sas, Output:Table_ae_incidence_1percent_AT.lst, 02MAR09

Table 41: All Adverse Events by Severity and System Organ Class, AT

Severity=MILD

		TachoSil N=149			Standard N=150			Total N=299		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
TOTAL	TOTAL	61	41	94	57	38	108	118	39	202
BLOOD AND LYMPHATIC SYSTEM DISORDERS	TOTAL	3	2	3	5	3	5	8	3	8
	Anaemia	3	2	3	5	3	5	8	3	8
CARDIAC DISORDERS	TOTAL	14	9	15	9	6	9	23	8	24
	Arrhythmia	-	-	-	1	1	1	1	0	1
	Atrial fibrillation	9	6	9	5	3	5	14	5	14
	Atrial tachycardia	1	1	1	-	-	-	1	0	1
	Bradycardia	-	-	-	1	1	1	1	0	1
	Supraventricular tachycardia	1	1	1	-	-	-	1	0	1
	Tachyarrhythmia	1	1	1	2	1	2	3	1	3
	Tachycardia	2	1	2	-	-	-	2	1	2
	Ventricular arrhythmia	1	1	1	-	-	-	1	0	1
EAR AND LABYRINTH DISORDERS	TOTAL	1	1	1	-	-	-	1	0	1
	Vertigo	1	1	1	-	-	-	1	0	1
GASTROINTESTINAL DISORDERS	TOTAL	10	7	12	11	7	19	21	7	31
	Constipation	5	3	5	9	6	9	14	5	14
	Diarrhoea	1	1	1	2	1	2	3	1	3
	Flatulence	2	1	2	7	5	7	9	3	9
	Nausea	3	2	3	-	-	-	3	1	3
	Oesophagitis	-	-	-	1	1	1	1	0	1
	Vomiting	1	1	1	-	-	-	1	0	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	6	4	6	5	3	5	11	4	11
	Oedema	1	1	1	-	-	-	1	0	1
	Oedema peripheral	-	-	-	1	1	1	1	0	1
	Pain	-	-	-	1	1	1	1	0	1
	Pyrexia	5	3	5	3	2	3	8	3	8
IMMUNE SYSTEM DISORDERS	TOTAL	-	-	-	2	1	2	2	1	2

(Continued)

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events
Program:Table_ae_all_by_severity_AT.sas, Output:Table_ae_all_by_severity_AT.lst, 02MAR09

Table 41: All Adverse Events by Severity and System Organ Class, AT

Severity=MILD

		TachoSil N=149			Standard N=150			Total N=299		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
IMMUNE SYSTEM DISORDERS	Drug hypersensitivity	-	-	-	1	1	1	1	0	1
	Hypersensitivity	-	-	-	1	1	1	1	0	1
INFECTIONS AND INFESTATIONS	TOTAL	11	7	15	10	7	10	21	7	25
	Bronchitis	-	-	-	1	1	1	1	0	1
	Cystitis	2	1	2	1	1	1	3	1	3
	Gastroenteritis	1	1	1	-	-	-	1	0	1
	Infection	1	1	1	-	-	-	1	0	1
	Oesophageal candidiasis	1	1	1	-	-	-	1	0	1
	Pneumonia	6	4	8	6	4	6	12	4	14
	Post procedural pneumonia	1	1	1	-	-	-	1	0	1
	Urinary tract infection	-	-	-	1	1	1	1	0	1
	Wound infection	1	1	1	1	1	1	2	1	2
INJURY, POISONING AND PROCEDURAL	TOTAL	6	4	6	5	3	8	11	4	14
COMPLICATIONS	Anaemia postoperative	2	1	2	-	-	-	2	1	2
	Haemothorax	2	1	2	1	1	1	3	1	3
	Nerve injury	1	1	1	-	-	-	1	0	1
	Post procedural haematoma	-	-	-	2	1	2	2	1	2
	Post procedural haemorrhage	-	-	-	1	1	1	1	0	1
	Postoperative fever	-	-	-	1	1	1	1	0	1
	Procedural pain	-	-	-	2	1	3	2	1	3
	Psychosis postoperative	1	1	1	-	-	-	1	0	1
INVESTIGATIONS	TOTAL	3	2	3	3	2	3	6	2	6
	Blood electrolytes decreased	1	1	1	-	-	-	1	0	1
	Blood pH decreased	1	1	1	-	-	-	1	0	1
	C-reactive protein increased	-	-	-	1	1	1	1	0	1
	Haemoglobin decreased	-	-	-	1	1	1	1	0	1
	Respiratory rate increased	1	1	1	-	-	-	1	0	1

(Continued)

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events
Program:Table_ae_all_by_severity_AT.sas, Output:Table_ae_all_by_severity_AT.lst, 02MAR09

Table 41: All Adverse Events by Severity and System Organ Class, AT

Severity=MILD

		TachoSil N=149			Standard N=150			Total N=299		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
INVESTIGATIONS	Weight increased	-	-	-	1	1	1	1	0	1
METABOLISM AND NUTRITION DISORDERS	TOTAL	2	1	2	1	1	1	3	1	3
	Dehydration	1	1	1	-	-	-	1	0	1
	Diabetes mellitus	1	1	1	-	-	-	1	0	1
	Hypokalaemia	-	-	-	1	1	1	1	0	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE	TOTAL	-	-	-	2	1	2	2	1	2
DISORDERS	Back pain	-	-	-	1	1	1	1	0	1
	Musculoskeletal pain	-	-	-	1	1	1	1	0	1
NERVOUS SYSTEM DISORDERS	TOTAL	2	1	2	3	2	3	5	2	5
	Headache	1	1	1	-	-	-	1	0	1
	Vocal cord paralysis	1	1	1	3	2	3	4	1	4
PSYCHIATRIC DISORDERS	TOTAL	2	1	3	3	2	3	5	2	6
	Sleep disorder	2	1	3	3	2	3	5	2	6
RENAL AND URINARY DISORDERS	TOTAL	3	2	3	1	1	1	4	1	4
	Haematuria	1	1	1	-	-	-	1	0	1
	Renal failure	-	-	-	1	1	1	1	0	1
	Renal failure chronic	1	1	1	-	-	-	1	0	1
	Urinary retention	1	1	1	-	-	-	1	0	1
RESPIRATORY, THORACIC AND MEDIASTINAL	TOTAL	17	11	19	24	16	29	41	14	48
DISORDERS	Atelectasis	3	2	3	6	4	6	9	3	9
	Bronchopleural fistula	2	1	3	6	4	6	8	3	9
	Chronic obstructive pulmonary disease	-	-	-	1	1	1	1	0	1
	Cough	1	1	1	1	1	1	2	1	2
	Dyspnoea	1	1	1	2	1	2	3	1	3
	Emphysema	1	1	1	1	1	1	2	1	2
	Hydrothorax	1	1	1	-	-	-	1	0	1
	Increased bronchial secretion	-	-	-	1	1	1	1	0	1

(Continued)

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events
Program:Table_ae_all_by_severity_AT.sas, Output:Table_ae_all_by_severity_AT.lst, 02MAR09

Table 41: All Adverse Events by Severity and System Organ Class, AT

Severity=MILD

		TachoSil N=149			Standard N=150			Total N=299		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
RESPIRATORY, THORACIC AND MEDIASTINAL	Lung disorder	2	1	2	4	3	4	6	2	6
DISORDERS	Lung infiltration	-	-	-	1	1	1	1	0	1
	Pharyngolaryngeal pain	-	-	-	1	1	1	1	0	1
	Pleural effusion	4	3	4	2	1	2	6	2	6
	Pneumothorax	2	1	2	3	2	3	5	2	5
	Respiratory failure	1	1	1	-	-	-	1	0	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	TOTAL	3	2	3	2	1	2	5	2	5
	Dermatitis allergic	-	-	-	1	1	1	1	0	1
	Eczema	-	-	-	1	1	1	1	0	1
	Pruritus	3	2	3	-	-	-	3	1	3
VASCULAR DISORDERS	TOTAL	1	1	1	6	4	6	7	2	7
	Haemorrhage	-	-	-	1	1	1	1	0	1
	Hypertension	1	1	1	4	3	4	5	2	5
	Phlebitis	-	-	-	1	1	1	1	0	1

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events
Program:Table_ae_all_by_severity_AT.sas, Output:Table_ae_all_by_severity_AT.lst, 02MAR09

Table 41: All Adverse Events by Severity and System Organ Class, AT

Severity=MODERATE

		TachoSil N=149			Standard N=150			Total N=299		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
TOTAL	TOTAL	22	15	37	13	9	17	35	12	54
BLOOD AND LYMPHATIC SYSTEM DISORDERS	TOTAL	1	1	1	-	-	-	1	0	1
	Anaemia	1	1	1	-	-	-	1	0	1
CARDIAC DISORDERS	TOTAL	2	1	2	2	1	2	4	1	4
	Atrial fibrillation	2	1	2	-	-	-	2	1	2
	Tachyarrhythmia	-	-	-	2	1	2	2	1	2
GASTROINTESTINAL DISORDERS	TOTAL	1	1	1	-	-	-	1	0	1
	Nausea	1	1	1	-	-	-	1	0	1
GENERAL DISORDERS AND ADMINISTRATION SITE	TOTAL	3	2	5	1	1	1	4	1	6
CONDITIONS	Fatigue	1	1	1	-	-	-	1	0	1
	Localised oedema	-	-	-	1	1	1	1	0	1
	Malaise	1	1	1	-	-	-	1	0	1
	Pain	2	1	2	-	-	-	2	1	2
	Pyrexia	1	1	1	-	-	-	1	0	1
INFECTIONS AND INFESTATIONS	TOTAL	4	3	4	3	2	3	7	2	7
	Bronchitis acute	1	1	1	-	-	-	1	0	1
	Bronchitis bacterial	1	1	1	-	-	-	1	0	1
	Pneumonia	2	1	2	3	2	3	5	2	5
INJURY, POISONING AND PROCEDURAL	TOTAL	-	-	-	1	1	1	1	0	1
COMPLICATIONS	Anaemia postoperative	-	-	-	1	1	1	1	0	1
INVESTIGATIONS	TOTAL	1	1	1	-	-	-	1	0	1
	Electrocardiogram ST segment elevation	1	1	1	-	-	-	1	0	1
METABOLISM AND NUTRITION DISORDERS	TOTAL	1	1	1	-	-	-	1	0	1
	Diabetes mellitus	1	1	1	-	-	-	1	0	1
NERVOUS SYSTEM DISORDERS	TOTAL	2	1	2	2	1	2	4	1	4
	Cerebral haemorrhage	-	-	-	1	1	1	1	0	1
	Nervous system disorder	1	1	1	-	-	-	1	0	1

(Continued)

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events
Program:Table_ae_all_by_severity_AT.sas, Output:Table_ae_all_by_severity_AT.lst, 02MAR09

Table 41: All Adverse Events by Severity and System Organ Class, AT

Severity=MODERATE

		TachoSil N=149			Standard N=150			Total N=299		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
NERVOUS SYSTEM DISORDERS	Paresis	-	-	-	1	1	1	1	0	1
	Syncope vasovagal	1	1	1	-	-	-	1	0	1
PSYCHIATRIC DISORDERS	TOTAL	1	1	1	-	-	-	1	0	1
	Delirium	1	1	1	-	-	-	1	0	1
RESPIRATORY, THORACIC AND MEDIASTINAL	TOTAL	13	9	14	7	5	8	20	7	22
DISORDERS	Atelectasis	4	3	4	3	2	3	7	2	7
	Bronchopleural fistula	1	1	1	1	1	2	2	1	3
	Chylothorax	2	1	2	-	-	-	2	1	2
	Dyspnoea	1	1	1	-	-	-	1	0	1
	Hydropneumothorax	-	-	-	1	1	1	1	0	1
	Hypoxia	1	1	1	-	-	-	1	0	1
	Increased bronchial secretion	1	1	1	-	-	-	1	0	1
	Pleural effusion	1	1	1	-	-	-	1	0	1
	Pneumothorax	2	1	2	2	1	2	4	1	4
	Sputum retention	1	1	1	-	-	-	1	0	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	TOTAL	2	1	2	-	-	-	2	1	2
	Pruritus	1	1	1	-	-	-	1	0	1
	Subcutaneous emphysema	1	1	1	-	-	-	1	0	1
VASCULAR DISORDERS	TOTAL	3	2	3	-	-	-	3	1	3
	Hypertension	1	1	1	-	-	-	1	0	1
	Hypotension	2	1	2	-	-	-	2	1	2

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events
Program:Table_ae_all_by_severity_AT.sas, Output:Table_ae_all_by_severity_AT.lst, 02MAR09

Table 41: All Adverse Events by Severity and System Organ Class, AT

Severity=SEVERE

		TachoSil N=149			Standard N=150			Total N=299		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
TOTAL	TOTAL	8	5	9	7	5	9	15	5	18
GASTROINTESTINAL DISORDERS	TOTAL	1	1	1	-	-	-	1	0	1
	Ileus	1	1	1	-	-	-	1	0	1
GENERAL DISORDERS AND ADMINISTRATION SITE	TOTAL	1	1	1	-	-	-	1	0	1
CONDITIONS	Drug ineffective	1	1	1	-	-	-	1	0	1
HEPATOBILIARY DISORDERS	TOTAL	-	-	-	1	1	1	1	0	1
	Jaundice	-	-	-	1	1	1	1	0	1
INFECTIONS AND INFESTATIONS	TOTAL	1	1	1	1	1	1	2	1	2
	Candida sepsis	1	1	1	-	-	-	1	0	1
	Pneumonia	-	-	-	1	1	1	1	0	1
INJURY, POISONING AND PROCEDURAL	TOTAL	1	1	1	1	1	1	2	1	2
COMPLICATIONS	Post procedural haemorrhage	1	1	1	1	1	1	2	1	2
NERVOUS SYSTEM DISORDERS	TOTAL	1	1	1	-	-	-	1	0	1
	Cerebrovascular accident	1	1	1	-	-	-	1	0	1
RESPIRATORY, THORACIC AND MEDIASTINAL	TOTAL	3	2	4	4	3	4	7	2	8
DISORDERS	Atelectasis	-	-	-	1	1	1	1	0	1
	Bronchial fistula	1	1	1	-	-	-	1	0	1
	Bronchopleural fistula	-	-	-	2	1	2	2	1	2
	Lung disorder	1	1	1	-	-	-	1	0	1
	Pneumonia aspiration	1	1	1	-	-	-	1	0	1
	Pulmonary embolism	-	-	-	1	1	1	1	0	1
	Pulmonary infarction	1	1	1	-	-	-	1	0	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	TOTAL	-	-	-	1	1	1	1	0	1
	Erythema	-	-	-	1	1	1	1	0	1
SURGICAL AND MEDICAL PROCEDURES	TOTAL	-	-	-	1	1	1	1	0	1
	Medical device removal	-	-	-	1	1	1	1	0	1

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events
Program:Table_ae_all_by_severity_AT.sas, Output:Table_ae_all_by_severity_AT.lst, 02MAR09

Table 42: All Adverse Events by Causality and System Organ Class, AT

Only possible/probable causalities

Relationship to trial drug=POSSIBLE

		TachoSil N=149			Standard N=150			Total N=299		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
TOTAL	TOTAL	6	4	6	2	1	2	8	3	8
GENERAL DISORDERS AND ADMINISTRATION SITE	TOTAL	3	2	3	-	-	-	3	1	3
CONDITIONS	Drug ineffective	1	1	1	-	-	-	1	0	1
	Pyrexia	2	1	2	-	-	-	2	1	2
RESPIRATORY, THORACIC AND MEDIASTINAL	TOTAL	3	2	3	2	1	2	5	2	5
DISORDERS	Bronchopleural fistula	-	-	-	1	1	1	1	0	1
	Lung disorder	1	1	1	1	1	1	2	1	2
	Pleural effusion	1	1	1	-	-	-	1	0	1
	Pneumothorax	1	1	1	-	-	-	1	0	1

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events
Program:Table_ae_all_by_causality_AT.sas, Output:Table_ae_all_by_causality_AT.lst, 02MAR09

Table 42: All Adverse Events by Causality and System Organ Class, AT
Only possible/probable causalities

Relationship to trial drug=PROBABLE

		TachoSil N=149			Standard N=150			Total N=299		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
TOTAL	TOTAL	5	3	6	2	1	2	7	2	8
GENERAL DISORDERS AND ADMINISTRATION SITE	TOTAL	1	1	1	-	-	-	1	0	1
CONDITIONS	Pyrexia	1	1	1	-	-	-	1	0	1
RESPIRATORY, THORACIC AND MEDIASTINAL	TOTAL	4	3	4	2	1	2	6	2	6
DISORDERS	Bronchopleural fistula	1	1	1	-	-	-	1	0	1
	Lung disorder	1	1	1	-	-	-	1	0	1
	Pleural effusion	2	1	2	1	1	1	3	1	3
	Pneumothorax	-	-	-	1	1	1	1	0	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	TOTAL	1	1	1	-	-	-	1	0	1
	Pruritus	1	1	1	-	-	-	1	0	1

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events
Program:Table_ae_all_by_causality_AT.sas, Output:Table_ae_all_by_causality_AT.lst, 02MAR09

Table 43: Severe Adverse Events by Causality and System Organ Class, AT

Only possible/probable causalities

Relationship to trial drug=POSSIBLE

		TachoSil N=149		
		n	%	E
System Organ Class	Preferred Term			
TOTAL	TOTAL	1	1	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	1	1	1
	Drug ineffective	1	1	1

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events
Program:Table_severe_ae_all_by_causality_AT.sas, Output:Table_severe_ae_all_by_causality_AT.lst, 02MAR09

Table 44: All Severe Serious Adverse Events by Causality and System Organ Class, AT

Only possible/probable causalities

Relationship to trial drug=POSSIBLE

		TachoSil N=149		
		n	%	E
System Organ Class	Preferred Term			
TOTAL	TOTAL	1	1	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	1	1	1
	Drug ineffective	1	1	1

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events
Program:Table_severe_sae_all_by_causality_AT.sas, Output:Table_severe_sae_all_by_causality_AT.lst, 02MAR09

Table 45: All Serious Adverse Events by System Organ Class, AT

		TachoSil N=149			Standard N=150			Total N=299		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
TOTAL	TOTAL	16	11	19	12	8	13	28	9	32
CARDIAC DISORDERS	TOTAL	-	-	-	1	1	1	1	0	1
	Atrial fibrillation	-	-	-	1	1	1	1	0	1
GASTROINTESTINAL DISORDERS	TOTAL	1	1	1	-	-	-	1	0	1
	Ileus	1	1	1	-	-	-	1	0	1
GENERAL DISORDERS AND ADMINISTRATION SITE	TOTAL	1	1	1	-	-	-	1	0	1
CONDITIONS	Drug ineffective	1	1	1	-	-	-	1	0	1
HEPATOBILIARY DISORDERS	TOTAL	-	-	-	1	1	1	1	0	1
	Jaundice	-	-	-	1	1	1	1	0	1
INFECTIONS AND INFESTATIONS	TOTAL	3	2	3	3	2	3	6	2	6
	Candida sepsis	1	1	1	-	-	-	1	0	1
	Pneumonia	2	1	2	3	2	3	5	2	5
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	TOTAL	1	1	1	2	1	2	3	1	3
	Haemothorax	-	-	-	1	1	1	1	0	1
	Post procedural haemorrhage	1	1	1	1	1	1	2	1	2
NERVOUS SYSTEM DISORDERS	TOTAL	2	1	2	2	1	2	4	1	4
	Cerebrovascular accident	1	1	1	-	-	-	1	0	1
	Vocal cord paralysis	1	1	1	2	1	2	3	1	3
RESPIRATORY, THORACIC AND MEDIASTINAL	TOTAL	10	7	11	4	3	4	14	5	15
DISORDERS	Atelectasis	2	1	2	-	-	-	2	1	2
	Bronchial fistula	1	1	1	-	-	-	1	0	1
	Bronchopleural fistula	-	-	-	2	1	2	2	1	2
	Chylothorax	1	1	1	-	-	-	1	0	1
	Lung disorder	1	1	1	-	-	-	1	0	1
	Pleural effusion	1	1	1	-	-	-	1	0	1
	Pneumonia aspiration	1	1	1	-	-	-	1	0	1
	Pneumothorax	2	1	2	1	1	1	3	1	3
	Pulmonary embolism	-	-	-	1	1	1	1	0	1
	Pulmonary infarction	1	1	1	-	-	-	1	0	1

(Continued)

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events
Program:Table_sae_all_AT.sas, Output:Table_sae_all_AT.lst, 02MAR09

Table 45: All Serious Adverse Events by System Organ Class, AT

		TachoSil N=149			Standard N=150			Total N=299		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Respiratory failure	1	1	1	-	-	-	1	0	1

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events
Program:Table_sae_all_AT.sas, Output:Table_sae_all_AT.lst, 02MAR09

Table 46: Serious Adverse Events by Severity and System Organ Class, AT

Severity=MILD

		TachoSil N=149			Standard N=150			Total N=299		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
TOTAL	TOTAL	4	3	4	6	4	6	10	3	10
CARDIAC DISORDERS	TOTAL	-	-	-	1	1	1	1	0	1
	Atrial fibrillation	-	-	-	1	1	1	1	0	1
INFECTIONS AND INFESTATIONS	TOTAL	1	1	1	1	1	1	2	1	2
	Pneumonia	1	1	1	1	1	1	2	1	2
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	TOTAL	-	-	-	1	1	1	1	0	1
	Haemothorax	-	-	-	1	1	1	1	0	1
NERVOUS SYSTEM DISORDERS	TOTAL	1	1	1	2	1	2	3	1	3
	Vocal cord paralysis	1	1	1	2	1	2	3	1	3
RESPIRATORY, THORACIC AND MEDIASTINAL	TOTAL	2	1	2	1	1	1	3	1	3
DISORDERS	Pneumothorax	1	1	1	1	1	1	2	1	2
	Respiratory failure	1	1	1	-	-	-	1	0	1

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events
Program:Table_sae_all_by_severity_AT.sas, Output:Table_sae_all_by_severity_AT.lst, 02MAR09

Table 46: Serious Adverse Events by Severity and System Organ Class, AT

Severity=MODERATE

		TachoSil N=149			Standard N=150			Total N=299		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
TOTAL	TOTAL	6	4	6	1	1	1	7	2	7
INFECTIONS AND INFESTATIONS	TOTAL	1	1	1	1	1	1	2	1	2
	Pneumonia	1	1	1	1	1	1	2	1	2
RESPIRATORY, THORACIC AND MEDIASTINAL	TOTAL	5	3	5	-	-	-	5	2	5
DISORDERS	Atelectasis	2	1	2	-	-	-	2	1	2
	Chylothorax	1	1	1	-	-	-	1	0	1
	Pleural effusion	1	1	1	-	-	-	1	0	1
	Pneumothorax	1	1	1	-	-	-	1	0	1

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events
Program:Table_sae_all_by_severity_AT.sas, Output:Table_sae_all_by_severity_AT.lst, 02MAR09

Table 46: Serious Adverse Events by Severity and System Organ Class, AT

Severity=SEVERE

		TachoSil N=149			Standard N=150			Total N=299		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
TOTAL	TOTAL	8	5	9	5	3	6	13	4	15
GASTROINTESTINAL DISORDERS	TOTAL	1	1	1	-	-	-	1	0	1
	Ileus	1	1	1	-	-	-	1	0	1
GENERAL DISORDERS AND ADMINISTRATION SITE	TOTAL	1	1	1	-	-	-	1	0	1
CONDITIONS	Drug ineffective	1	1	1	-	-	-	1	0	1
HEPATOBILIARY DISORDERS	TOTAL	-	-	-	1	1	1	1	0	1
	Jaundice	-	-	-	1	1	1	1	0	1
INFECTIONS AND INFESTATIONS	TOTAL	1	1	1	1	1	1	2	1	2
	Candida sepsis	1	1	1	-	-	-	1	0	1
	Pneumonia	-	-	-	1	1	1	1	0	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	TOTAL	1	1	1	1	1	1	2	1	2
	Post procedural haemorrhage	1	1	1	1	1	1	2	1	2
NERVOUS SYSTEM DISORDERS	TOTAL	1	1	1	-	-	-	1	0	1
	Cerebrovascular accident	1	1	1	-	-	-	1	0	1
RESPIRATORY, THORACIC AND MEDIASTINAL	TOTAL	3	2	4	3	2	3	6	2	7
DISORDERS	Bronchial fistula	1	1	1	-	-	-	1	0	1
	Bronchopleural fistula	-	-	-	2	1	2	2	1	2
	Lung disorder	1	1	1	-	-	-	1	0	1
	Pneumonia aspiration	1	1	1	-	-	-	1	0	1
	Pulmonary embolism	-	-	-	1	1	1	1	0	1
	Pulmonary infarction	1	1	1	-	-	-	1	0	1

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events
Program:Table_sae_all_by_severity_AT.sas, Output:Table_sae_all_by_severity_AT.lst, 02MAR09

Table 47: Serious Adverse Events by Causality and System Organ Class, AT

Only possible/probable causalities

Relationship to trial drug=POSSIBLE

		TachoSil N=149		
		n	%	E
System Organ Class	Preferred Term			
TOTAL	TOTAL	3	2	3
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	1	1	1
	Drug ineffective	1	1	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	2	1	2
	Pleural effusion	1	1	1
	Pneumothorax	1	1	1

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events
Program:Table_sae_all_by_causality_AT.sas, Output:Table_sae_all_by_causality_AT.lst, 02MAR09

Table 48: Deaths by System Organ Class, AT

		TachoSil N=149			Standard N=150			Total N=299		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
TOTAL	TOTAL	3	2	5	1	1	1	4	1	6
INFECTIONS AND INFESTATIONS	TOTAL	1	1	1	-	-	-	1	0	1
	Candida sepsis	1	1	1	-	-	-	1	0	1
NERVOUS SYSTEM DISORDERS	TOTAL	1	1	1	-	-	-	1	0	1
	Cerebrovascular accident	1	1	1	-	-	-	1	0	1
RESPIRATORY, THORACIC AND MEDIASTINAL	TOTAL	2	1	3	1	1	1	3	1	4
DISORDERS	Atelectasis	1	1	1	-	-	-	1	0	1
	Bronchial fistula	1	1	1	-	-	-	1	0	1
	Bronchopleural fistula	-	-	-	1	1	1	1	0	1
	Pneumonia aspiration	1	1	1	-	-	-	1	0	1

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events
Program:Table_deaths_AT.sas, Output:Table_deaths_AT.lst, 02MAR09

Table 49: Adverse Events Leading to Withdrawal by System Organ Class, AT

		TachoSil N=149		
		n	%	E
System Organ Class	Preferred Term			
TOTAL	TOTAL	2	1	2
INFECTIONS AND INFESTATIONS	TOTAL	1	1	1
	Candida sepsis	1	1	1
NERVOUS SYSTEM DISORDERS	TOTAL	1	1	1
	Cerebrovascular accident	1	1	1

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events
Program:Table_ae_all_reason_for_withdrawal_AT.sas, Output:Table_ae_all_reason_for_withdrawal_AT.lst, 02MAR09

Table 50: Vital Signs - Temperature Recordings, AT

	TACHOSIL						STANDARD						All					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
SCREENING																		
AXILLA	71	36.5	0.3	36.5	36.0	37.3	72	36.4	0.3	36.5	35.4	37.3	143	36.5	0.3	36.5	35.4	37.3
EAR	51	36.5	0.4	36.4	35.6	37.4	52	36.5	0.4	36.4	35.5	37.4	103	36.5	0.4	36.4	35.5	37.4
ORALLY	6	36.8	0.7	36.5	36.2	38.1	6	36.4	0.3	36.4	36.0	36.8	12	36.6	0.6	36.4	36.0	38.1
RECTALLY	18	37.1	0.3	37.1	36.5	37.8	15	37.2	0.4	37.2	36.6	37.9	33	37.2	0.3	37.1	36.5	37.9
DAY 0 PRE-RANDOM																		
AXILLA	72	36.5	0.3	36.5	35.7	37.5	69	36.4	0.3	36.5	35.0	37.1	141	36.5	0.3	36.5	35.0	37.5
EAR	50	36.5	0.4	36.5	35.6	37.4	52	36.3	0.7	36.3	31.8	37.3	102	36.4	0.6	36.4	31.8	37.4
ORALLY	6	36.4	0.1	36.4	36.2	36.5	6	36.5	0.2	36.5	36.2	36.9	12	36.4	0.2	36.4	36.2	36.9
RECTALLY	11	37.4	0.7	37.4	36.2	38.9	17	37.5	0.5	37.6	36.6	38.3	28	37.4	0.6	37.5	36.2	38.9
DAY 1																		
AXILLA	72	36.8	0.5	36.7	36.0	38.5	75	36.7	0.5	36.6	35.4	37.9	147	36.7	0.5	36.6	35.4	38.5
EAR	49	36.8	0.5	36.8	36.0	37.8	52	36.9	0.6	36.9	36.0	38.2	101	36.9	0.5	36.8	36.0	38.2
ORALLY	6	36.4	0.2	36.3	36.3	36.8	5	37.5	0.8	37.4	36.4	38.5	11	36.9	0.8	36.5	36.3	38.5
RECTALLY	21	37.6	0.6	37.8	36.1	38.3	16	37.8	0.4	37.8	37.2	38.5	37	37.7	0.5	37.8	36.1	38.5
DAY 2																		
AXILLA	70	36.8	0.5	36.6	36.0	39.2	72	36.7	0.5	36.6	35.2	37.9	142	36.7	0.5	36.6	35.2	39.2
EAR	49	36.6	0.5	36.6	35.7	37.7	53	36.8	0.5	36.7	35.8	38.1	102	36.7	0.5	36.6	35.7	38.1
ORALLY	7	36.7	0.5	36.8	36.1	37.3	5	36.8	0.4	36.6	36.4	37.4	12	36.7	0.4	36.7	36.1	37.4
RECTALLY	17	37.7	0.7	37.7	36.0	39.0	17	37.5	0.3	37.4	36.9	38.2	34	37.6	0.6	37.5	36.0	39.0
DAY 3																		
AXILLA	59	36.8	0.6	36.6	36.0	39.0	66	36.6	0.5	36.6	35.2	38.0	125	36.7	0.5	36.6	35.2	39.0
EAR	47	36.5	0.4	36.5	35.4	37.5	51	36.7	0.4	36.6	36.0	37.6	98	36.6	0.4	36.6	35.4	37.6
ORALLY	5	36.4	0.1	36.5	36.3	36.5	4	36.9	0.4	36.8	36.6	37.4	9	36.6	0.3	36.5	36.3	37.4
RECTALLY	15	37.4	0.5	37.4	36.5	38.1	13	37.4	0.6	37.3	36.4	38.5	28	37.4	0.5	37.4	36.4	38.5
DAY 4																		
AXILLA	14	36.5	0.6	36.6	35.0	37.3	23	36.5	0.4	36.5	35.8	37.6	37	36.5	0.5	36.6	35.0	37.6
EAR	28	36.5	0.5	36.5	35.4	37.8	29	36.8	0.7	36.6	36.0	38.4	57	36.7	0.6	36.6	35.4	38.4
ORALLY	1	37.3	-	37.3	37.3	37.3	-	-	-	-	-	-	1	37.3	-	37.3	37.3	37.3
RECTALLY	7	37.4	0.4	37.3	36.8	38.0	7	37.3	0.3	37.4	36.9	37.8	14	37.3	0.3	37.4	36.8	38.0

(Continued)

Program:Table_vitalsigns_temperature_AT.sas, Output:Table_vitalsigns_temperature_AT.lst, 02MAR09

Table 50: Vital Signs - Temperature Recordings, AT

	TACHOSIL						STANDARD						All					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
DAY 5																		
AXILLA	9	36.4	0.6	36.5	35.0	37.1	16	36.4	0.5	36.5	35.4	37.4	25	36.4	0.5	36.5	35.0	37.4
EAR	23	36.4	0.5	36.4	35.8	38.0	24	36.5	0.5	36.4	35.8	38.0	47	36.5	0.5	36.4	35.8	38.0
ORALLY	1	36.4	-	36.4	36.4	36.4	-	-	-	-	-	-	1	36.4	-	36.4	36.4	36.4
RECTALLY	4	37.3	0.6	37.5	36.4	37.8	5	37.3	0.4	37.2	36.9	37.8	9	37.3	0.5	37.2	36.4	37.8
DAY 6																		
AXILLA	3	36.6	0.3	36.6	36.4	36.9	12	36.4	0.3	36.6	36.0	36.8	15	36.5	0.3	36.6	36.0	36.9
EAR	15	36.2	1.3	36.4	32.0	37.4	18	36.5	0.3	36.4	36.0	37.0	33	36.4	0.9	36.4	32.0	37.4
ORALLY	1	36.5	-	36.5	36.5	36.5	-	-	-	-	-	-	1	36.5	-	36.5	36.5	36.5
RECTALLY	3	36.9	0.1	36.8	36.8	37.0	5	37.2	0.2	37.2	36.9	37.4	8	37.1	0.2	37.1	36.8	37.4
DAY 7																		
AXILLA	3	36.3	0.1	36.3	36.2	36.4	8	36.3	0.3	36.3	36.0	36.8	11	36.3	0.2	36.3	36.0	36.8
EAR	9	36.5	0.6	36.4	36.0	38.0	10	36.5	0.5	36.7	35.4	36.9	19	36.5	0.5	36.6	35.4	38.0
RECTALLY	1	37.2	-	37.2	37.2	37.2	4	37.2	0.2	37.1	37.0	37.5	5	37.2	0.2	37.2	37.0	37.5
DAY 8																		
AXILLA	3	36.2	0.3	36.2	36.0	36.5	7	36.4	0.2	36.4	36.0	36.6	10	36.3	0.2	36.4	36.0	36.6
EAR	4	36.4	0.3	36.4	36.1	36.7	8	36.5	0.3	36.6	36.0	36.8	12	36.5	0.3	36.6	36.0	36.8
RECTALLY	1	37.2	-	37.2	37.2	37.2	3	37.1	0.2	37.0	37.0	37.3	4	37.1	0.2	37.1	37.0	37.3
DAY 9																		
AXILLA	3	36.2	0.3	36.2	36.0	36.5	5	36.4	0.2	36.5	36.2	36.6	8	36.4	0.2	36.4	36.0	36.6
EAR	4	37.0	0.8	37.0	36.0	37.8	7	36.4	0.3	36.2	36.2	37.0	11	36.6	0.6	36.4	36.0	37.8
RECTALLY	1	37.0	-	37.0	37.0	37.0	-	-	-	-	-	-	1	37.0	-	37.0	37.0	37.0
DAY 10																		
AXILLA	2	36.4	0.1	36.4	36.3	36.5	4	36.5	0.1	36.5	36.4	36.6	6	36.5	0.1	36.5	36.3	36.6
EAR	3	37.1	0.6	36.8	36.8	37.8	5	36.2	0.2	36.2	36.0	36.5	8	36.6	0.6	36.5	36.0	37.8
RECTALLY	1	36.3	-	36.3	36.3	36.3	1	36.8	-	36.8	36.8	36.8	2	36.6	0.4	36.6	36.3	36.8
DAY 11																		
AXILLA	-	-	-	-	-	-	3	36.6	0.1	36.6	36.5	36.6	3	36.6	0.1	36.6	36.5	36.6
EAR	3	37.0	0.7	36.6	36.5	37.8	4	36.6	0.3	36.7	36.2	36.8	7	36.8	0.5	36.6	36.2	37.8
DAY 12																		
AXILLA	1	36.2	-	36.2	36.2	36.2	2	36.4	0.3	36.4	36.2	36.6	3	36.3	0.2	36.2	36.2	36.6

(Continued)

Program:Table_vitalsigns_temperature_AT.sas, Output:Table_vitalsigns_temperature_AT.lst, 02MAR09

Table 50: Vital Signs - Temperature Recordings, AT

	TACHOSIL						STANDARD						All					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
DAY 12																		
EAR	2	36.3	0.1	36.3	36.2	36.4	3	36.4	0.2	36.4	36.3	36.6	5	36.4	0.1	36.4	36.2	36.6
DAY 13																		
AXILLA	-	-	-	-	-	-	2	36.5	0.2	36.5	36.3	36.6	2	36.5	0.2	36.5	36.3	36.6
EAR	2	36.8	1.0	36.8	36.1	37.5	2	36.4	0.4	36.4	36.1	36.6	4	36.6	0.7	36.4	36.1	37.5
DAY 14																		
AXILLA	-	-	-	-	-	-	3	36.4	0.2	36.4	36.2	36.6	3	36.4	0.2	36.4	36.2	36.6
EAR	1	36.5	-	36.5	36.5	36.5	2	35.9	0.7	35.9	35.4	36.4	3	36.1	0.6	36.4	35.4	36.5
RECTALLY	1	36.5	-	36.5	36.5	36.5	-	-	-	-	-	-	1	36.5	-	36.5	36.5	36.5
DAY 15																		
AXILLA	-	-	-	-	-	-	2	36.3	0.1	36.3	36.2	36.4	2	36.3	0.1	36.3	36.2	36.4
EAR	1	36.0	-	36.0	36.0	36.0	2	36.7	0.4	36.7	36.4	37.0	3	36.5	0.5	36.4	36.0	37.0
DAY 16																		
AXILLA	-	-	-	-	-	-	1	36.2	-	36.2	36.2	36.2	1	36.2	-	36.2	36.2	36.2
EAR	-	-	-	-	-	-	1	36.4	-	36.4	36.4	36.4	1	36.4	-	36.4	36.4	36.4
RECTALLY	1	36.8	-	36.8	36.8	36.8	-	-	-	-	-	-	1	36.8	-	36.8	36.8	36.8
DAY 17																		
AXILLA	-	-	-	-	-	-	1	36.3	-	36.3	36.3	36.3	1	36.3	-	36.3	36.3	36.3
EAR	-	-	-	-	-	-	1	36.6	-	36.6	36.6	36.6	1	36.6	-	36.6	36.6	36.6
DAY 18																		
AXILLA	-	-	-	-	-	-	1	36.0	-	36.0	36.0	36.0	1	36.0	-	36.0	36.0	36.0
EAR	-	-	-	-	-	-	1	36.4	-	36.4	36.4	36.4	1	36.4	-	36.4	36.4	36.4
DAY 19																		
AXILLA	-	-	-	-	-	-	1	36.2	-	36.2	36.2	36.2	1	36.2	-	36.2	36.2	36.2
EAR	-	-	-	-	-	-	1	36.4	-	36.4	36.4	36.4	1	36.4	-	36.4	36.4	36.4
DAY 20																		
AXILLA	-	-	-	-	-	-	1	36.5	-	36.5	36.5	36.5	1	36.5	-	36.5	36.5	36.5
EAR	-	-	-	-	-	-	1	36.4	-	36.4	36.4	36.4	1	36.4	-	36.4	36.4	36.4
DAY 21																		
AXILLA	-	-	-	-	-	-	1	36.6	-	36.6	36.6	36.6	1	36.6	-	36.6	36.6	36.6

(Continued)

Program:Table_vitalsigns_temperature_AT.sas, Output:Table_vitalsigns_temperature_AT.lst, 02MAR09

Table 50: Vital Signs - Temperature Recordings, AT

	TACHOSIL						STANDARD						All					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
DRAIN REMOVAL																		
AXILLA	73	36.6	0.5	36.5	35.3	38.4	69	36.5	0.5	36.5	35.6	38.0	142	36.6	0.5	36.5	35.3	38.4
EAR	48	36.5	0.5	36.4	35.6	38.1	51	36.6	0.5	36.5	36.0	38.0	99	36.5	0.5	36.4	35.6	38.1
ORALLY	7	36.4	0.2	36.4	36.1	36.8	5	37.1	0.8	36.8	36.6	38.5	12	36.7	0.6	36.6	36.1	38.5
RECTALLY	16	37.5	0.7	37.5	36.0	38.7	14	37.1	0.4	37.2	36.0	38.0	30	37.3	0.6	37.3	36.0	38.7
DISCHARGE																		
AXILLA	74	36.5	0.3	36.5	35.6	37.3	71	36.5	0.4	36.5	36.0	37.9	145	36.5	0.3	36.5	35.6	37.9
EAR	47	36.4	0.3	36.4	35.6	37.2	50	36.4	0.4	36.4	35.0	37.4	97	36.4	0.4	36.4	35.0	37.4
ORALLY	6	36.4	0.3	36.4	36.1	36.8	5	36.5	0.3	36.4	36.2	37.0	11	36.5	0.3	36.4	36.1	37.0
RECTALLY	7	37.0	0.4	37.2	36.2	37.5	9	37.2	0.2	37.2	37.0	37.5	16	37.1	0.3	37.2	36.2	37.5

Program:Table_vitalsigns_temperature_AT.sas, Output:Table_vitalsigns_temperature_AT.lst, 02MAR09

Table 51: Follow-up Physical Examination - Clinically Significant Changes, AT

Description of observed changes	Tachosil	Standard
AFTER OPERATION OF CANCER IN THE UPPER RIGHT LOBUS	1	.
ATRIAL FIBRILATION PHLEBITIS LEFT LOWER AREA	.	1
ATRIAL FIBRILLATION	1	.
ATRIAL FIBRILLATION, ASYMPTOMATIC	1	.
CHEST PAIN	.	1
CLINICALLY AND RADIOLOGICAL PNEUMONIA	1	.
CUT AFTER SURGERY RIGHT ARTEROLATERAL CHESTWALL	1	.
CUT CHEST WALL	.	1
CUT FROM SURGERY RIGHT THORAX WALL	1	.
CUT IN THE SKIN AFTER THOMHOTOMY	1	.
CUT LEFT CHEST WALL	1	1
CUT LEFT THORACIC WALL	.	2
CUT RIGHT CHEST WALL	2	1
CUT RIGHT LATERAL THORACIC WALL	.	1
CUT RIGHT SKIN AFTER THORACOTOMY	1	.
CUT RIGHT THORACIC WALL	2	4
CUT RIGHT THORASIC WALL	1	.
CUT SKIN THORAXWALL RIGHT	.	1
CUT THORACIC WALL	1	1
CUT THORACIC WALL RIGHT	1	.
CUT THORAIC WALL	1	.
HEIMLICH DRAINAGE	.	1
HEISSERKEIT (CROAKINESS)	1	.
HOARSE	1	.
INCISION	2	2
LOSS IN WEIGHT 10 KG/ LONG POSTOPERATIVE PERIODE	1	.
N. LARYNGEUS RECURRENS PARESIS	.	1
N. RECURRENS PARESIS	.	1
ONGOING TREATMENT FOR PNEUMONIA	.	1
PNEUMOTHORAX, PROLONGED AIR-DRAINAGE, HEIMLICH VENTIL	.	1
REDUCED ACTIVITY/PERFORMANCE SCORE (WHO-2), NCS	1	.
SCAR OF LUNG SURGERY	.	1
SCAR OF POSTLATERAL INCISION (LOBECTOMY)	.	1
SCAR OF SURGICAL INCISION	1	.
SCAR OF THORACIC INCISION	11	9
SCAR OF THORACIC INCITION	2	2

Program:Table_physicalex_discharge_AT.sas, Output:Table_physicalex_discharge_AT.lst, 02MAR09

Table 51: Follow-up Physical Examination - Clinically Significant Changes, AT

Description of observed changes	Tachosil	Standard
SILENT CHEST RIGHT LOWER THORAX NCS	1	.
SILENT LEFT LOWER CHEST (CONSEQUENCE OF FORMER OPERATION, NCS)	1	.
SKIN LEFT CHEST WALL	.	1
STILL NEED OXYGEN WHEN DISCHARGE	1	.
WOUND OF THORACIC INCISION	.	1
WOUND PAIN	.	1
Total	39	37

Program:Table_physicalex_discharge_AT.sas, Output:Table_physicalex_discharge_AT.lst, 02MAR09

Table 52: Sub-group Analyses, Duration of post-operative air leakage (primary endpoint), ITT

Log-Rank tests of equality over treatments stratified by centre:

Sub-group	Number of subjects			Chi-Square	df	p-value
	Total	Tachosil	Standard			
Subjects aged 65 or under	155	75	80	5.3781	1	0.0204
Subjects aged 66 or over	144	73	71	1.4348	1	0.2310
Male subjects	201	102	99	2.9005	1	0.0886
Female subjects	98	46	52	0.3413	1	0.5591

Centres contributing with only a few patients were pooled with other centres for purposes of the analysis:
thus centres Zürich, Essen and Göteborg were pooled into a single centre
and centres Leuven and Vienna were likewise pooled into a single centre
Program:tab_pe_subgroup.sas, Output:tab_pe_subgroup.lst, 02MAR09

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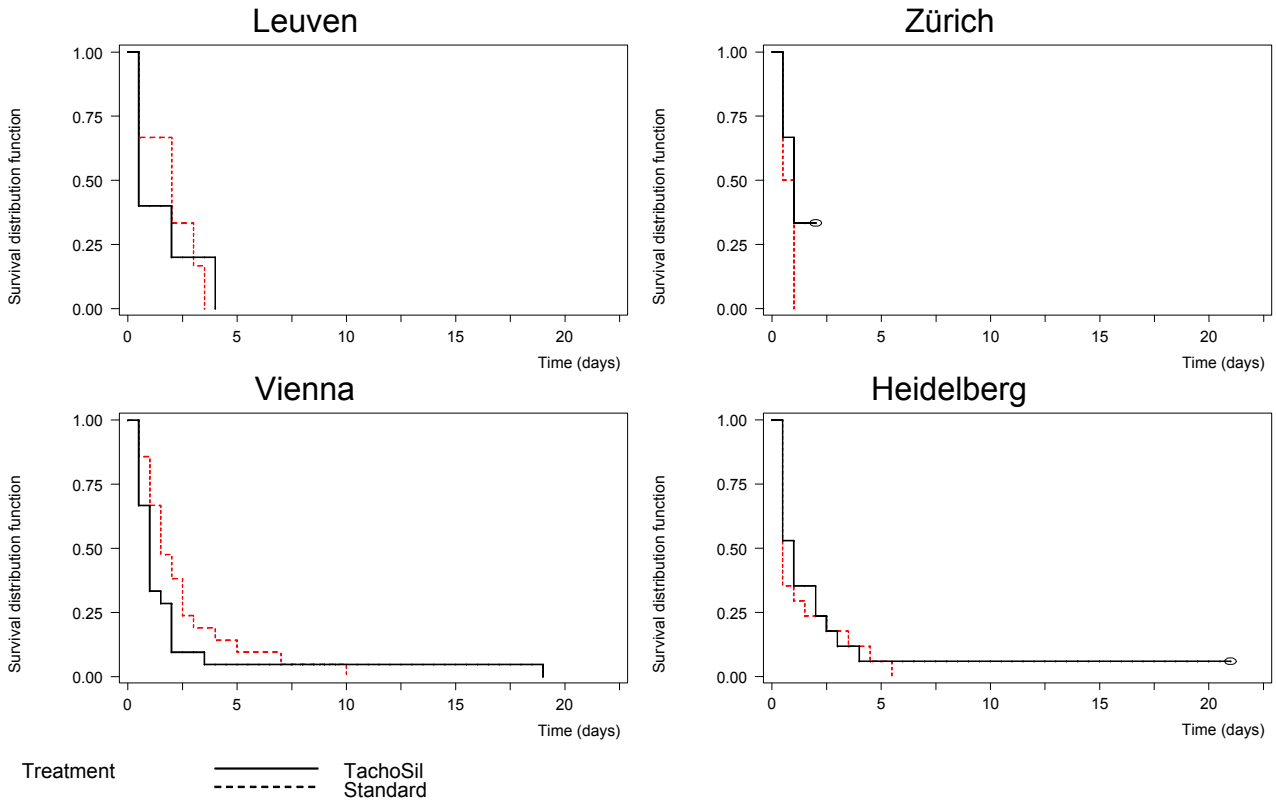
Figure 01a: Duration of Post-Operative Air Leakage, ITT

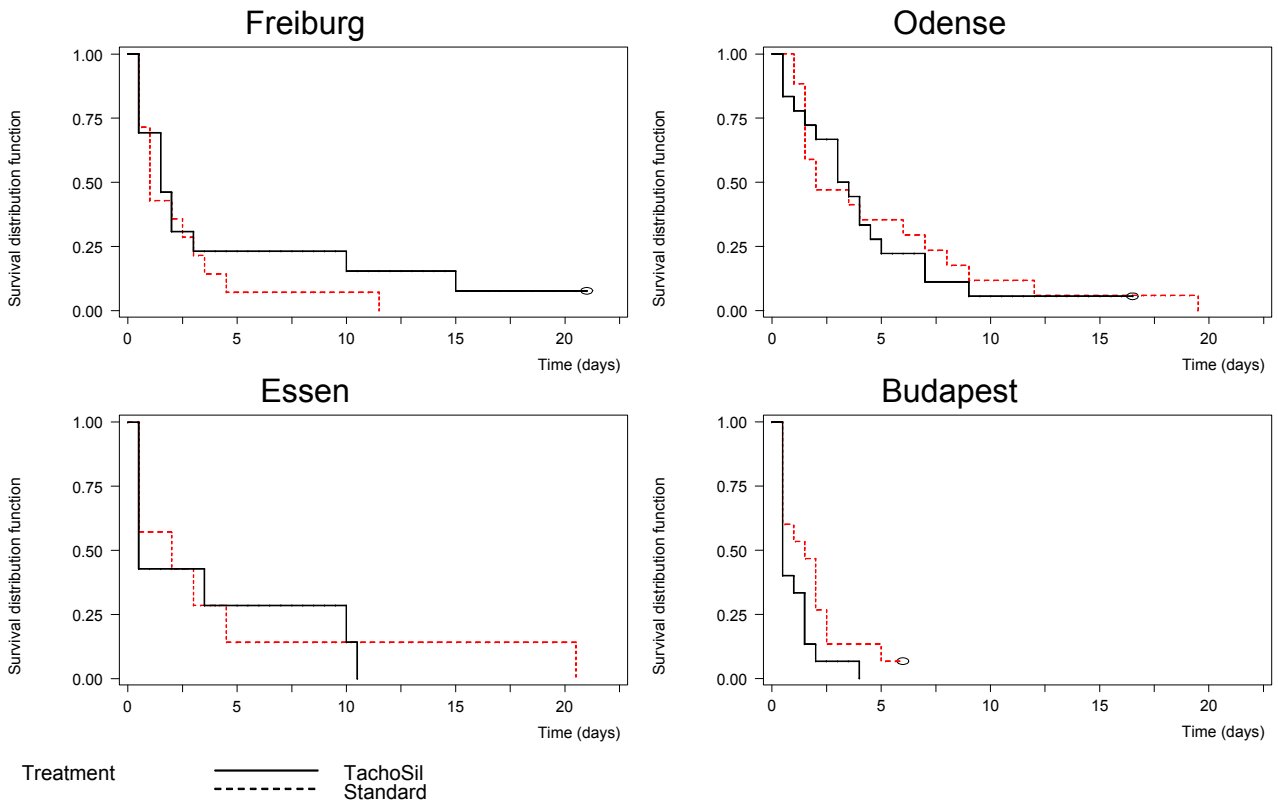
Log Rank Test for Equality over Treatments Stratified by Centre:
Chi-Square=4.7387, df= 1, p=0.0295



Program:fig_pe.sas, Output:fig_pe_ITT_A/_B/_C.cgm, 02MAR09

Figure 01b: Duration of Post-Operative Air Leakage, ITT

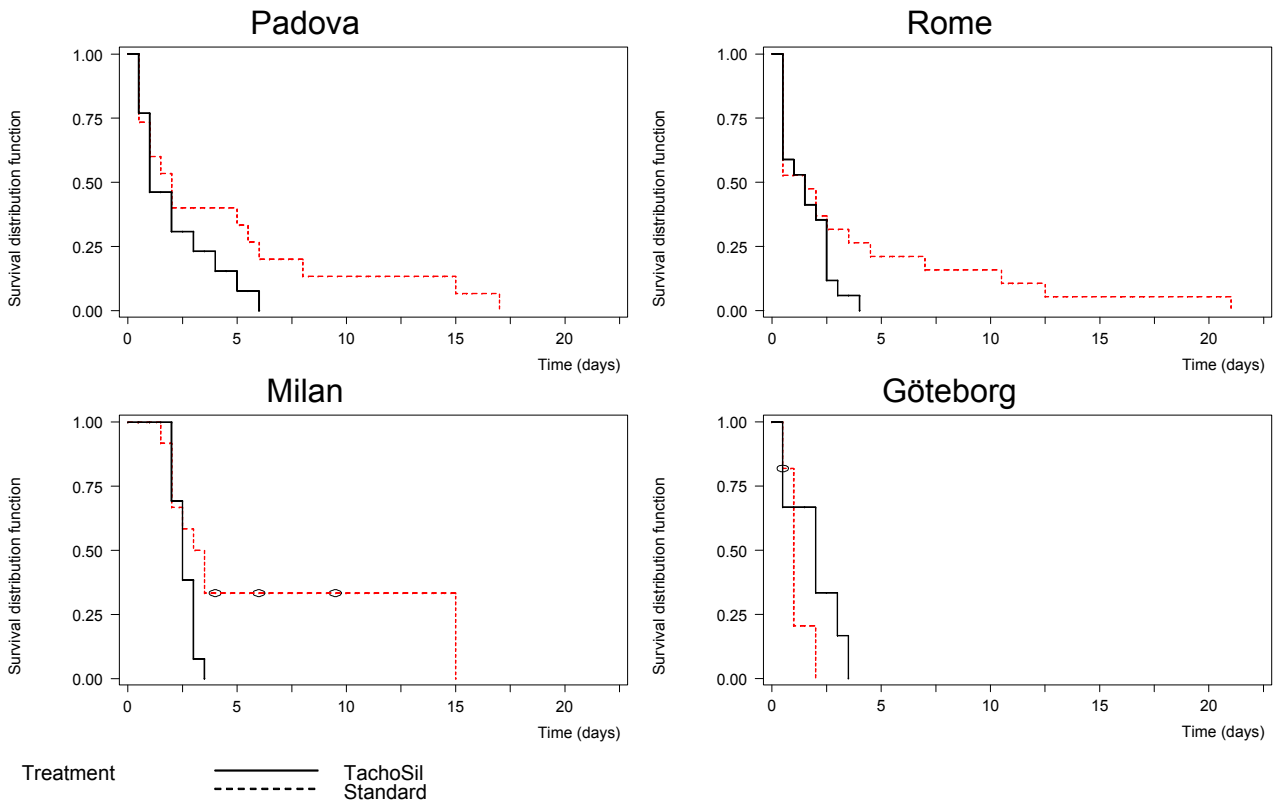
Log Rank Test for Equality over Treatments Stratified by Centre:
Chi-Square=4.7387, df= 1, p=0.0295



Program:fig_pe.sas, Output:fig_pe_ITT_A/_B/_C.cgm, 02MAR09

Figure 01c: Duration of Post-Operative Air Leakage, ITT

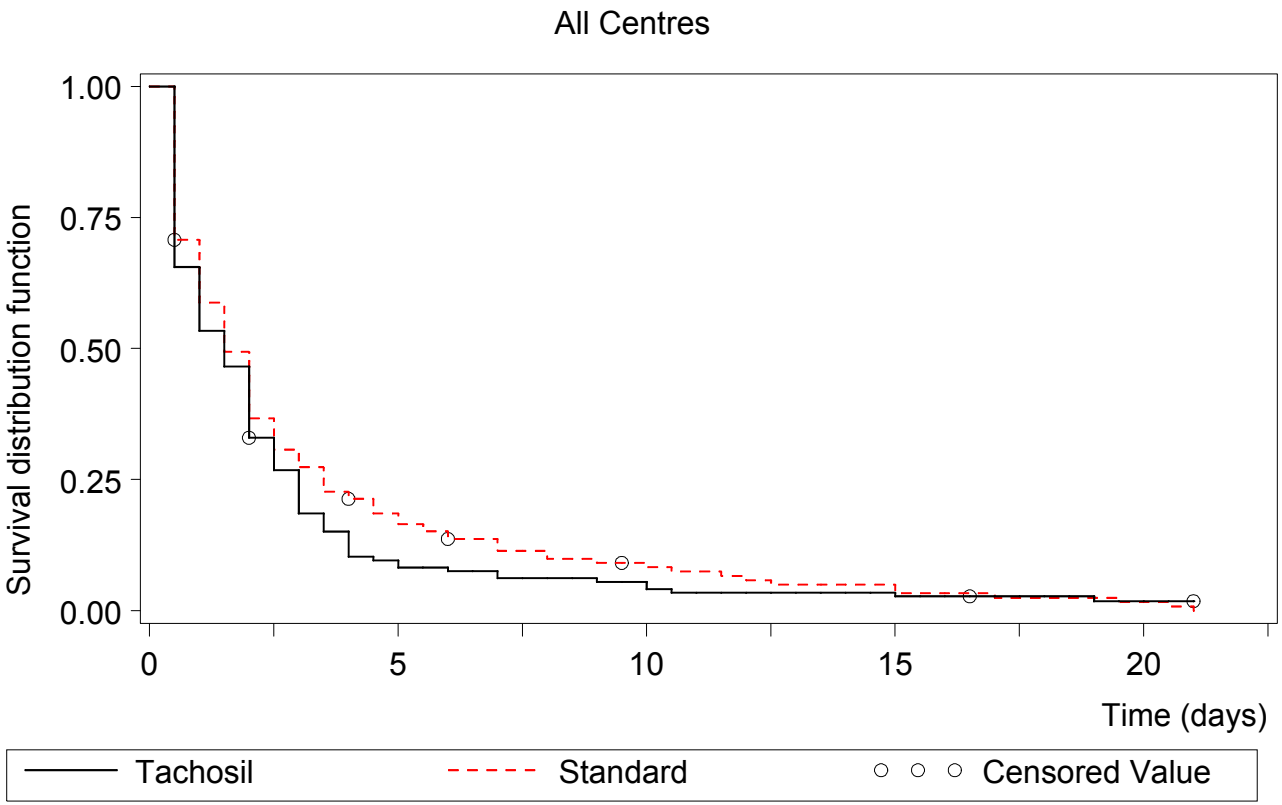
Log Rank Test for Equality over Treatments Stratified by Centre:
Chi-Square=4.7387, df= 1, p=0.0295



Program:fig_pe.sas, Output:fig_pe_ITT_A/_B/_C.cgm, 02MAR09

Figure 01d: Duration of Post-Operative Air Leakage, All Centres, ITT

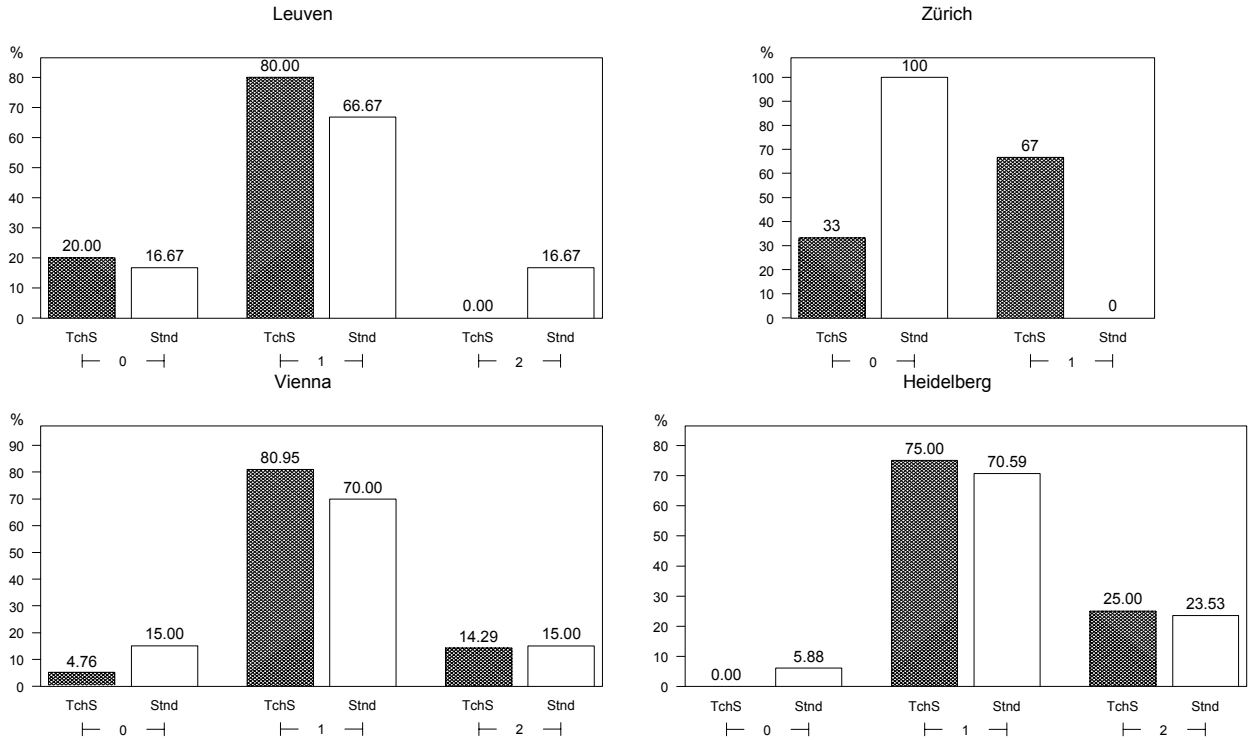
Log Rank Test for Equality over Treatments Stratified by Centre:
Chi-Square=4.7387, df= 1, p=0.0295



Program:fig_pe.sas, Output:fig_pe_ITT_D.cgm, 02MAR09

Figure 02a: Reduction of Intra-operative Air Leakage Intensity after First Application of Trial Treatment, ITT

Wilcoxon test (across all centres):
STANDARD: Score= 19885, n=145, TACHOSIL: Score= 22893, n=147, z-value=-2.0333 , p=0.0420

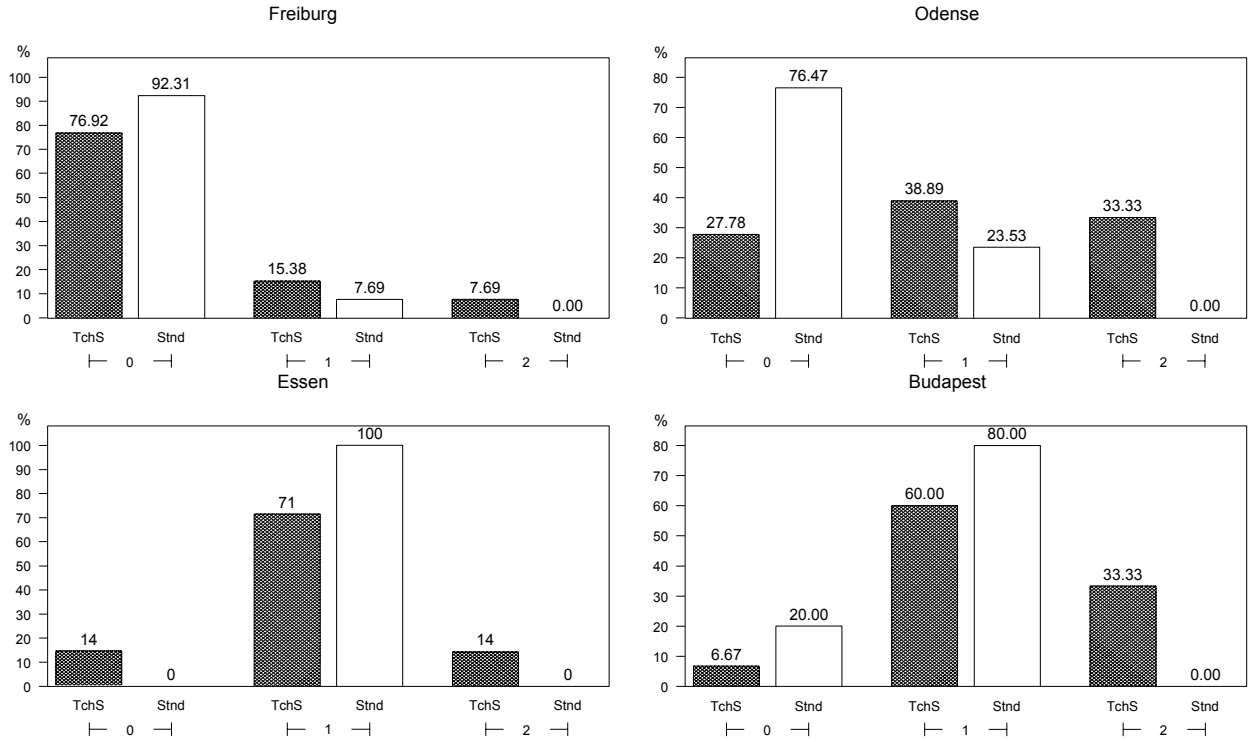


TchS = TachoSil Stnd = Standard

Program:figure_reduction_in_airleakage_intensity.sas, Output:figure_reduction_in_airleakage_intensity_ITT_A/_B/_C.cgm, 02MAR09

Figure 02b: Reduction of Intra-operative Air Leakage Intensity after First Application of Trial Treatment, ITT

Wilcoxon test (across all centres):
STANDARD: Score= 19885, n=145, TACHOSIL: Score= 22893, n=147, z-value=-2.0333 , p=0.0420

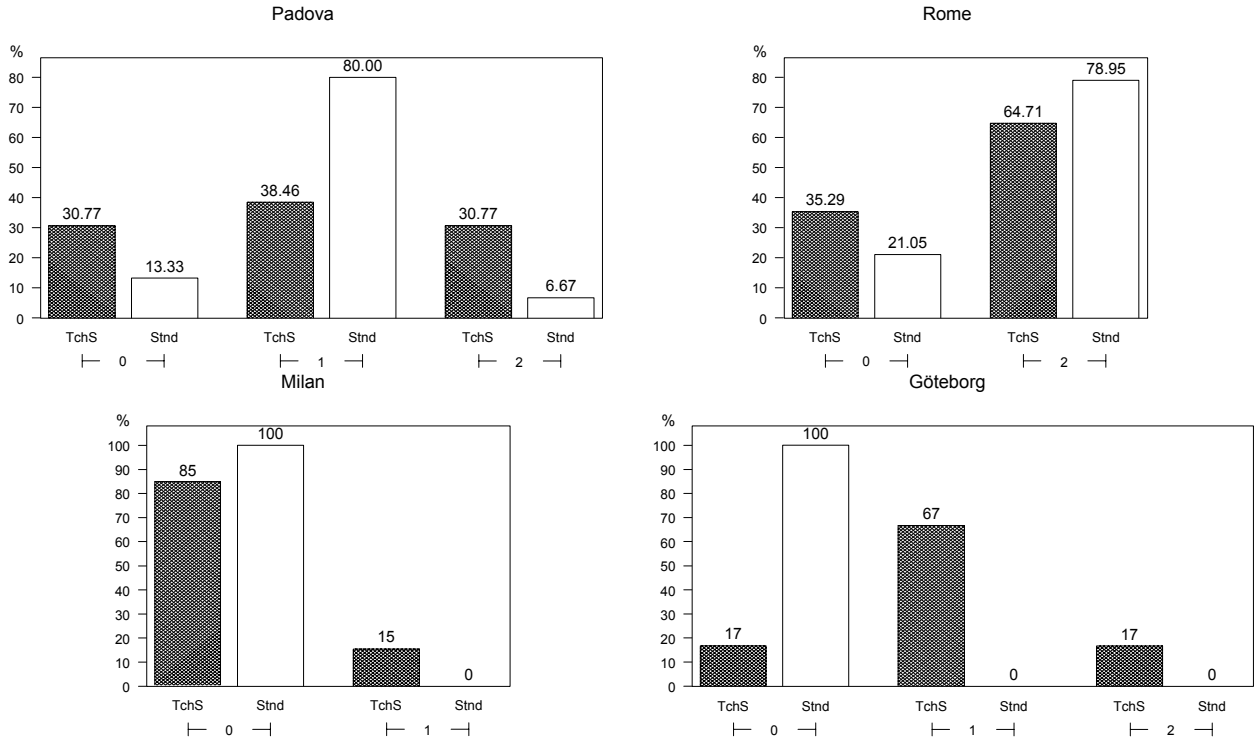


TchS = TachoSil Stnd = Standard

Program:figure_reduction_in_airleakage_intensity.sas, Output:figure_reduction_in_airleakage_intensity_ITT_A/_B/_C.cgm, 02MAR09

Figure 02c: Reduction of Intra-operative Air Leakage Intensity after First Application of Trial Treatment, ITT

Wilcoxon test (across all centres):
STANDARD: Score= 19885, n=145, TACHOSIL: Score= 22893, n=147, z-value=-2.0333 , p=0.0420

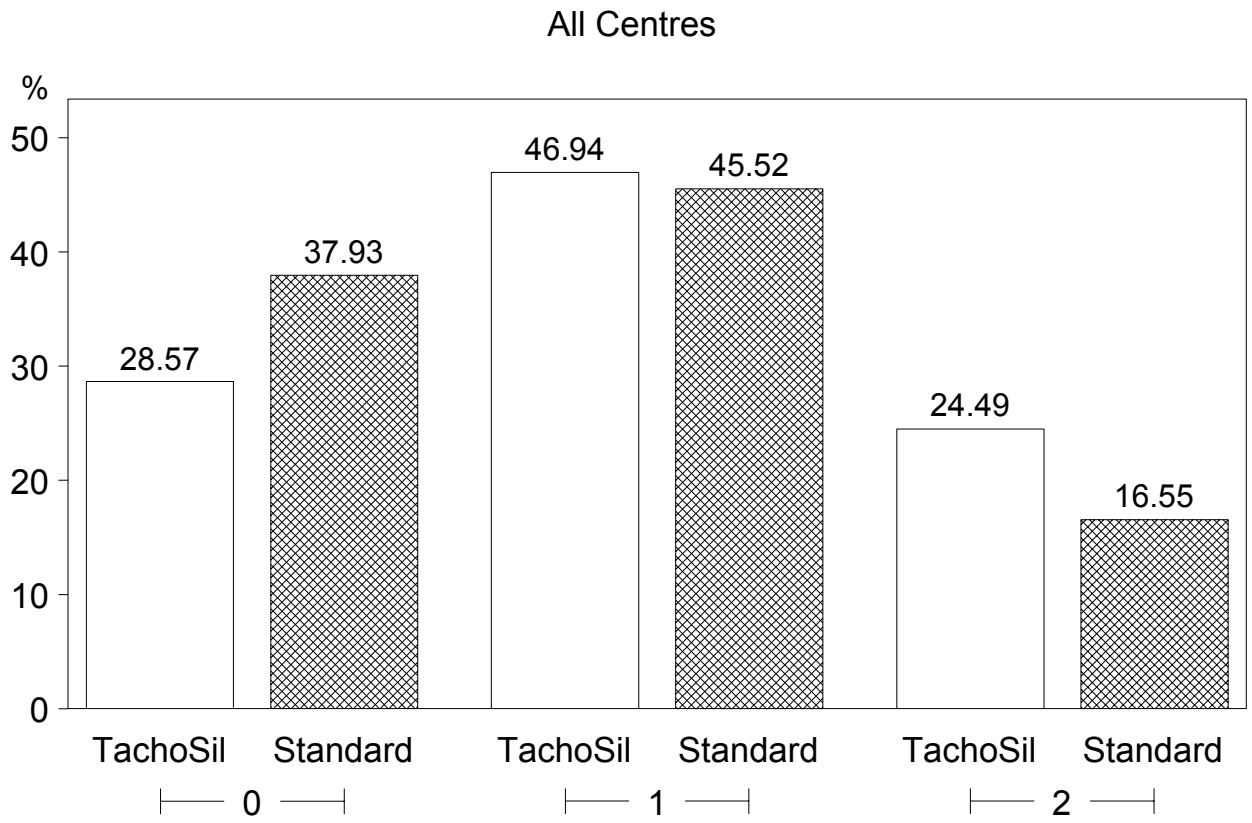


TchS = TachoSil Stnd = Standard

Program:figure_reduction_in_airleakage_intensity.sas, Output:figure_reduction_in_airleakage_intensity_ITT_A/_B/_C.cgm, 02MAR09

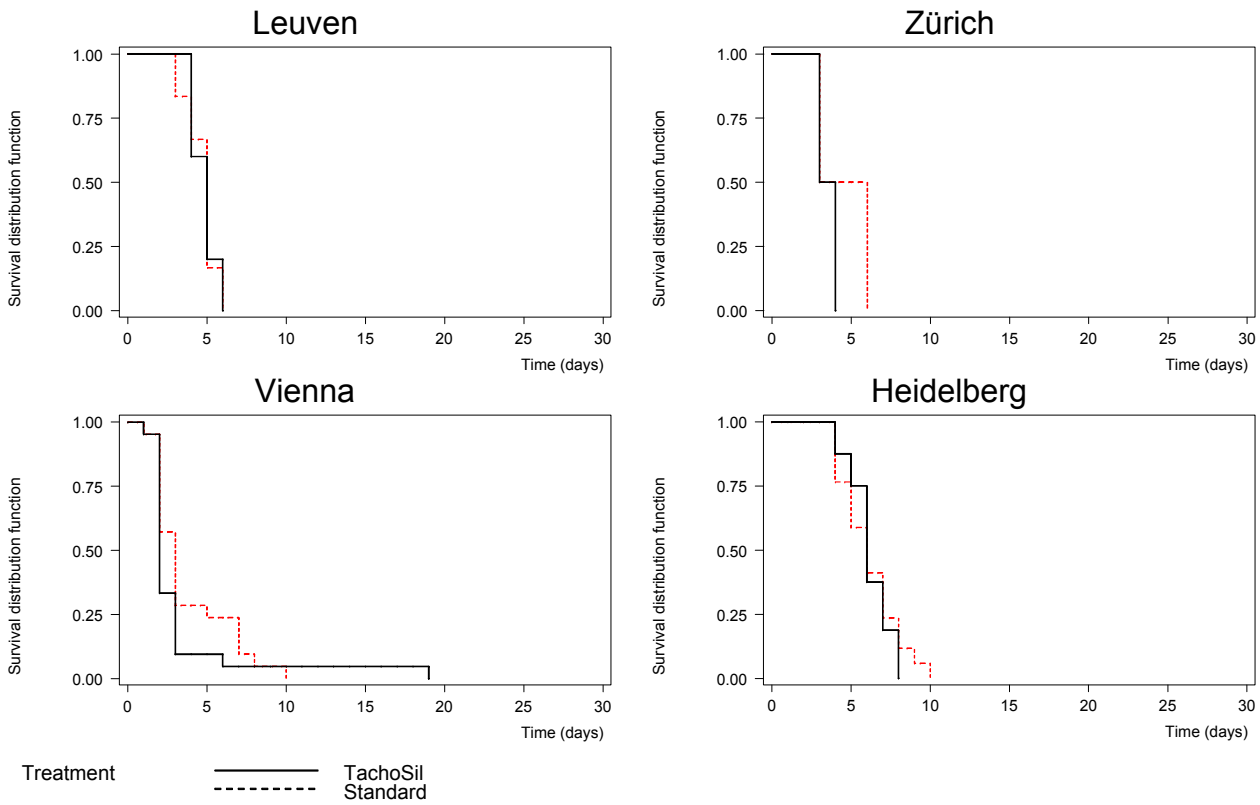
Figure 02d: Reduction of Intra-operative Air Leakage Intensity after First Application of Trial Treatment, All, ITT

Wilcoxon test (across all centres):
STANDARD: Score= 19885, n=145, TACHOSIL: Score= 22893, n=147, z-value=-2.0333 , p=0.0420



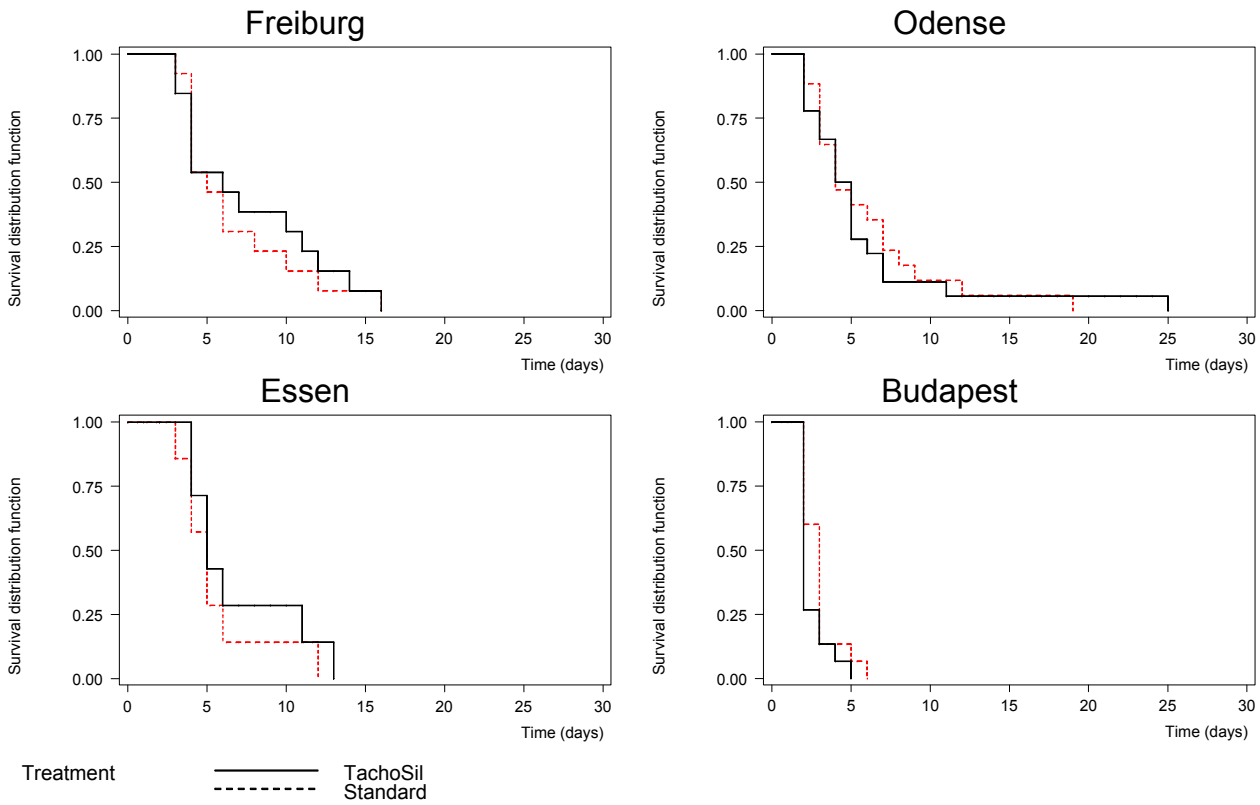
Program:figure_reduction_in_airleakage_intensity.sas, Output:figure_reduction_in_airleakage_intensity_ITT_D.cgm, 02MAR09

Figure 03a: Duration of Chest Tube Drainage - Life Table Estimates, ITT



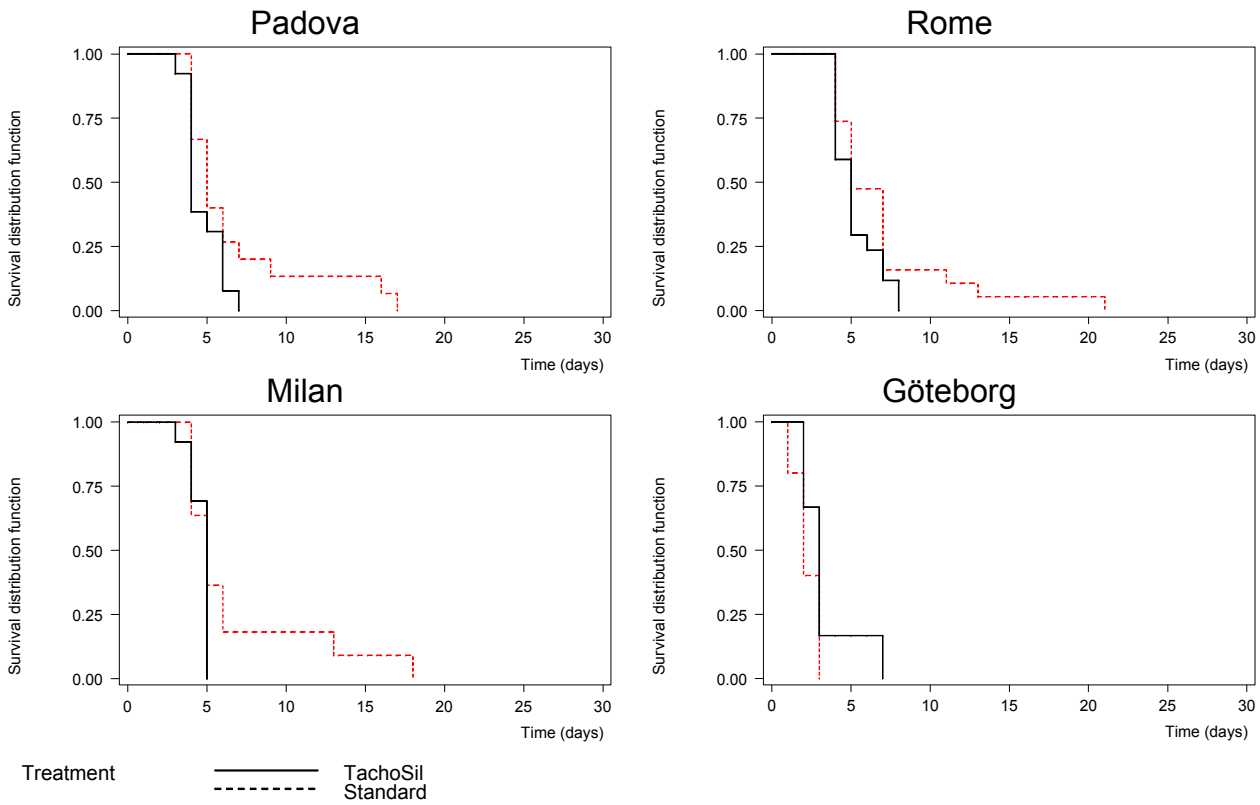
Program:fig_duration_drain.sas, Output:fig_duration_drain_ITT_A/_B/_C.cgm, 02MAR09

Figure 03b: Duration of Chest Tube Drainage - Life Table Estimates, ITT



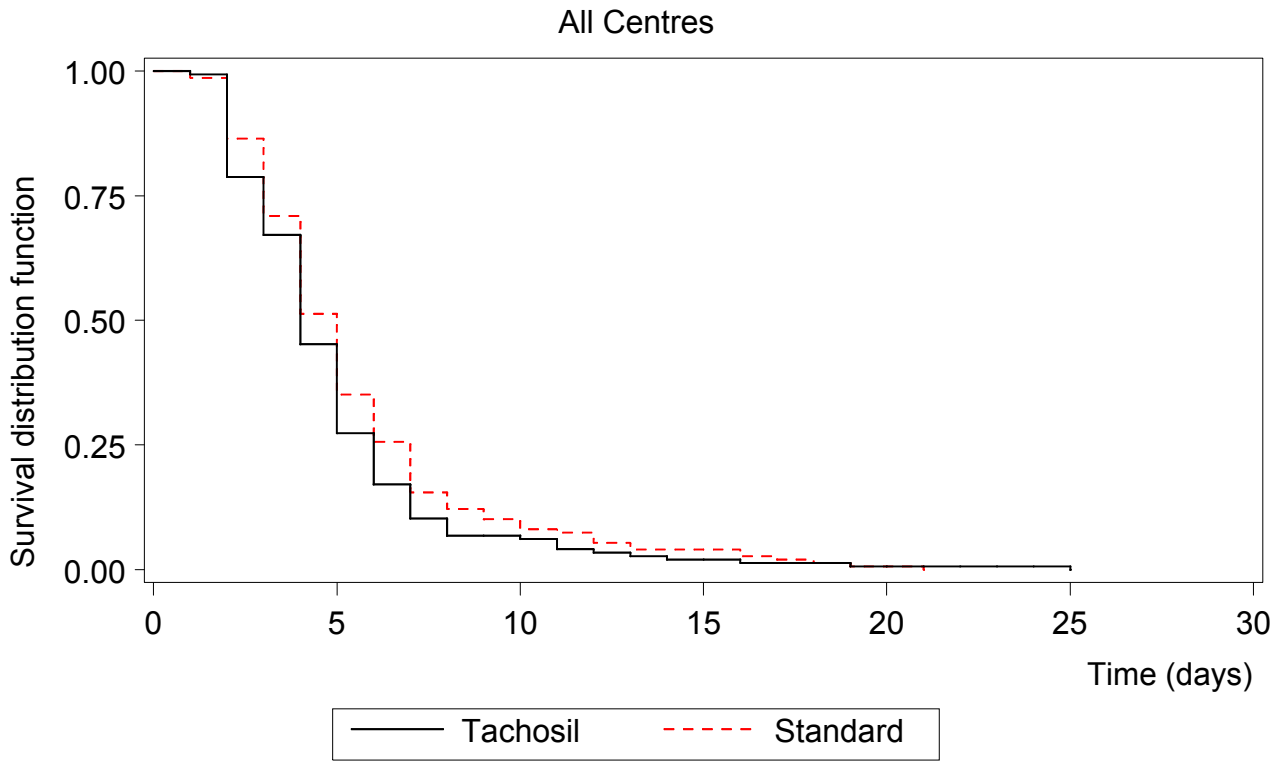
Program:fig_duration_drain.sas, Output:fig_duration_drain_ITT_A/_B/_C.cgm, 02MAR09

Figure 03c: Duration of Chest Tube Drainage - Life Table Estimates, ITT



Program:fig_duration_drain.sas, Output:fig_duration_drain_ITT_A/_B/_C.cgm, 02MAR09

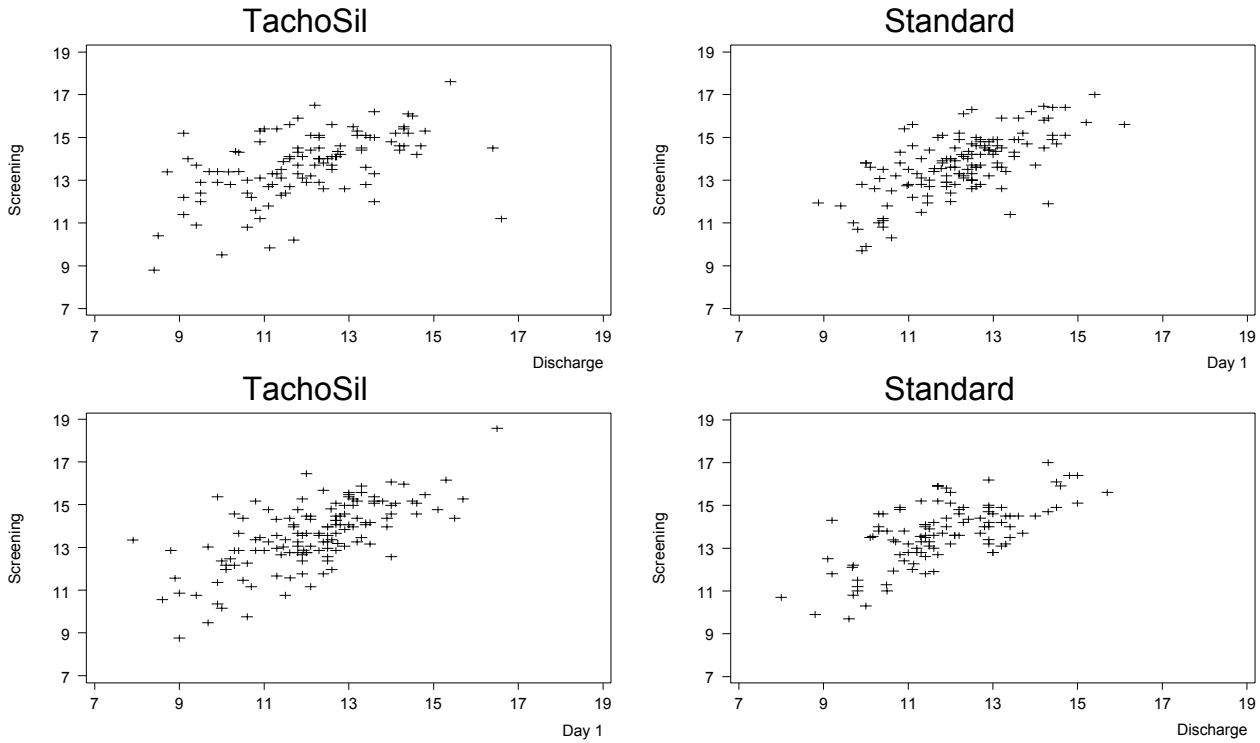
Figure 03d: Duration of Chest Tube Drainage - Life Table Estimates, All Centres, ITT



Program:fig_duration_drain.sas, Output:fig_duration_drain_ITT_D.cgm, 02MAR09

Figure 4a: Laboratory Test Scatter Plots: Screening vs Day1 & Screening vs Discharge, Haemoglobin, AT

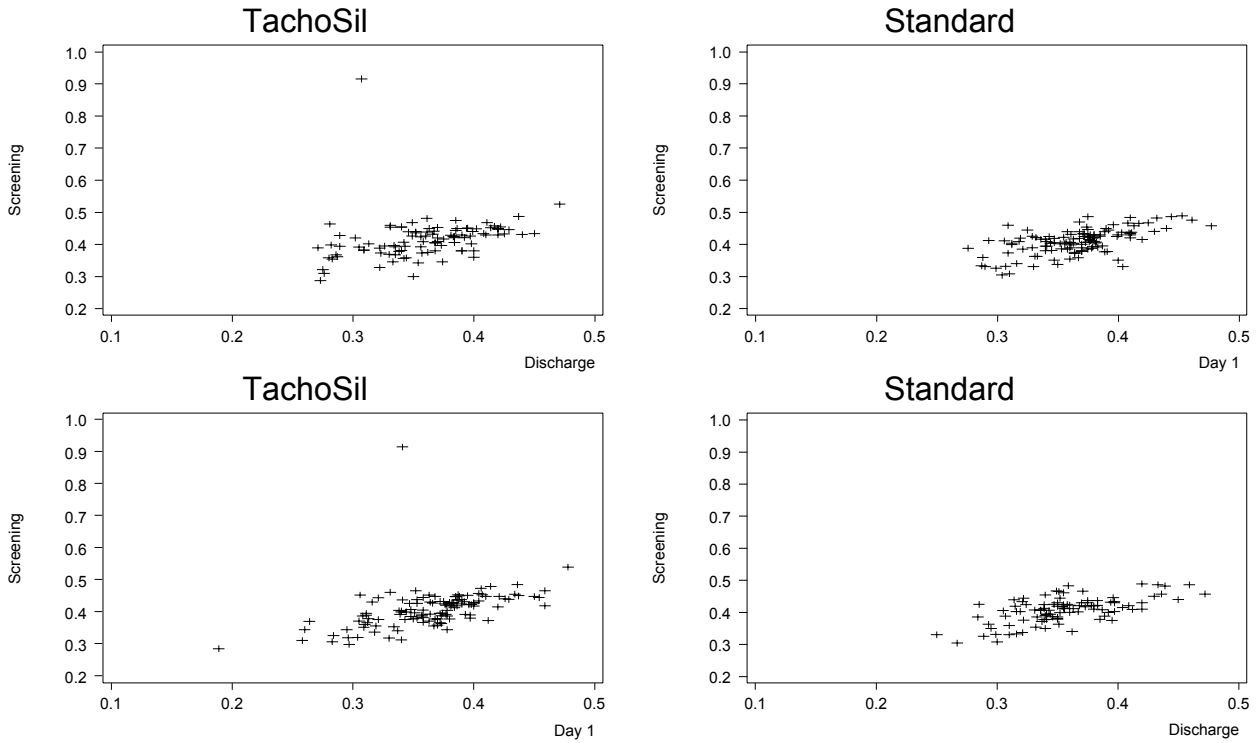
Lab test = Haemoglobin result (g/dl)



Program:fig_laboratory.sas, Output:fig_laboratory_A.cgm, 02MAR09

Figure 4b: Laboratory Test Scatter Plots: Screening vs Day1 & Screening vs Discharge, Haematocrit, AT

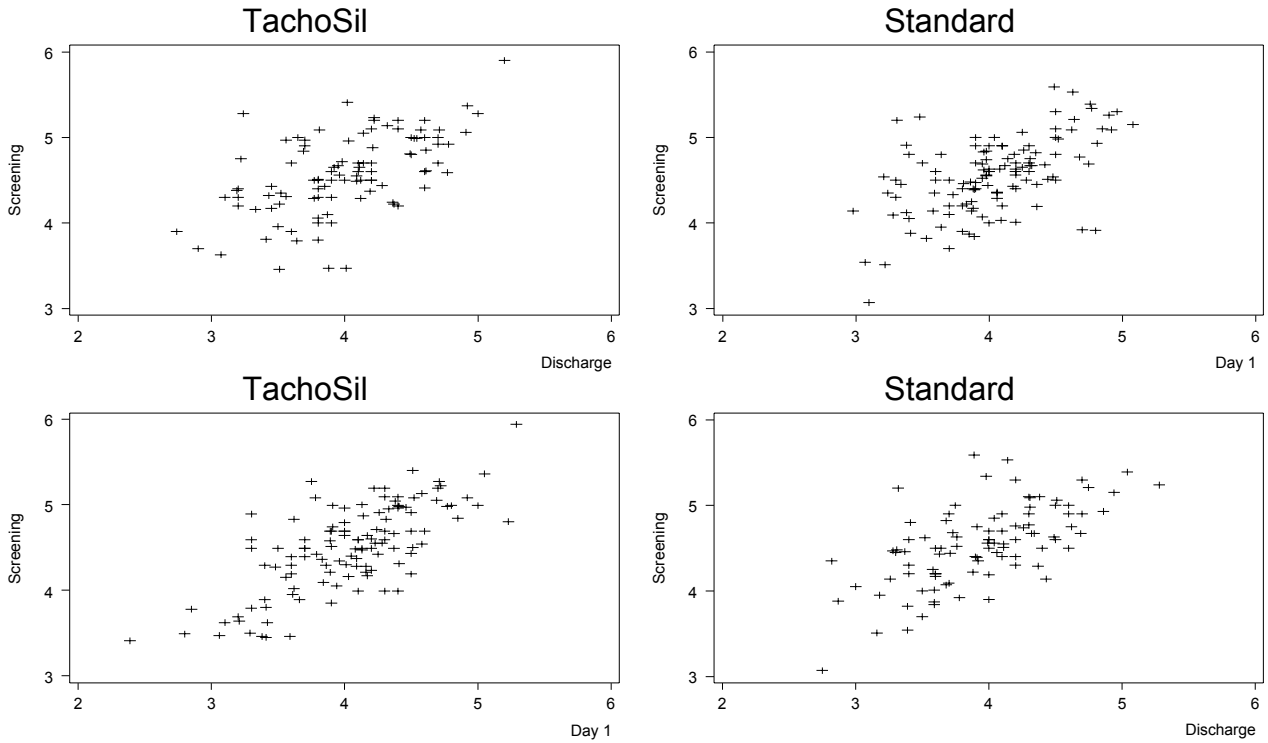
Lab test = Haematocrit result (ratio)



Program:fig_laboratory.sas, Output:fig_laboratory_B.cgm, 02MAR09

Figure 4c: Laboratory Test Scatter Plots: Screening vs Day1 & Screening vs Discharge, Erythrocyte Count, AT

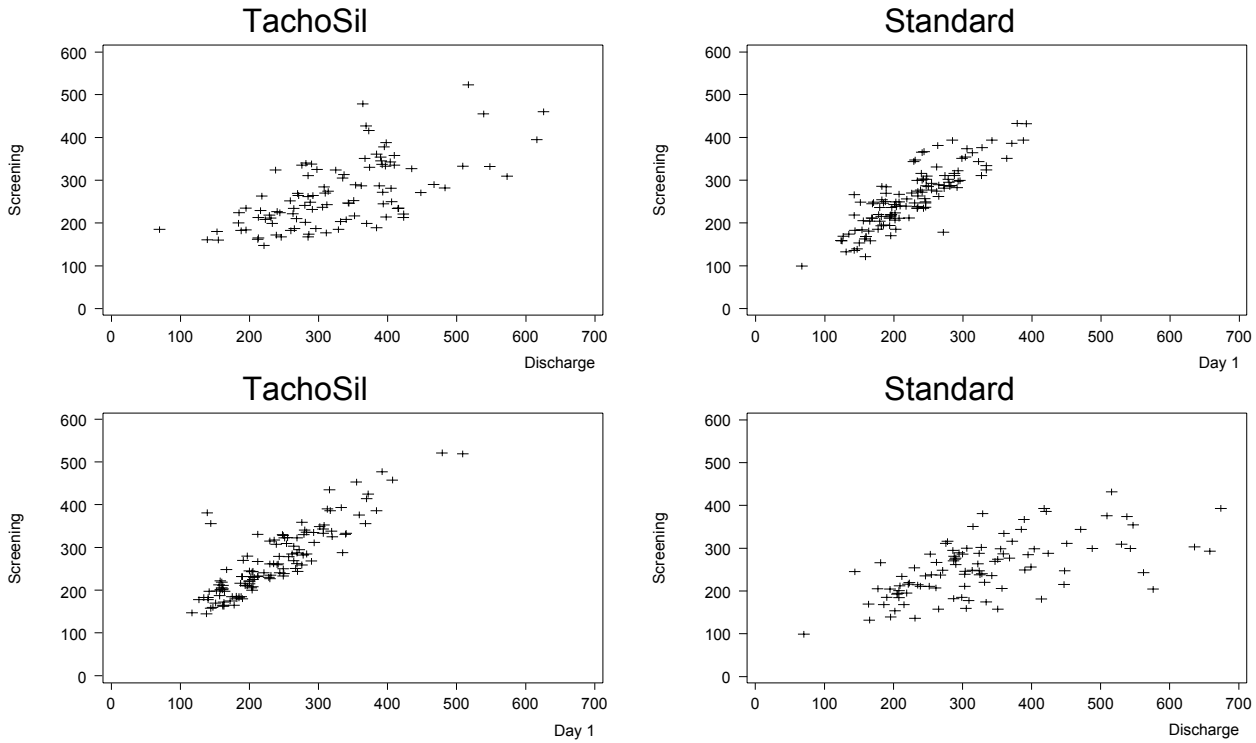
Lab test = Erythrocyte Count result (10^12/L)



Program:fig_laboratory.sas, Output:fig_laboratory_C.cgm, 02MAR09

Figure 4d: Laboratory Test Scatter Plots: Screening vs Day1 & Screening vs Discharge, Platelet Count, AT

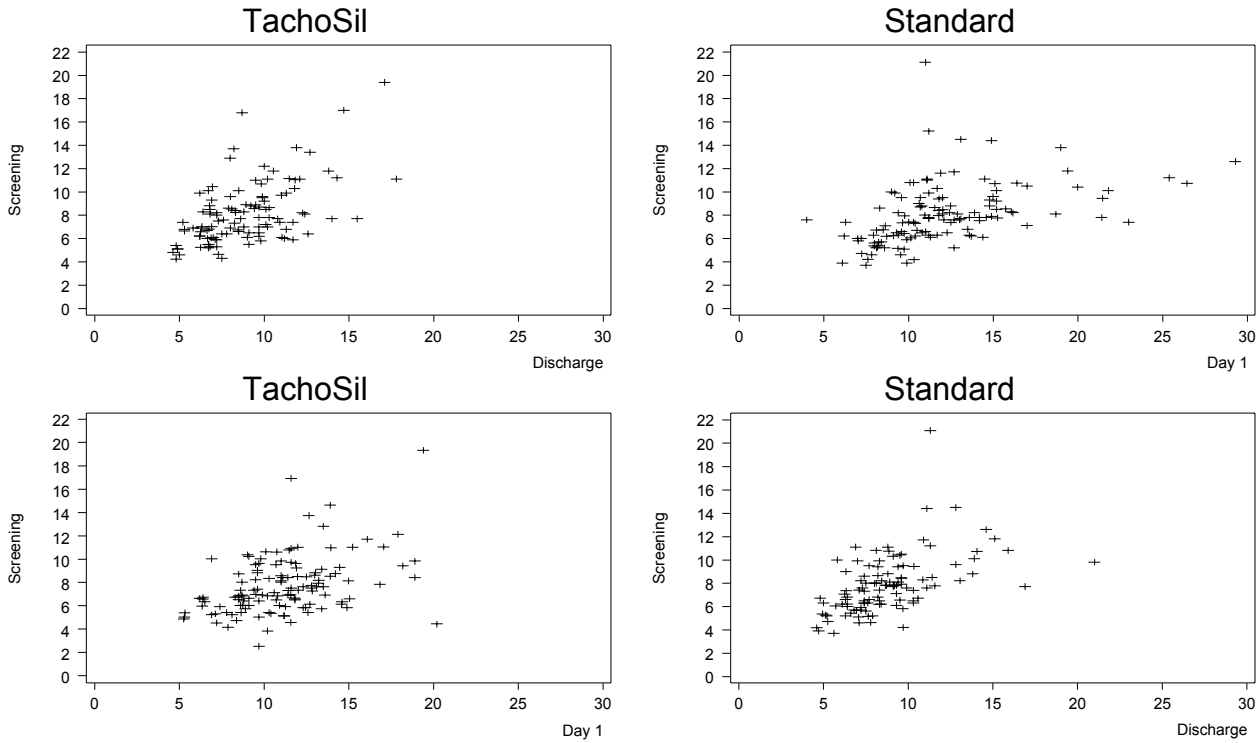
Lab test = Platelet Count result (10^9/L)



Program:fig_laboratory.sas, Output:fig_laboratory_D.cgm, 02MAR09

Figure 4e: Laboratory Test Scatter Plots: Screening vs Day1 & Screening vs Discharge, Leukocyte Count, AT

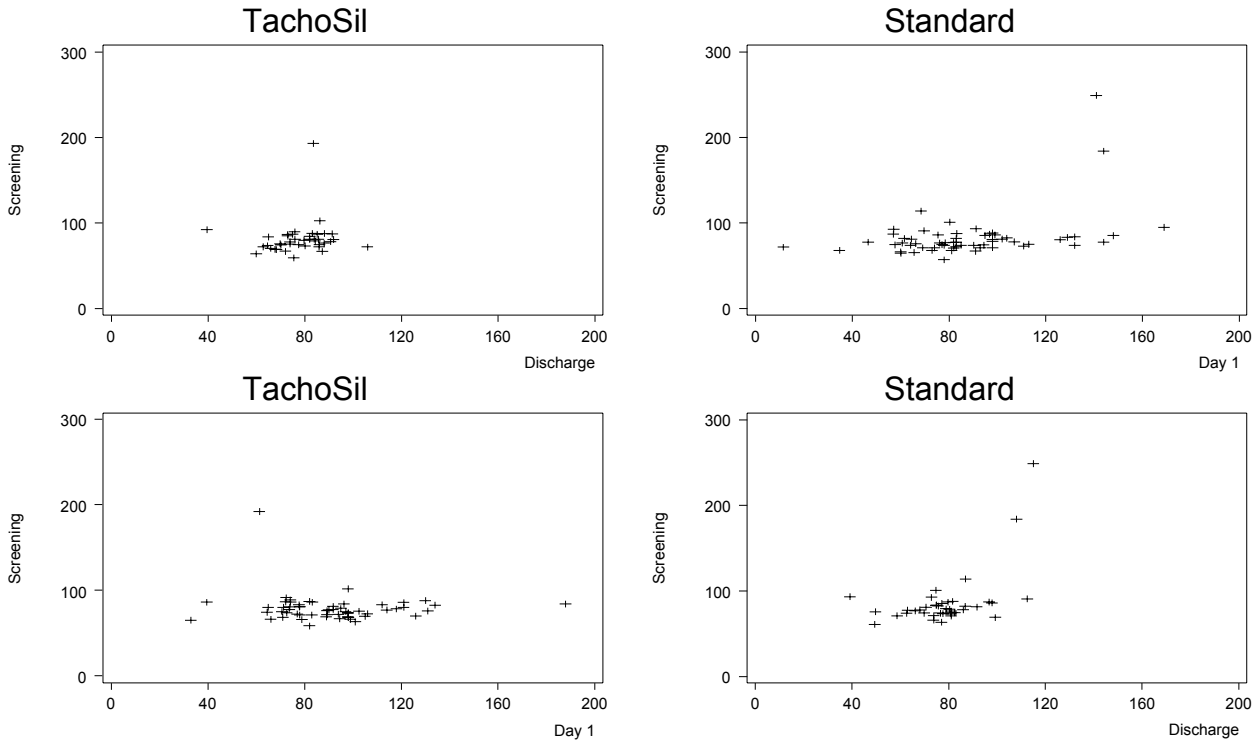
Lab test = Leukocyte Count result (10^9/L)



Program:fig_laboratory.sas, Output:fig_laboratory_E.cgm, 02MAR09

Figure 4f: Laboratory Test Scatter Plots: Screening vs Day1 & Screening vs Discharge, pO2, AT

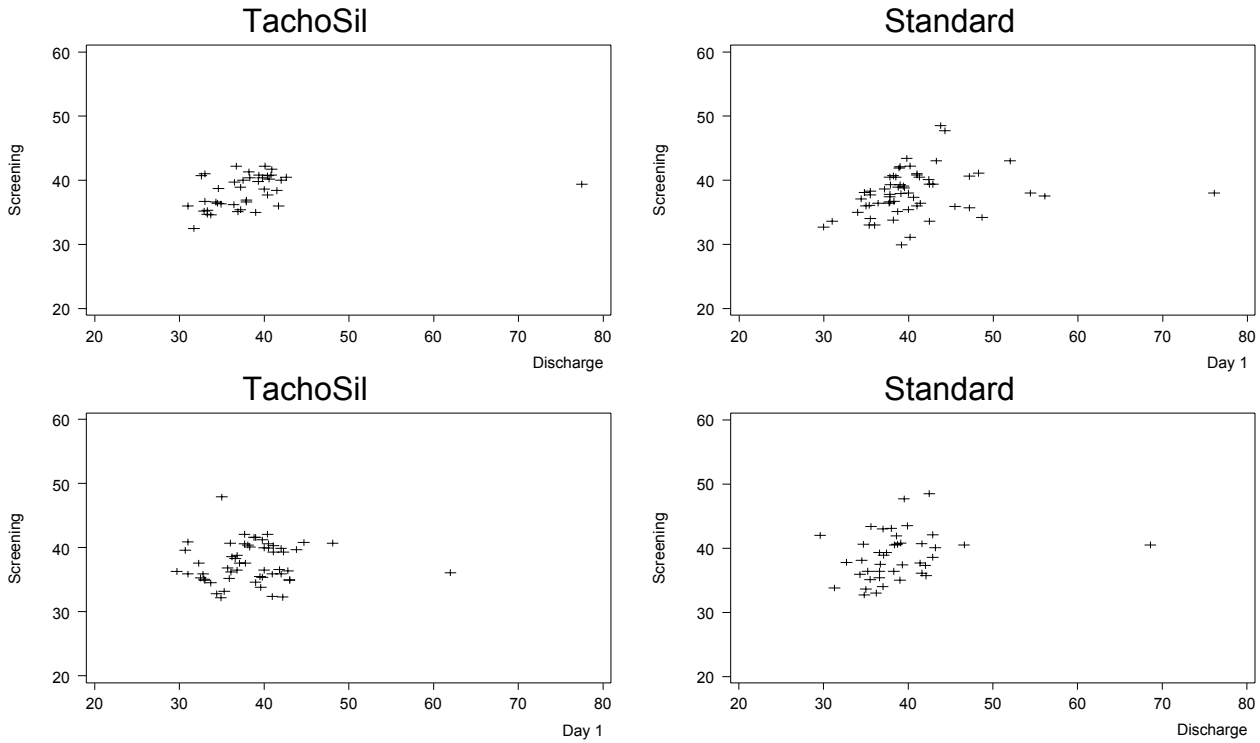
Lab test = pO2 result (mm HG)



Program:fig_laboratory.sas, Output:fig_laboratory_F.cgm, 02MAR09

Figure 4g: Laboratory Test Scatter Plots: Screening vs Day1 & Screening vs Discharge, pCO2, AT

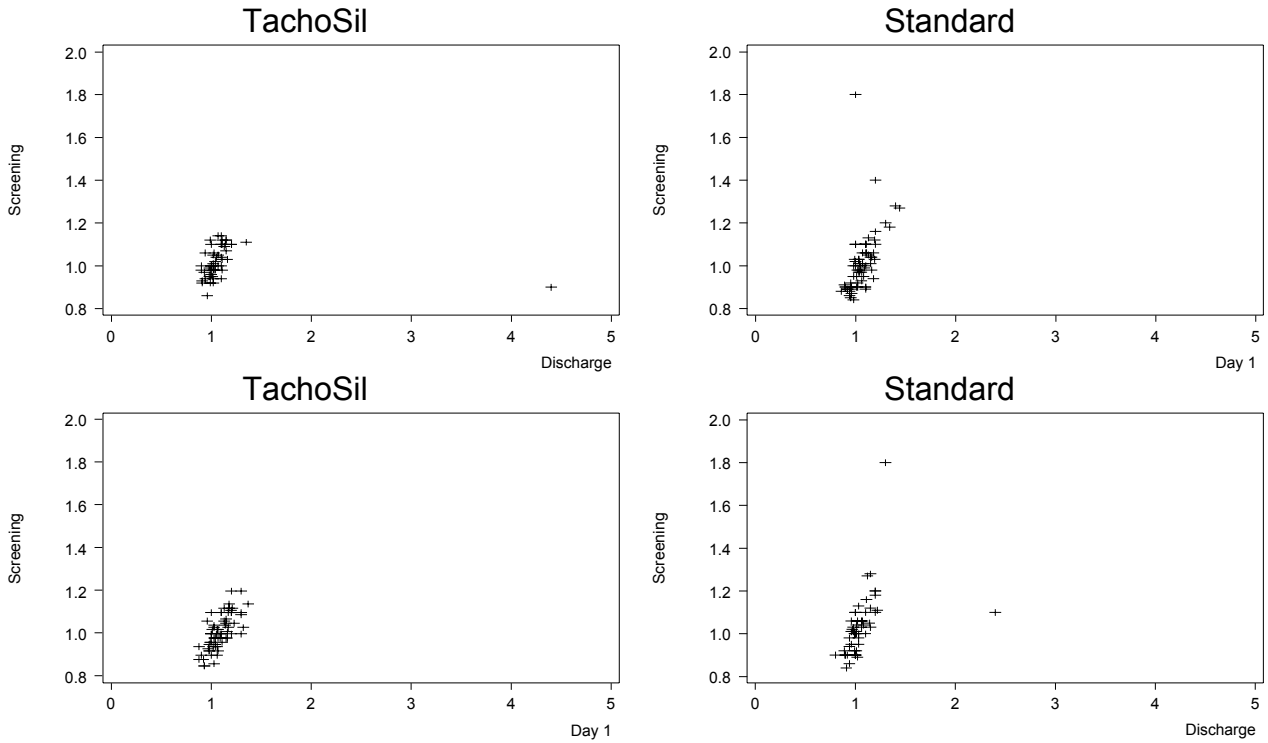
Lab test = pCO2 result (mm HG)



Program:fig_laboratory.sas, Output:fig_laboratory_G.cgm, 02MAR09

Figure 4h: Laboratory Test Scatter Plots: Screening vs Day1 & Screening vs Discharge, INR, AT

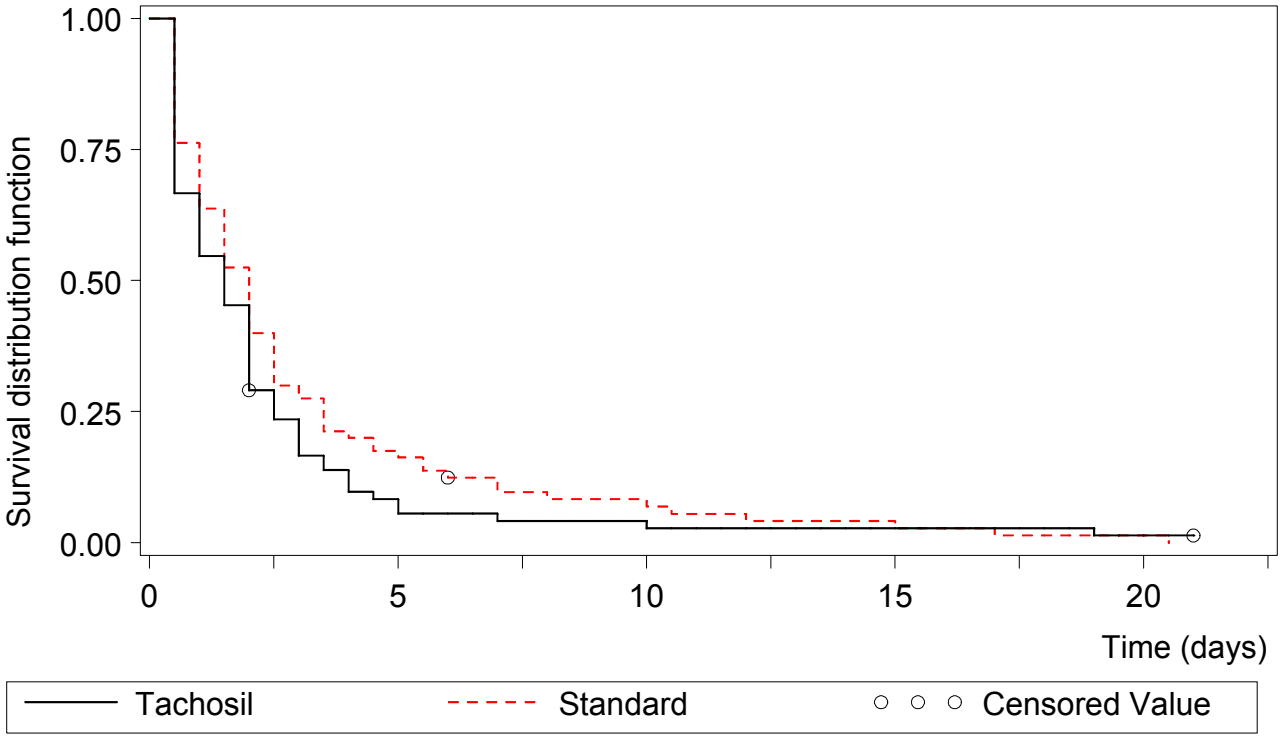
Lab test = INR result



Program:fig_laboratory.sas, Output:fig_laboratory_H.cgm, 02MAR09

Figure 5a: Sub-group Analysis: Duration of Post-Operative Air Leakage, Subjects Aged 65 or Under, ITT

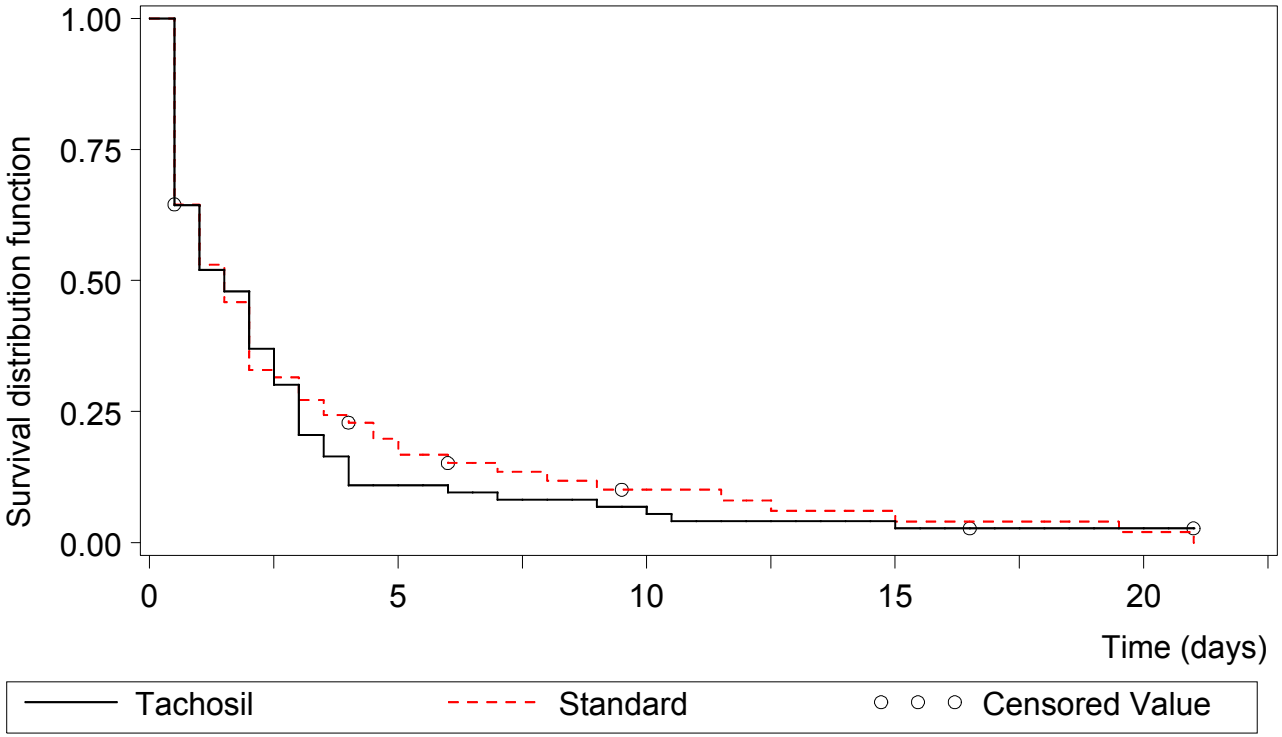
Log Rank Test for Equality over Treatments Stratified by Centre:
Chi-Square=5.3781, df= 1, p=0.0204



Program:fig_pe_SUBGROUP.sas, Output:fig_pe_SUBGROUP_UNDER65.cgm, 02MAR09

Figure 5b: Sub-group Analysis: Duration of Post-Operative Air Leakage, Subjects Aged 66 or Over, ITT

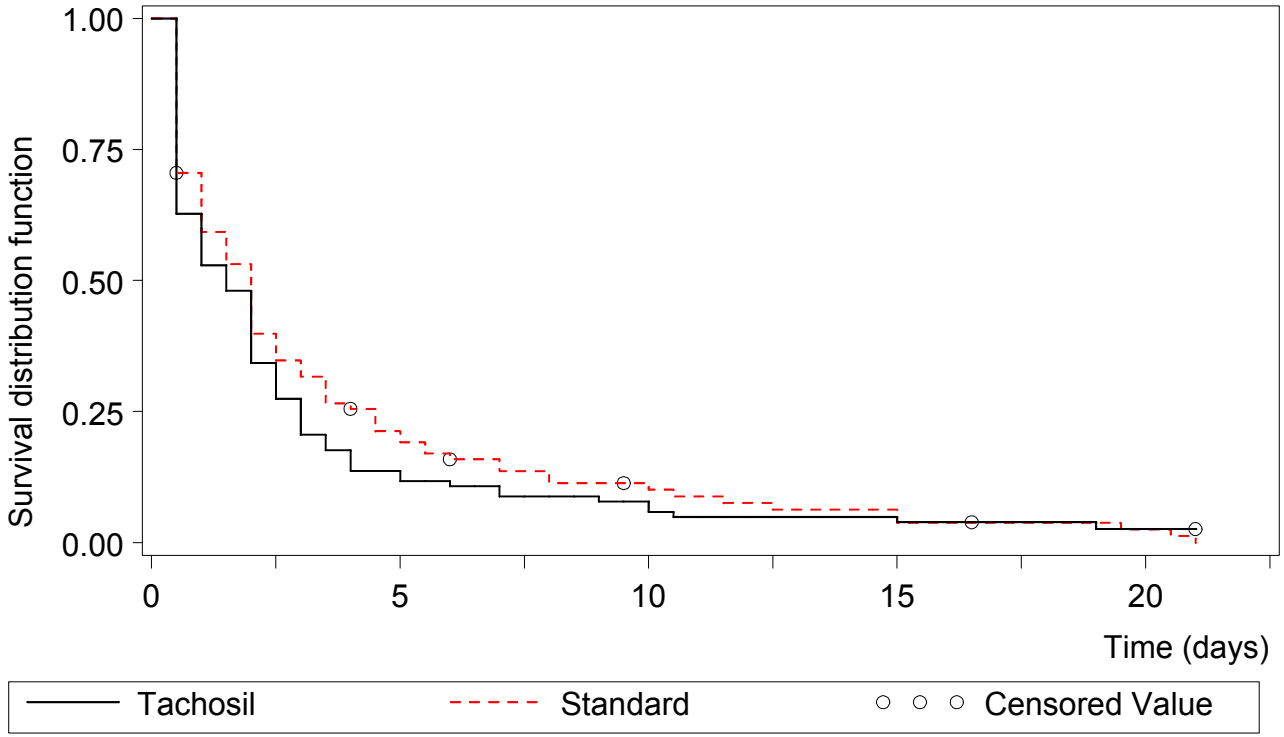
Log Rank Test for Equality over Treatments Stratified by Centre:
Chi-Square=1.4348, df= 1, p=0.2310



Program:fig_pe_SUBGROUP.sas, Output:fig_pe_SUBGROUP_OVER65.cgm, 02MAR09

Figure 5c: Sub-group Analysis: Duration of Post-Operative Air Leakage, Male Subjects, ITT

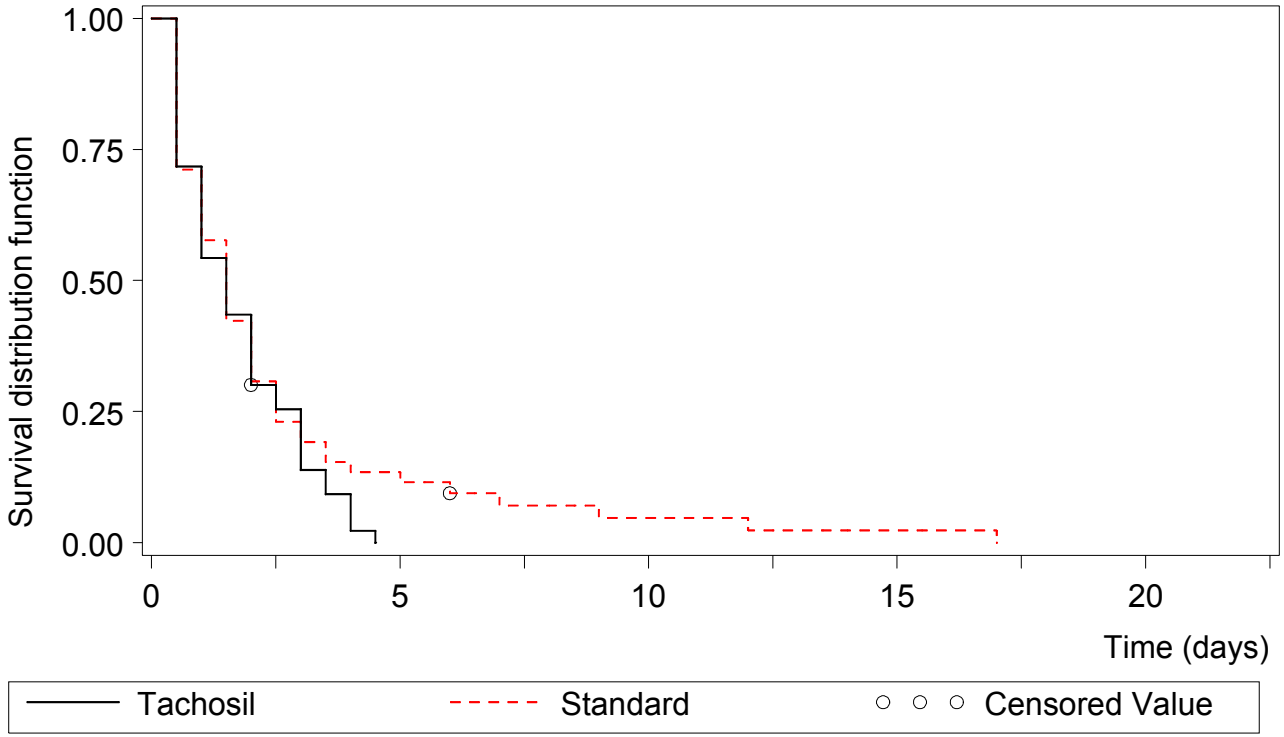
Log Rank Test for Equality over Treatments Stratified by Centre:
Chi-Square=2.9005, df= 1, p=0.0886



Program:fig_pe_SUBGROUP.sas, Output:fig_pe_SUBGROUP_MALE.cgm, 02MAR09

Figure 5d: Sub-group Analysis: Duration of Post-Operative Air Leakage, Female Subjects, ITT

Log Rank Test for Equality over Treatments Stratified by Centre:
Chi-Square=0.3413, df= 1, p=0.5591



Program:fig_pe_SUBGROUP.sas, Output:fig_pe_SUBGROUP_FEMALE.cgm, 02MAR09

APPROVALS

Clinical Trial Protocol

Title:

Protocol TC-021-IM Lung resection trial with TachoSil versus standard surgical treatm

ID:

TC-021-IM

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

Name **Reason for signature**	**Outcome** **Date for signature**
Kristian M. Windfeld compliance with statistical principles	Approved 26.Oct.2005 15:01:32

Document ID: C00005603

Version: 1.0

CLINICAL TRIAL PROTOCOL SIGNATURES

Short title: TachoSil® versus standard surgical treatment for air leakage in pulmonary lobectomy

Title: An open, randomised, prospective, multi-centre, parallel-group trial to compare efficacy and safety of TachoSil® versus standard surgical treatment in patients undergoing pulmonary lobectomy for lung malignancy and requiring treatment for air leakage

Trial ID: TC-019-IN

Approval of compliance with guideline and medical principles:

Senior Vice President

Alejandra Mørk, MSc, PhD
International Product Development
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DK-4000 Roskilde, Denmark

26/10-2005 14[00]
Date/Local time

Signature

Date protocol last modified: 26 October 2005

CLINICAL TRIAL PROTOCOL

Short title: TachoSil® versus standard surgical treatment for air leakage in pulmonary lobectomy

Title: An open, randomised, prospective, multi-centre, parallel-group trial to compare efficacy and safety of TachoSil® versus standard surgical treatment in patients undergoing pulmonary lobectomy for lung malignancy and requiring treatment for air leakage

Trial ID: TC-021-IM

Sponsor: Nycomed
International Medical Affairs
Langebjerg 1, DK-4000 Roskilde
Tel.: +45 4677 1111
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Trial phase: Therapeutic confirmatory / Phase IIIb

Date protocol last modified: 26 October 2005

The protocol version includes no Amendments

This trial will be conducted in accordance with Good Clinical Practice (GCP).

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For signatures see separate page

Summary

Objectives:

To compare sealing efficacy and safety of TachoSil® (hereafter referred to as TachoSil) versus standard surgical treatment as secondary management of intra-operative pulmonary air leakage after lobectomy in subjects with lung malignancies with or without metastases.

Methodology:

Open, randomised, prospective, multi-centre, parallel-group, phase IIIb trial with two treatment arms. A centralised telephone randomisation (Interactive Voice Response System (IVRS), see Section 9.5) to TachoSil or standard surgical treatment will be used when subjects have qualified for inclusion after lobectomy, i.e. have intra-operative air leakage grade 1 or 2 (15). Subjects will be followed from screening to follow-up with assessments at screening, on the day of surgery (day 0), every day until removal of the chest drain, at discharge from ward and at follow-up one month after surgery.

The present trial constitutes an appropriate controlled setting for obtaining data on the potential antibody formation following exposure to the exogenous constituents of TachoSil. The testing of neo-antigenicity requires sampling of pre- and post-exposure serum. Sampling, storage and analysis of serum for neo-antigenicity test will only be done following separate consent by the subject. The serum samples will be analysed and reported separately.

Number of subjects:

300, 150 in each treatment arm.

Diagnosis and main criterion for inclusion:

Air leakage grade 1 and 2 after lung lobectomy in subjects with lung malignancy with or without metastases.

Trial product, dose and mode of administration:

TachoSil is a sterile ready-to-use absorbable medicated sponge (hereafter referred to as sponge) for intra-operative topical application. It consists of an equine collagen sponge (9.5 x 4.8 x 0.5 cm) coated with human fibrinogen (5.5 mg/cm^2) and human thrombin (2.0 IU/cm^2). Before use, TachoSil should be pre-moistened with physiological saline solution. TachoSil is to be applied under aseptic conditions. The application of TachoSil should be to

all lung resection area(s), specifically the hilar area. The resection closure line should be cleansed of blood and other fluids before application of TachoSil.

Duration of treatment:
One intra-operative application.

Comparative treatment, dose and mode of administration:
Standard management of air leakage sites in the control group must be done with sutures, staples or even with no treatment according to the routine of the site.

Additional trial treatment (rescue treatment):
If needed, additional post-randomisation rescue treatment may be applied. This includes any available surgical technique or sealant (fibrin or non-fibrin sealant), except the use of TachoSil in subjects randomised to standard surgical treatment. The use of rescue treatment must be recorded including the time of application.

Criteria for evaluation:
Primary efficacy endpoint
- Duration of post-operative air leakage.

Secondary efficacy endpoint
- Reduction of intra-operative air leakage intensity after first application of trial treatment.

Descriptive variables
- Total number of days to removal of chest drain: Time of drain removal is when last chest drainage tube is removed.
- Pre-defined post-operative complications.

Safety
Adverse Events (AEs) will be recorded from informed consent is given until the end of protocol-required post treatment follow-up period (1 month ± 10 days). The processing and reporting of AEs will follow current Nycomed Standard Operating Procedures.

Clinical laboratory tests (haematology, coagulation factor (INR), blood gases, and pulmonary function tests) at screening and discharge and - if done routinely at the site - also on Day 1.

Clinically abnormal laboratory tests that suggest a disease and/or organ toxicity and require active management will be reported as AEs. A pregnancy test will be taken at Screening.

No safety committee/person and no interim safety analyses are planned.

Statistical methods:

The primary efficacy endpoint, duration of post-operative air leakage, will be analysed using life table analysis. Since air leakage is recorded at nominal time points, i.e. evening on day of operation, 1st shift at day after operation etc., the actual time points of sealing are not observed. It may be attributed to one of the time intervals Day $0_{operation}$ - Day $0_{evening}$, Day $0_{evening}$ - Day $1_{morning}$, Day $1_{morning}$ - Day $1_{evening}$, etc.. Subjects, who do not obtain absence of air leakage, will be censored at the time of the last assessment. The Log-rank test of equality over treatments will be performed controlling for centre, and the survival curves will be estimated and presented by centre using the life table method. If rescue treatment is applied, the duration of post-operative air leakage will be included in the ITT analysis as censored at the last scheduled time point according to the protocol. An exploratory parametric survival analysis of the primary endpoint, which takes account of the interval censoring and the actual time points of assessment, will be performed using an accelerated failure time model with treatment and centre effect included.

The secondary endpoint, reduction in intra-operative air leakage intensity, will be analysed by a Wilcoxon test. A test level of α= 5% will be used. Adverse events will be tabulated. Laboratory variables, surgery variables, trial treatment variables, drug accountability, and duration of drainage will be summarised by descriptive statistics. No interim analyses will be performed.

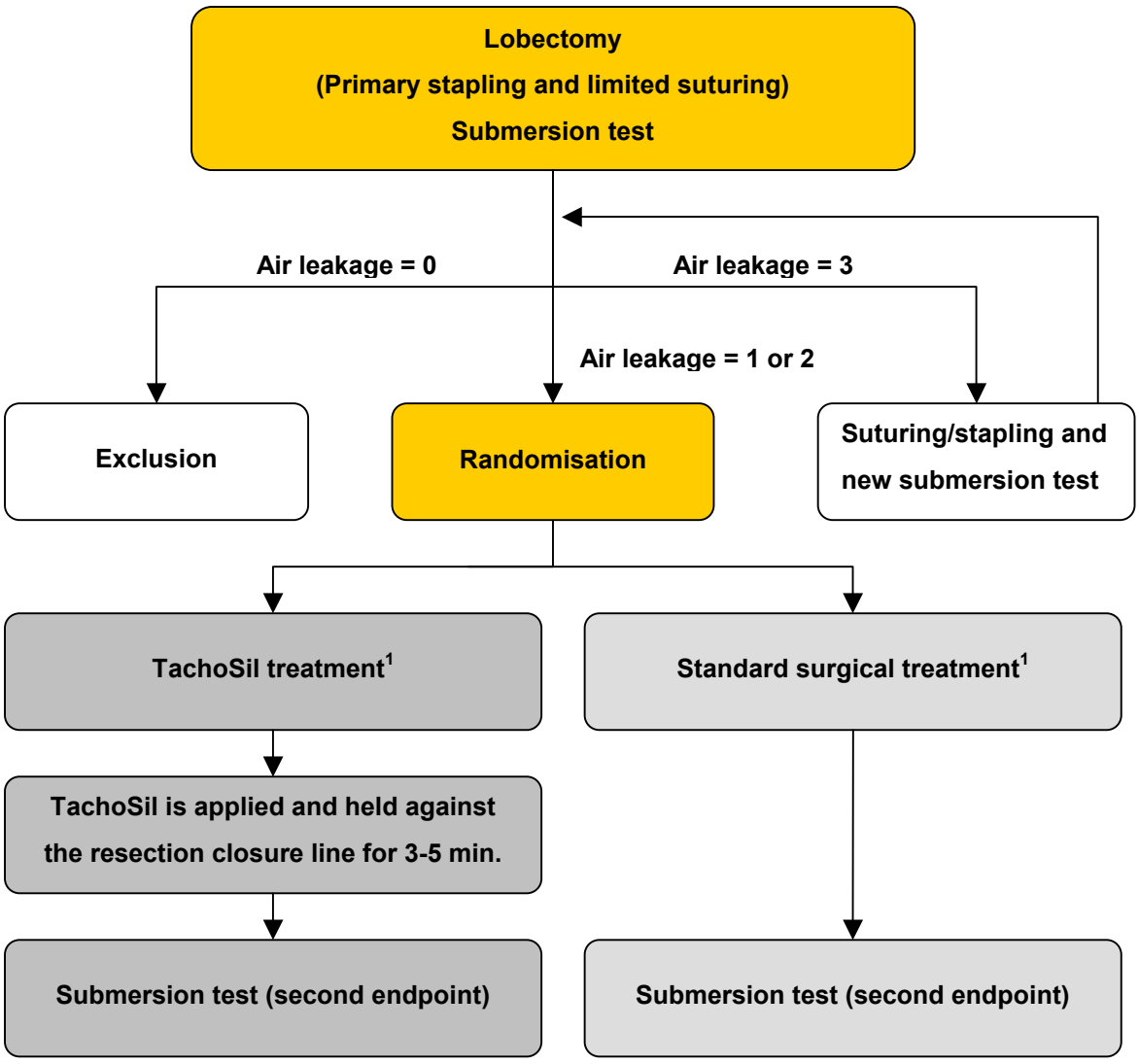
Flow Chart

Day of assessment Activities/assess-ments for CRF-entry	Screening (- 7 days)	Surgery Day 0 (*before* surgery)	Surgery Day 0 (*during* and *after* surgery)	Day 1	Day 2 until cessation of air leakage	Day of chest drain removal	Discharge from hospital	Follow-up 1 month (+/- 10 days)
Informed consent	X							
Inclusion/Exclusion criteria	X		X					
Demographic data/ Smoking/Alcohol	X							
Vital signs[1]	X	X		X	X	X	X	
Physical examination	X[2]						X	
Past and concomitant illness	X[2]	X[2]		X	X	X	X	
Concomitant medication	X[2]	X		X	X	X	X	
Pregnancy test	X[3]							
ECG	X							
Laboratory tests (haematology, blood gases, INR)	X[3]			(X)[4]			X[10]	
Pulmonary function: FEV_1, TLC, RV	X							
Chest X-ray	(X)[4]			(X)[4]		X[8]	X	(X)[4]
Adverse events	X	X	X	X	X	X	X	X
Stapling and primary suturing		(X)[5]	(X)[5]					
Pulmonary lobectomy			X					
Air leakage tests by water submersion			X					
IVRS Randomisation			X					
Trial treatment of air leakage			X					
Surgery and trial treatment variables			X					
Drug accountability			X					
Drainage volume assessment				X	X	(X)		
Sentinel Seal/ Air leakage test (cough)			X[6]	X[7]	X[7]	X		
(Post-operative) complications			X	X	X	X	X	X
Removal of drains						X[9]		
End of trial								X
Additional blood sample for neo-antigenicity test	(X)[5]							(X)[5]

1: Include body temperature, heart rate, blood pressure and respiratory rate.
2: To be recorded in CRF only if the subject is randomised.
3: Pregnancy test and laboratory tests must be repeated if done more than 48 hours before surgery.
4: If done routinely.
5: Not mandatory.
6: 3-5 hours after surgery.

7: Twice a day (day- and evening shift) until cessation of air leakage. If drainage is needed, suction must be maintained at least three days.
8: Chest X-rays must be performed (before removal of drains) and on the following day.
9: Drains should be removed simultaneously after evaluation of air leakage. Date and time of drain removal will be recorded. Time of removal is when last chest drainage tube is removed.
10: On the day of discharge or the day before according to hospital standard procedure.

Intra-Operative Flow Chart



1: If air leakage control is considered insufficient after the first application of trial treatment, trial treatments (application of TachoSil or standard surgical treatment) may be repeated until air leakage is sufficiently controlled.

Table of Content

List of Abbreviations and Definitions of Terms

AE:	Adverse Event
AUC:	Area under the Curve
BPWG:	Working Group on Blood Products
BTPS:	Body Temperature (37^{o}C) and Pressure (P_B) Saturated with water vapour
CA:	Competent Authority
CI:	Confidence Interval
CHMP:	Committee for Proprietary Medicinal Products
CPV:	Central Pharmacovigilance
CRF:	Case Report Form
CRO:	Contract Research Organisation
CS:	Clinical Supply
CTM:	Co-ordinating Trial Manager
CV:	Curriculum Vitae
CDU:	Chest Drainage Unit
DHP:	Data Handling Plan
DVP:	Data Validation Plan
ECG:	ElectroCardioGram
ELISA:	Enzyme-Linked Immuno Sorbent Assay
EMEA:	European Medicines Agency
EU:	European Union
FEV-1:	Forced Expiratory Volume – 1 second
G:	gravity force
GCP:	Good Clinical Practice
GMP:	Good Manufacturing Practice
ICH:	International Conference on Harmonization
IEC:	Independent Ethics Committee
IMP:	Investigational Medicinal Product
INR:	International Normalized Ratio
ITT:	Intention-To-Treat
IUD:	Intrauterine Device
IVRS:	Interactive Voice Response System
NCS:	Not Clinical Significant
OR:	Odds Ratio
PDS:	Polydioxanone
PP:	Per-Protocol

RV:	Residual Volume
SAE:	Serious Adverse Event
SAP:	Statistical Analyses Plan
SDV:	Source Document Verification
SE:	Sampling Error
SmPC:	Summary of Product Characteristics
SOP:	Standard Operation Procedures
SUSAR:	Suspected Unexpected Serious Adverse Reaction
TachoSil:	TachoSil®
TLC:	Total Lung Capacity
Trial ID:	Trial Identification Number

1 Ethical Rationale

The trial will be conducted according to the ethical principles contained in the Declaration of Helsinki, latest edition (1). Written informed consents will be obtained from all subjects before any trial-specific procedures are done. Investigator will explain the trial and its procedures to each subject verbally and the subjects will receive a Subject Information Sheet in order to acquaint themselves with the trial details. Subjects will be asked to sign the Informed Consent Form only after they have been given sufficient time to consider participation in the trial. Sampling, storage and analysis of serum for neo-antigenicity test will only be done following separate consent by the subject.

All subjects will receive active management of air leakage, if deemed necessary by the surgeon. Stapling and suturing are not mandatory as primary managements. The suturing or stapling method for air leakage management is widely used for control of intra-operative air leakage in lung surgery.

Post-randomisation treatment in the Standard surgical treatment group (control group) is left at the surgeons discretion, it could be re-suturing or no treatment. The need for surgical treatment in this group depends on the individual type and site of lung resection performed. This is according to routine surgical standards.

Persisting air leakage after pulmonary surgery may have untoward consequences for post-operative complications, overall morbidity, hospitalisation costs and health care costs. The use of TachoSil may have beneficial effects on these variables if air leakage is indeed prevented or reduced by using TachoSil.

The trial is designed to evaluate the efficacy and safety of TachoSil as air leakage treatment in lung surgery. TachoSil is expected not to cause serious adverse reactions as its efficacy and safety have been demonstrated in controlled clinical studies either with TachoSil or its predecessor product TachoComb® H (2, 3, 4, 5). TachoSil is registered since 2004 by the EMEA for supportive treatment in surgery for improvement of haemostasis where standard techniques are insufficient.

The immunological safety profile of TachoSil is expected to be improved in comparison with its predecessors products TachoComb® and TachoComb® H as TachoSil is made of human components only.

Benefits and Risks and Discomfort

The use of TachoSil may reduce the incidence and intensity of air leakage after lung surgery. The benefits of this may be a reduced period of chest tube drain, fewer post-operative adverse events and a shortened stay in hospital. Collagen sponge products with similar coagulation factors as TachoSil have been used extensively in the past decade with no untoward consequences for the subjects. The use of TachoSil is therefore expected to be safe and without risks although the possibility of unforeseen adverse events can not be completely ruled out. Subjects in the control group will receive standard surgical treatment that is a general surgical routine.

Management of air leakage is expected to be achieved with the trial treatment. If this, however, is not the case, the surgeon may use any other method to control the air leakage. The risk of participation in the trial is therefore minimal.

2 Legal Aspects

The trial will be conducted in accordance with the Declaration of Helsinki (1), ICH Good Clinical Practice (7), the EU Directive (2001/20/EC) (8), the EU Directive 95/46/EC (9), 21CRF Part 54 (10), and any applicable local regulation.

2.1 Subject Information and Informed Consent Form

Prior to any trial-related activity, the Investigator must give the subject oral and written information about the trial in a form that the subject can understand. Investigator must ensure that the subject is fully informed about the aims of the trial, procedures, potential risks, any discomforts and expected benefits. The subject must be left with ample time according to local requirements to consider and to pose questions, before consenting.

Furthermore the subject must agree that authorised sponsor trial personnel or their representatives, Regulatory Authorities including foreign Authorities and Ethics Committees will be granted direct access to the subject's original data/personal medical records (including photocopying source data in an anonymous form). The subject must also agree that his/her data will be processed and stored in an anonymous form for evaluation of this trial and any later overviews and that his/her data may also be transferred in an anonymous form to third parties (e.g. other companies or authorities), which may be located in other countries with potentially different regulations for data protection. Data will follow the development of the product and be used for documentation of the product’s efficacy and

safety. Data will only be transferred to involved parties within the authority given by official agencies.

It must be emphasised that participation is voluntary and that the subject has the right to withdraw from the trial at any time without prejudice.

A physician must obtain the subject's voluntary, personally signed and dated Informed Consent prior to any trial-related procedure. The Informed Consent Form will state that any data obtained will be kept even if the consent is withdrawn, but that no new data will be collected from the subject and added to existing data or a database. The Informed Consent will be prepared with check boxes ("yes" and "no") with the possibility to consent to the neo-antigenicity test separately.

2.2 Independent Ethics Committees

The protocol, any issued amendments, the Subject Information/Informed Consent Form and any other documents required (e.g. SmPC, CV of Principal Investigator, agreements between sponsor and trial sites etc.) must be submitted to the relevant Independent Ethics Committee (IEC) according to the European Commission guidance (11) and any applicable local regulations. Either the favourable opinion or approval of the IEC must be obtained before initiation of the trial.

According to national regulations it is the responsibility of Sponsor, Principal Investigator to obtain approval from the IECs and to meet the ICH requirement for yearly updates to the IEC. If the Investigator is the applicant for an Ethics Committee opinion, Nycomed will provide the required documents for the submission.

Any further substantial amendments must be submitted to the relevant IEC according to the European Commission guidance (11) and any applicable local regulations. Either an approval or a notification must be obtained before implementation.

At the end of the trial, Nycomed will notify the IEC within 90 days. In case of an early termination or temporary halt by Nycomed, the IEC should be notified within 15 days.

2.3 Authorities

According to the European Commission guidance (12) and any applicable local regulations the Competent Authorities (CAs) must receive all required documents and clinical trial authorisation (either an approval or notification) must be obtained before initiation of the trial.

The CA must receive any substantial amendment according to the European Commission guidance (12) and any applicable local regulations. Either an approval/notification must be obtained before implementation.

At the end of the trial, Nycomed will notify the CA within 90 days.

3 Critical Documents

Before the trial is initiated at an investigational site, the following documents from the site must be in the hands of Nycomed:

- Written agreements including financial agreements between Nycomed and Investigators.
- Current, signed and dated curriculum vitae for the Co-ordinating and Principal Investigator(s) and for other personnel listed on the log of staff.
- Signed and dated protocol agreement with the original signature of the Principal Investigator.
- Signed and dated substantial protocol amendment agreement(s), if any.
- Written IEC approval/vote according to local requirements.
- Subject Information and Informed Consent Form in local language (notified/approved by IEC).
- Health Authority approval/notification (according to local regulations).
- A copy of the log of staff document and delegation forms.
- Signed and dated laboratory normal ranges.
- Financial disclosure statement signed and dated by Investigator (10). The statement has to be obtained from the Investigator once a year and 1 year after the last follow up visit.

4 Introduction

TachoSil is formulated as a haemostatic and tissue sealant. It consists of an equine collagen sponge coated with two haemostatically active proteins, human fibrinogen and human thrombin. The active side is coloured with Riboflavin. Unlike conventional fibrin sealants the components of TachoSil are activated after application in a fixed combination and in this way adhere to the tissue (resection surface) providing a haemostatic seal, which is resistant to

moderate/oozing haemorrhage. TachoSil is therefore indicated for supportive treatment in surgery creating improved local haemostasis, where standard techniques are insufficient.

TachoSil is a further development of TachoComb® and TachoComb® H and differs from these only by the fibrin glue components. TachoSil is made of human components only. More than 800.000 patients have been treated with TachoComb®.

TachoSil has recently been authorised by the EMEA for supportive treatment in surgery for improvement of haemostasis where standard techniques are insufficient. Its efficacy and safety have been demonstrated in controlled studies.

For further information on efficacy and safety, see the TachoSil Investigator´s Brochure (13) and the SmPC (18).

It is acknowledged that TachoSil has good adhesive properties and provides tissue sealing as well. The present trial will be conducted in order to evaluate the efficacy and safety of TachoSil as air leakage treatment in lung surgery.

TachoSil has previously been clinically tested in pulmonary lobectomy (2). This trial included 189 subjects scheduled for lobectomy due to lung cancer. The trial design was essentially identical to the present trial, except for the following: (*i*) Subjects with absence of persistent air leakage (grade 0) following lobectomy and primary stapling were included, and *(ii*) the primary efficacy endpoint was incidence of air leakage 48 hours after surgery. Unexpectedly about half of the subjects achieved a grade 0 air leakage following the primary stapling, thus eroding the power of the trial. This caused the outcome of the planned analyses of difference in treatment efficacy to be statistically insignificant.

In the intention-to-treat (ITT) analysis of all subjects, regardless of the degree of air leakage present at randomisation, the incidence of air leakage 48 (±6) hours after surgery (primary efficacy endpoint) was 34% for TachoSil and 37% for standard treatment (p=0.76). The odds ratio (OR) of presence of air leakage with TachoSil compared to standard treatment was 0.91 (95% CI: 0.48-1.72). Assessment of secondary endpoints showed no significant differences between the treatment groups. However, ITT analyses of the sub-population of subjects with persistent air leakage after primary stapling (grade 1-2; n=89) indicated efficacy of TachoSil (analyses not pre-defined in protocol). In summary, the results were:

- Persisting air leakage at 48 hours was present in 39% and 49% of TachoSil and standard treatment, respectively (p=0.29). The OR of TachoSil compared with the standard treatment was 0.61 (95% CI: 0.24 1.56). Due to the small number of subjects presenting with air leakage at randomisation this favourable trend failed to reach statistical significance.
- Reduction of intra-operative air leakage intensity after the first application of trial treatment was more pronounced in the TachoSil group compared with standard treatment (p=0.015).
- The mean area under the curve (AUC) of post-operative air leakage intensity was significantly lower for TachoSil than for the standard treatment (p=0.047).
- While the duration of postoperative air leakage was reduced in TachoSil treated subjects (1.9 vs. 2.7 days, p=0.015) the duration of postoperative chest tube drainage did not differ between the treatment groups.

For further information on non-clinical studies and clinical trials, see the TachoSil Investigator's Brochure (13).

Sampling, storage and analysis of serum for neo-antigenicity test will only be done following separate consent by the subject. The serum samples will be analysed and reported separately.

An appropriate controlled setting for obtaining data on the potential antibody formation following exposure to the exogenous constituents of TachoSil will be performed with those subjects who voluntarily agree to two additional blood draws. The testing of neo-antigenicity requires sampling of pre- and post-exposure serum. Although the neo-antigenicity test is an integral part of the protocol:
1) a separate analytical protocol will be prepared for the neo-antigenicity testing,
2) proper validation of the ELISA test will be done prior to analysis, and
3) neo-antigenicity analysis and reporting will be done separately, i.e. not as part of the Clinical Trial Report for TC-021-IM.

5 Objective

To compare sealing efficacy and safety of TachoSil versus standard surgical treatment as secondary management of intra-operative pulmonary air leakage after lobectomy in subjects with lung malignancies with or without metastases.

6 Overall Design and Plan of Trial

Open, randomised, prospective, multi-centre, parallel-group phase IIIb trial with two treatment arms to which subjects will be evenly distributed. Randomisation to TachoSil or standard surgical treatment will be done after lobectomy with Interactive Voice Response System (IVRS) (see Section 9.5) when intra-operative air leakage has been assessed; air leakage grades 1 and 2 qualify for inclusion. The centralised randomisation system will ensure allocation concealment to prevent selection bias, as recommended in the CONSORT statement (14). Subjects with air leakage grade 3 may be reassessed for randomisation after (further) stapling and/or suturing. The trial is open, since the appearance of TachoSil makes it impossible to blind the two treatments during surgery.

The prospective and controlled trial design as well as the use of objective endpoints are recommended by authorities along with recommendations to compare efficacy with standard treatment without fibrin sealant (6).

6.1 Efficacy Variables

6.1.1 Primary Efficacy Endpoint

- Duration of post-operative air leakage:
  Assessment of this endpoint is in accordance with the schedule of air leakage assessments made at the evening of the day of operation (Day 0) and then subsequently twice daily (at morning and evening shifts). Assessment of air leakage is done by observing bubbles in a standardized chest drainage unit. In case of no apparent air leakage at rest the assessment should be done with cough provocation.

6.1.2 Secondary Efficacy Endpoints

- Reduction of intra-operative air leakage intensity after first application of trial treatment.

6.1.3 Descriptive Variables

- Total number of days until removal of the (last) chest drain.
- Predefined post-operative complications: i.e. pneumonia, pulmonary embolism, atelectasis of the lung, surgical wound infection, cardiac arrhythmia, emphysema of the lung, need for additional chest drainage, need for re-operation, need for respiratory assistance, bleeding, and need for blood transfusion.

6.2 Method Guidelines

The protocol was developed in accordance with the Declaration of Helsinki (1), ICH Good Clinical Practice (7), the EU Directive (2001/20/EC) (8), the EU Directive 95/46/EC (9), 21CRF Part 54 (10) and any applicable local regulation.

The prospective and controlled trial design as well as the use of objective endpoints are recommended by authorities along with recommendations to compare efficacy with standard treatment without fibrin sealant (6).

6.3 Trial Schedule

Planned inclusion of first subject:	Q1 2006
Planned recruitment period:	15 month
Planned completion of the last subject:	Q2 2007
Planned completion of Clinical Trial Report:	Q4 2007

In case of unexpected difficulties with recruitment of the planned 300 subjects within 15 months, the trial schedule may be extended.

7 Trial Population

The trial population consists of subjects scheduled for lung lobectomy due to lung malignancies with or without metastases.

7.1 Number of Subjects to be Studied

For a total of 300 subjects to be randomised it is expected that approximately 600 patients will have to be screened. The screening failure rate of 50 % is based on the experience in a previous lung trial, TC-013-IN. It is planned that 12-16 sites in Europe will participate. Each site should aim to randomise at least 25 subjects, i.e. approximately 50 patients need to be screened. A competitive enrolment will be allowed with a maximum of 50 randomised subjects per site. For calculation of sample size, see Section 15.1.

The subject will be given a screening number and - if randomised - a subject number; initials will consist of two letters: the first letter in the first and last name of the subject.

7.2 Inclusion Criteria

Subjects with a diagnosis of lung malignancy with or without metastases may be included in the trial if the entry criteria apply.

All inclusion criteria must be answered “yes” for a subject to participate in the trial.

At pre-operative screening

1. Has the subject given informed consent according to local requirements before any trial-related activities? (A trial-related activity is any procedure that would not have been performed during the routine management of the subject.)
2. Is the subject 18 years of age or above?
3. Is an elective lobectomy for lung malignancy with intrapulmonary lymphadenectomy (with antero- or postero-lateral incision) planned?

For female subjects of childbearing potential

4. Does the subject use adequate contraception (contraceptive pill, contraceptive implants, contraceptive injections or intrauterine device (IUD))?

After pulmonary lobectomy with intrapulmonary lymphadenectomy (and primary stapling and limited suturing if considered necessary by the surgeon).

5. Is the air leakage of grade 1 or 2?

If more than one resection site is affected after lobectomy, the highest grade applies as grade of entry, subjects with air leakage grade 3 may be reassessed for randomisation after further stapling and/or suturing. The air leaks should originate from the pulmonary parenchyma and not from the bronchi.

7.3 Exclusion Criteria

All exclusion criteria must be answered “no” for a subject to participate in the trial.

At pre-operative screening

1. Has the subject had previous lung surgery?
2. Has the subject had previous anti-tumour chemotherapy within the last 3 weeks?
3. Has the subject had radiotherapy for lung malignancy within the last 4 weeks?
4. Does the subject have a history of allergic reactions after application of human fibrinogen, human thrombin and/or collagen of any origin?
5. Is this an emergency surgery?

6. Does the subject have an FEV1 < 40%?
7. Has the subject previously been exposed to TachoComb, TachoComb H or TachoSil?
8. Does the subject have a present abuse of drugs or alcohol?
9. Has the subject participated in any other trials with an investigational drug or device within 30 days prior to inclusion in this trial?
10. Does the subject participate or plan to participate in another clinical trial during the trial period?

For female subjects of childbearing potential

11. Is the pregnancy test positive before application of trial treatment?
12. Is the subject breast feeding?

After pulmonary lobectomy with intrapulmonary lymphadenectomy (and primary stapling and limited suturing, if considered necessary by the surgeon).

13. Did serious surgical complications occur including need for surgical adhesiolysis of the remaining lung tissue?
14. Was pneumonectomy performed?
15. Was wedge resection of the lung performed?
16. Was any fibrin glue sealant (including TachoSil) used before randomisation?

Subjects that were found eligible for participation at screening, but did not fulfil the entry criteria at randomisation, will not be randomised in the trial. Only the screening section of the CRF will be filled in for these subjects.

7.4 Withdrawal of Subjects

Subjects may withdraw from the trial at any time. If a subject intends withdrawal, he/she must immediately contact the Investigator and inform him/her of the decision. The subject is free to withdraw without stating a reason, withdrawal will have no consequences for his/her further treatment.

The subject may require that all previously retained identifiable samples, e.g. neo-antigenicity test, must be destroyed to prevent future analyses, according to national provisions.

Air leakage treatment other than trial treatment should be avoided if at all possible. If rescue treatment is needed, any treatment available may be used – including fibrin sealants. Please

observe that TachoSil can NOT be used as rescue treatment to subjects randomised to standard surgical treatment.

Investigator may withdraw a randomised subject from the trial due to adverse events (AEs) or if the condition of the subject requires treatment outside the scope of the protocol.

In case of withdrawal/premature termination before discharge from the ward, procedures according to protocol at discharge must be followed and observations documented in the CRF. The reason(s) for withdrawal must be stated in the CRF. A subject that discontinues prematurely after discharge from hospital must, if possible, be called in for a last visit. Even if the subject is not able/willing to attend the visit, the "End of trial" page in the CRF must be completed.

In case of withdrawal at any time during the trial, all AEs must be followed by the Investigator at least until the subject has recovered or until one week post-treatment (whichever comes first) and until all queries related to AEs have been resolved (see Section 10.4).

7.5 Deviations from the Protocol

Every attempt should be made to comply with the protocol. If a deviation occurs, the reason, the date and any implications must be recorded with a Data Deviation Form and/or Note to File. Investigator and Monitor must discuss if the deviation has any consequences for the subject's continued participation in the trial. If there are any consequences, the discussion must be documented in the Investigator File and the Trial Master File.

8 Methods and Assessments / Measurements

Investigator must ensure that source documents such as official hospital records and original laboratory records exist as required and that Sponsor representatives as well as relevant persons from authorities must be given direct access to the source data. For specifications, see Section 12.1.

8.1 Visit Procedures

For an overall view of activities and assessments to be performed see the Flow Chart (page 7). The activities and assessments are described below for the day when first performed.

8.1.1 SCREENING (to be done within 7 days of surgery)

- **Informed consent.** Before any trial-related activities, the subject must personally sign and date the Informed Consent Form. For details please see Section 2.1
- **Inclusion/exclusion criteria at screening,** please see Sections 7.2-3.
- **Demographic data** include date of birth, sex, race, height and weight.
- **Smoking and use of alcohol.** The average weekly consumption will be recorded.
- **Vital signs** include body temperature, heart rate, blood pressure and respiratory rate. Temperature may be recorded rectally, orally, axillary or in the ear. The same method should be used throughout for a subject. Blood pressure and heart rate should be assessed after the subject has been sitting for 5 minutes.
- **Physical examination** according to normal pre-operative procedure (to be recorded in the CRF only if the subject is randomised). Physical examination includes examinations of the following systems: 1) Ears, eyes, nose, throat, neck; 2) Respiratory system; 3) Cardiovascular system; 4) Gastrointestinal system including mouth/pharynx; 5) Genito-urinary system, breasts; 6) Musculoskeletal system; 7) Central and peripheral nervous system and 8) Skin.
- **Past and concomitant illness,** please see Section 8.2 (to be recorded in the CRF only if the subject is randomised). Indication for pulmonary lobectomy (lung malignancy).
- **Concomitant medication,** please see Section 8.2 (to be recorded in the CRF only if the subject is randomised). Any steroid treatment should be recorded. Past and current lung therapy must be recorded, too.
- **Pregnancy test** must be performed in all female subjects of childbearing potential. Childbearing potential is considered until menopause has lasted for more than 12 months. Surgically hysterectomised and surgically sterilised females can be included on the same conditions as male patients. Pregnancy is an exclusion criterion. The screening pregnancy test must be done within 48 hours before surgery and will be performed with an urine stick.
- **ECG (ElectroCardioGram).** Will be assessed, normal, abnormal or clinical significant.
- **Laboratory tests** include the following if done as a standard at the site: haematology (haemoglobin; haematocrit; erythrocyte, leucocyte, platelet counts); blood gases (pO_2 and pCO_2) and coagulation status (INR).The laboratory tests at screening should be done in accordance with hospital standard procedure and within 48 hours before surgery. A subject must be excluded from the trial if the Investigator considers the coagulation status (INR value) to be clinically significant. Screening laboratory tests must be done within 48 hours before surgery.

Investigator must comment on all abnormal laboratory test results and indicate if the result is clinically significant (CS) or not (NCS) or if it is a sampling or laboratory error (SE). An abnormal test result has a value outside the normal range.

- **Pulmonary function tests** include FEV_1 (forced expiratory volume – 1 second). The FEV-1 value is normally recorded in absolute units (millilitre), but the term FEV-1 is routinely used in the sense of a relative value (%), therefore FEV-1 will be recorded in the CRF in % as relative to predicted value; TLC (total lung capacity); RV (residual volume). The variables may be assessed with any test system and will be recorded as BTPS.
- **Chest X-ray:** X-rays will be assessed for inflation of lung (full, incomplete, collapsed) as well as other pathology.
- **Baseline adverse events (AEs)** since the subject signed the Informed Consent Form. For registration of AEs, see Section 10.
- **Additional blood sample for neo-antigenicity test.**

Additional serum samples for the testing of **neo-antigenicity** following exposure to TachoSil will be analysed and reported separately (22, 23). The two required samplings should be obtained according to the following procedures:

- 2 ml blood serum obtained at screening and at follow-up (1 month ± 10 days of surgery).
- Serum from each blood sample to be separated following coagulation (sample stands for 30-60 min at 37 °C) followed by loosening the clot from the vial wall. Vial and loosened clot are stored overnight in refrigerator at 4 °C.
- The vial is centrifuged (10,000 G, 4 °C).
- The serum is transferred to new vial and divided in 10 aliquots, each of 100 microlitre.
- The aliquot samples should be stored at or below minus 18 °C. Shipment to central laboratory likewise at minus 18 °C will be performed before or at Close out visits.

The rationale for dividing the samples into small aliquots is that antibodies are instable if thawed and re-frozen. In contrast, antibodies are generally stable for years if kept at minus 18 °C. The 10 small aliquots thus ensure the possibility to re-analyse if needed without destroying the rest of the sample.

The storage period of the serum samples will end 2 years after the Clinical Trial Report (CTR) has been finalised.

8.1.2 DAY 0 - Day of Surgery

- **Vital signs** to be done before surgery. Please see Section 8.1.1.
- **Concomitant illness**. Any changes since screening to be recorded. Worsening must be recorded as AEs. Please see Section 8.2.
- **Concomitant medication.** Any changes in concomitant medication since screening. Please see Section 8.2.
- **Adverse events** since the subject signed the Informed Consent Form; please see Section 10.
- **Stapling and/or limited suturing** (before lobectomy), if considered necessary by the surgeon.
- **Pulmonary lobectomy** with either antero-lateral or postero-lateral incision and intrapulmonary lymphadenectomy.
- **Stapling and/or limited suturing** (after lobectomy), if considered necessary by the surgeon.
- **Air leakage test by water submersion (First test).** After the above procedures (before randomisation), all parenchymal resection sites will be identified and air leakage will be assessed by water submersion test under standard airway pressure of 20-25 cm H_2O. (A resection site is defined as any site with potential air leakage including stapling lines, areas of resection a.o.). The submersion test is performed as follows (15):
  Sterile physiological saline is poured into the chest cavity and the lung submerged and inflated to check for sites and degree of air bubbles. Each surgical site is graded under an inflation pressure of 20-25 cm H2O.

Grade 0/absent:	no apparent leak
Grade 1/mild:	countable bubbles
Grade 2/moderate:	stream of bubbles
Grade 3/severe:	coalesced bubbles

  In case of several sites, severity will be taken from the site with the highest grade. Any site with air leakage grade 3 must have further stapling or limited suturing of the collapsed lung followed by submersion test until grade 0, 1 or 2 is obtained.

Please observe that only subjects with resection site air leakage grade 1 and 2 are eligible for randomisation.

- **IVRS Randomisation.** Interactive Voice Response System (IVRS) will be used to randomise subjects to treatment groups (please see Section 9.5).

- **Trial treatment variables** include the location of the resection site. For TachoSil subjects the number of sponges used and the pack number (TC-XXX) on the cartons of TachoSil used must be recorded (please see Section 9.2).
  For standard surgical treatment subjects stapling (size used for lung tissue) or suturing method (continuous, singular), suturing thread (PDS, proline, vicryle, other), size of suture (diameter 3.0, 4.0 etc.) or other methods if any must be recorded. If treatment to close air leakage sites other than trial treatment, i.e. rescue treatment, is needed, the method must be recorded.
  TachoSil can be used to close air leakage sites in the TachoSil treatment group but not as a haemostatic. Also please see Section 7.4, Withdrawal of subjects.
- **Surgery variables** describe the surgery, i.e. thoracic incision (antero-/postero-lateral), application of lymphadenectomy, specification of lobectomy site (right or left; upper, middle or lower), time of day for last submersion test, time of incision and time when surgery ended.
- Record **type of lung malignancy** according to the pathology report.
- **Drug accountability.** For details please see Section 9.4.
- **Trial treatment of air leakage** sites of grade 1 and 2 must be performed with either TachoSil or standard surgical treatment according to randomisation.

TachoSil:

TachoSil is to be applied under aseptic conditions. The application of TachoSil should be to all lung resection area(s), specifically the hilar area. Prior to application the resection site(s) should be cleansed, e.g. from blood, disinfectants and other fluids. After removal of TachoSil from the sterile package the sponge should be pre-moistened in saline solution and then applied immediately. Another appropriate way to apply TachoSil is to use it dry and press a moistened pad against it. The yellow, active side of the TachoSil sponge is applied to the resection area and held against it with gentle pressure for 3-5 minutes. Pressure is applied with either a moistened surgical glove or a moist pad. The sponge must cover the resection site(s) at least 1–2 cm beyond the margins. If more than one sponge is needed, the individual sponges must overlap. A sponge can be cut with sterile scissors as needed. Any cut off surplus pieces must be discarded. Due to strong affinity of collagen to blood, TachoSil may also stick to surgical instruments or gloves covered with blood. This may be avoided by pre-moistening surgical instruments and gloves with physiological saline.

Standard surgical treatment:

For subjects randomised to standard surgical treatment, the resection site(s) must be closed at the discretion of the surgeon. This could be re-suturing, stapling or even no treatment.

- **Air leakage test by water submersion (Second test).** Intensity of air leakage after the first application of trial treatment will be assessed by water submersion test as above.

The flow is described in the Intra-operative Flow Chart, page 9. If air leakage control is considered insufficient after the first application of trial treatment, this may be repeated. If air leakage is insufficiently controlled after the second application, trial treatment may be repeated again.

If the surgeon needs to use other measures than trial treatment, i.e. rescue treatment, to manage air leakage before closing the chest cavity, the subject will be considered a treatment failure. Rescue treatment includes any available surgical technique or sealant (fibrin or non-fibrin) except the use of TachoSil in subjects randomised to standard surgical treatment.

- The presence of air leakage (twice a day assessment from Day 0 until cessation) will be assessed using the Sentinel Seal Dual Collection Chamber System (Ref. Number: 8888 – 571513 from Tyco) at continuous suction of 10-15 cm H2O. The system allows determination of air leakage by air bubbles appearing in a water reservoir.

After closing the chest cavity, two chest drain tubes (an upper and a lower chest drainage site) will be connected to the Sentinel Seal chest drainage unit (CDU). If drainage is needed, a continuous post-surgical suction of 10-15 cm H_2O for at least three days is mandatory. After three days, drainage may be maintained, but without suction. Suction should not necessarily be “continuous”, it could be stopped e.g. for 30 min to permit mobilisation of the subject. After five post-operative days of air leakage, the Investigator should consider re-operation. An increase of air leakage must be recorded as an AE. Nycomed will provide the necessary number of Sentinel Seal CDU’s to the sites. The same system has to be used by all participating trial sites.

- **Air leakage test / provocation (cough).** Presence of air leakage post-operatively will be assessed between 3 and 5 hours after completion of surgery at rest with the Sentinel Seal CDU as described above. The time of day of the assessment will be recorded.
  If there is no apparent air leakage at rest, **provocation by coughing** will be performed at continued suction of 10-15 cm H_2O. In this condition with no residual air, the subject will be asked to cough, and the appearance of air bubbles in the CDU will be assessed at the second or third effective coughing. If no air bubbles develop, air leakage will be considered absent.

Please observe: Duration of post-operative air leakage is the primary endpoint.

- Recording of **post-operative complications** including pneumonia, pulmonary embolism, atelectasis of the lung, bleeding, surgical wound infection, cardiac arrhythmia and emphysema of the lung must also be recorded as AE. The reason for additional chest drainage, need for re-operation, need for respiratory assistance and need for blood transfusion must be reported as AE, too. The number of units of blood substitution given for any type of substitution will be recorded in CRF as whole blood, packed RBC, fresh frozen plasma, and "other".

8.1.3 DAY 1

- **Vital signs**, please see Section 8.1.1.
- **Concomitant illness,** please see Section 8.2.
- **Concomitant medication,** please see Section 8.2.
- **Laboratory tests**, if done routinely (haematology, blood gases and coagulation status (INR)).
- **Chest X-ray** if done routinely. Please see Section 8.1.1.
- **Adverse events**
- **Volume of drainage** will be assessed between 05:00 and 10:00 a.m.
- **Air leakage test / provocation (cough).** Presence of air leakage will be assessed twice a day (morning and evening) at rest with the Sentinel Seal CDU, see Section 8.1.2. Time of assessment will be recorded. Assessment must be done before drains are removed. If drainage is needed, a continuous post-surgical suction of 10-15 cm H_2O for at least 3 days is mandatory.

Please observe: Duration of post-operative air leakage is the primary endpoint.

- Recording of **post-operative complications**, please see Section 8.1.2.

8.1.4 DAILY from DAY 2 until ABSENCE OF AIR LEAKAGE

- **Vital signs,** please see Section 8.1.1.
- **Concomitant illness,** please see Section 8.2.
- **Concomitant medication,** please see Section 8.2.
- **Adverse events**
- **Volume of drainage** will be assessed between 05:00 and 10:00 a.m.
- **Air leakage test / provocation (cough)**. Presence of air leakage will be assessed twice a day at rest with the Sentinel Seal CDU as described in Section 8.1.2. Time of assessment will be recorded. Assessment must be done before drains are removed.

If drainage is needed, a continuous post-surgical suction of 10-15 cm H_2O for at least 3 days is mandatory.

After 5 post-operative days of air leakage, re-operation should be considered.

Please observe: Duration of post-operative air leakage is the primary endpoint.

- Recording of **post-operative complications,** please see Section 8.1.2.

8.1.5 DAY of CHEST DRAIN REMOVAL

- **Vital signs,** please see Section 8.1.1.
- **Concomitant illness,** please see Section 8.2.
- **Concomitant medication,** please see Section 8.2.
- **Chest X-rays** should be performed on the day of chest drain removal (before removal) and the following day. For details please see Section 8.1.1.
- **Adverse events**
- **Volume of drainage** will be assessed between 05:00 and 10:00 a.m.
- **Air leakage test.** Drain(s) will be maintained at a standard suction pressure of 10 -15 cm H_2O for at least 3 days with persistent air leakage.
- Recording of **post-operative complications,** please see Section 8.1.2.
- **Removal of chest drainage tubes.** Will be done after the last assessment of air leakage respectively after absence of air leakage. Two drainage tubes should be used routinely; removal of the drains can be made on two separated days.
  The total threshold volume for removing the drain(s) is left at the physicians' discretion, but is usually (less than) 200 ml fluid/day. If the drainage tubes are removed on separate days, only the date of removal of the last tube should be recorded.
  Date and time of removal of the (last) drain(s) will be recorded.

8.1.6 DISCHARGE from Hospital

- **Vital signs,** please see Section 8.1.1.
- **Physical examination,** please see Section 8.1.1.
- **Concomitant illness,** please see Section 8.2.
- **Concomitant medication,** please see Section 8.2.
- **Laboratory tests**: haematology, blood gases and coagulation test. May be done the day before discharge if this is standard procedure at the site.
- **Chest X-ray.** For details please see Section 8.1.1.
- **Adverse events**
- Recording of **post-operative complications,** please see Section 8.1.2.

8.1.7 FOLLOW UP (1 month +/- 10 days after surgery)

The follow up visit should be done at site.

- **Chest X-ray** (if done routinely on the day of follow-up). For details please see Section 8.1.1.
- Recording of **post-operative complications**, please see Section 8.1.2.
- **Adverse events.** Investigator will ask non-leading questions about the occurrence of any adverse events.
- **End of trial.** If the subject was withdrawn from the trial, the reason (adverse event, non-compliance with protocol or other) will be recorded on the "End of trial page" in the CRF. Please see Section 7.4 for withdrawal of subjects.
- Additional blood sample for neo-antigenicity test. For details see Section 8.1.1.

8.1.8 Unscheduled Visits

Any visit that is not planned according to the protocol will be recorded including reason(s) for the visit and any actions taken.

8.2 Past and Concomitant Illness and Concomitant Medication

Definitions:

Past illness	any clinically relevant past medical condition or illness.
Concomitant illness	any illness that is present at the start of the trial.
Concomitant medication	any medication other than the trial product (TachoSil) that is taken during the trial – from screening to follow up. Air leakage treatment other than trial treatment should be avoided if at all possible.

A worsening in severity or frequency of a baseline concomitant illness as well as any new illness diagnosed during the trial, must be regarded as AEs whether or not they are considered to be related to the trial product and must be reported as such (please see Section 10).

Any changes in concomitant medication or treatment procedures must be recorded at each visit. Prophylactic anticoagulation treatment before surgery must be recorded; it should be recorded, too, if anticoagulant treatment was stopped within two days before surgery.

Concomitant medication excepted from this is medication/treatment in relation to the surgical intervention documented in advance, i.e. medication covering pre-medication (except anticoagulation therapy), anaesthesia and post-operative medication including pain management. Upon the request of Nycomed, Investigator must provide information of the above-mentioned medication. Any type of steroid treatment (local or systemic) must be recorded.

9 Trial Material

9.1 Investigational Medicinal Products

TachoSil

TachoSil is a sterile, ready-to-use, absorbable sponge for intra-operative topical application. It consists of an equine collagen sponge coated with the fibrin glue components human fibrinogen (5.5 mg/cm^2) and human thrombin (2.0 IU/cm^2). The active side is coloured with Riboflavin. TachoSil is manufactured, packed and labelled according to GMP. The sponge size is 9.5 x 4.8 x 0.5 cm.

For management of air leakage sites of TachoSil treated subjects, as many sponges as needed, should be used. The sponge(s) must cover the site(s) at least 1-2 cm beyond the immediate margins. If more than one sponge is needed, the individual sponges must overlap.

Standard Surgical Treatment

Standard management of air leakage sites in the control group must be done with sutures, staples or even with no treatment according to the routine at the site.

Rescue treatment

Any surgical sealing technique or sealant (non-fibrin or fibrin, except the application of TachoSil in subjects randomised to standard surgical treatment) used according to the routine at the site.

9.2 Packaging and Labelling

All trial products will be packed and labelled according to current GMP, Annex 13 (16) and national requirements under the responsibility of Clinical Trial Supply, International Pharmaceutical Affairs, Nycomed.

Each TachoSil carton contains one sponge, which is double-packed in two covers of which the inner cover (polystyrene blister sealed with a peel lacquer-laminate paper) is sterile. The outer aluminium cover is impermeable to air and fluid and contains a 3 g silica gel desiccant for absorption of any remaining humidity.

The inner cover is labelled:
TachoSil®
Batch No.: XXX
Expiry date: XXX

The carton and the outer aluminium cover are both labelled according to Annex 13 (16) and local requirements:

Translation of the label text will be done as needed and according to local requirements. In addition, the label for the carton will carry 2 tear-off labels to be affixed to the CRF and hospital file of the subject, respectively. These labels will contain trial identification (TC-021-IM) and pack number.

9.3 Delivery of TachoSil

Clinical Trial Supply, International Pharmaceutical Affairs, Nycomed is responsible for the delivery of TachoSil as well as import/export, local storage, transportation and distribution to Investigator.

9.4 Storage and Drug Accountability of Investigational Medicinal Product

It is the responsibility of Investigator to keep account of the TachoSil sponges dispensed to and returned from the subjects.

Storage. TachoSil must be kept in a safe and locked area with limited access during the duration of the trial. TachoSil must be stored at a room temperature not exceeding 25°C. The expiry date is printed on all three package elements. TachoSil is delivered in sterile cover and must be handled accordingly. Later sterilisation is not possible.

Drug accountability. Investigator will receive the necessary supply of TachoSil and will for each delivery sign a “Trial Medication Delivery Form” as confirmation of receipt. The individual pack numbers of the sponges (TC-XXX) will be listed in this delivery form in order

to register the numbers available to the individual Investigator. Other trial-related supplies such as CRFs will be listed in the “Clinical Supply Delivery Form”.

TachoSil should be applied by the Principal Investigator or by another qualified and experienced surgeon appointed by Principal Investigator. Investigator agrees to apply TachoSil only to subjects randomised to TachoSil treatment. The amount of sponges used for the individual subject will be recorded in the CRF and hospital files along with the pack number from the carton (tear-off labels). Investigator must keep and update the “Drug Accountability per Subject Form” where the use of all sponges should be accounted for. This form must be available to the Monitor for accountability checks. Any discrepancies must be explained in writing by the Investigator. The completed form, signed by Principal Investigator at the end of the trial, will be returned to Nycomed.

After completion of the trial, all unused TachoSil sponges and empty cartons must be returned to Clinical Trial Supply, International Pharmaceutical Affairs, Nycomed Denmark by using the “IMP return to CTS Form”. The number of returned sponges will be recorded by Monitor in the “Account of TachoSil Sponges per Site Form” and in the “IMP Return per Site Form” and must correspond to the numbers received and used.

A copy of the completed forms, “Clinical Supply Delivery Form”, “Drug Accountability per Subject Form”, “Account of TachoSil Sponges per Site Form” and “IMP Return per Site Form”, must be kept in the Investigator File.

9.5 Randomisation

Subject assignment

Subjects will be randomised to either TachoSil or standard surgical treatment. When a subject has qualified for participation according to Sections 7.2-3, the Investigator will dial a central Interactive Voice Response System (IVRS) by telephone. This external IVRS is used to secure total allocation blinding (14). After having received specific user (site) identification, the trial identification and the date of birth of the subject to be randomised, the IVRS informs Investigator of the subject number to be used for the subject and the trial treatment allocated to the subject, either TachoSil or standard surgical treatment.

A subject will always be given the lowest subject number available at the site. Investigator must record the subject number and the allocated trial treatment and keep a “Subject

Identification Code List", which connects subjects and randomisation numbers. If a subject is not randomised, Investigator must state the reason.

Subjects will be evenly distributed between the two treatments, TachoSil and standard surgical treatment. Block randomisation will be ordered by Co-ordinating Trial Manager (CTM) and performed by Clinical Trial Supply, Nycomed. Sealed randomisation lists for all subjects will be available at Nycomed, Clinical Trial Supply, but not at site. The randomisation lists will be stored at Clinical Trial Supply until the database has been released.

The trial will be open since the use of TachoSil (or standard surgical treatment) precludes blinding.

10 Safety

10.1 Definitions and Classifications

10.1.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

The following should not be recorded as an AE, if recorded at screening

- A pre-planned procedure, unless the condition for which the procedure was planned has worsened since baseline. However, complications to pre-planned procedures should be reported as adverse events.
- A pre-existing condition found as a result of screening procedures.
- Post-operative nausea, vomiting or pain that Investigator considers common and expectable post-operative findings, treated or untreated, should not be recorded as AEs. Any post-operative event considered by Investigator as either uncommon, unexpected or both must be recorded as an AE.
- Air leakage is an efficacy variable and will therefore not be recorded as an AE.
- Progression of pre-existing cancer should not be reported as an AE.

Clinical Laboratory Adverse Event

Any clinical laboratory abnormality that suggests a disease and/or organ toxicity and is of a severity, which requires active management, i.e. change of dose, medical treatment, discontinuation of drug, more frequent follow-up or diagnostic investigation.

10.1.2 Serious Adverse Event (SAE)

Any untoward medical occurrence or effect that at any dose

- Results in death.
- Is life-threatening. Life-threatening in the definition of a SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires hospitalisation or prolongation of existing hospitalisation. Only inpatient hospitalisation including an over-night admission will be regarded as an SAE.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is a medical important AE that is not immediately life-threatening or does not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

Non-Serious Adverse Event

Any AE, that does not meet the criteria for a SAE.

10.1.3 Adverse Reactions (AR)

All untoward and unintended responses to an IMP related to any dose administered.

10.2 Classification

Severity

Severity is a clinical observation and describes the intensity of the event.

- Mild: Transient symptoms, no interference with the subject's daily activities.
- Moderate: Marked symptoms, moderate interference with the subject's daily activities.
- Severe: Considerable interference with the subject's daily activities.

Causality

- Probable: Good reasons and sufficient documentation to assume a causal relationship.

- Possible: A causal relationship is conceivable and cannot be dismissed.
- Unlikely: The event is most likely related to an aetiology other than the trial product.
- Not related: An event for which sufficient information exists to conclude that the aetiology is unrelated to the trial product.

Outcome Categories

- Recovered: Fully recovered or the condition has returned to the level observed at baseline.
- Recovered with sequelae: As a result of the AE, the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf or paralysed).
- Not recovered.
- Fatal.
- Unknown.

10.3 Adverse Event Recording

All events that meet the definition of an AE and occur in the period from the subject signed the Informed Consent Form and until the end of the protocol required post-treatment follow-up period must be reported.

At each contact between the site and the subject (visit or phone), the subject will be asked, if he/she has experienced any problems since the last assessment. All AEs, either observed by Investigator or reported by the subject, must be recorded by Investigator. The subject will be asked about AEs, e.g.: “Have you experienced any health problems since the last contact?”

The Investigator must record all AEs on the standard Adverse Event Form. The Investigator must only record one AE per Form. For SAEs, the Serious Adverse Event Form must also be completed.

Investigator should record the diagnosis, if available. If no diagnosis is available the Investigator should record each sign and symptom as individual AEs.

The Investigator should make an evaluation of the seriousness and the causality between the investigational medicinal product and the AE.

10.4 Adverse Event Reporting

The Investigator must report all SAEs to the Monitor by fax or phone immediately (within 24 hours) upon obtaining knowledge about the event. The initial report must be promptly followed by detailed written reports.

Monitor must report all fatal or life-threatening SAEs to Nycomed Central Pharmacovigilance (CPV) within 24 hours of obtaining knowledge of the event. All other SAEs must be forwarded to CPV within 48 hours.

Nycomed will comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse reactions to the Competent Authorities (CA), the Independent Ethics Committees (IECs) and if applicable Investigators. CPV will be responsible for this reporting.

10.5 Follow-Up of Adverse Events

During and after participation of a subject in a clinical trial, the Investigator/Institution must ensure that adequate medical care is provided to the subject for any AEs, including clinically significant laboratory values, related to the trial. The Investigator/Institution must inform the subject when medical care is needed for any intercurrent illness(es) of which Investigator becomes aware. Until the end of the follow-up period (1 month +/- 10 days after surgery), all new AEs must be recorded.

All AEs, classified as serious or severe and possibly/probably related to the trial treatment, must be followed by Investigator until the subject has recovered, recovered with sequelae or died, and until all queries related to these AEs have been resolved.

All other AEs must be followed by Investigator until the subject has recovered or until the end of the protocol-required post-treatment follow-up period (whichever comes first), and until all AE-related queries for the subject have been resolved.

Investigator must forward follow-up information on SAEs to Monitor within 24 hours of obtaining knowledge hereof. Follow-up information should be supplied on the Adverse Event Extra Form and/or Serious Adverse Event Extra Form, both marked follow-up.

10.6 Pregnancy

Female subjects must be advised to notify the Investigator immediately if they become pregnant.

The Investigator must report any pregnancy in trial subjects to Monitor within 14 days of obtaining information of the subject being pregnant. Investigator must follow the pregnancy to termination or delivery. The infant must be followed at least until age one month. Miscarriage, stillbirth and any malformation/disease must be reported as a SAE.

The Investigator must report information on pregnancy outcome other than miscarriage, stillbirth and any malformation/disease and follow-up of the infant within 14 calendar days of obtaining the information using the Pregnancy Form and the Pregnancy Follow-up Form, respectively.

Consent of a parent must be obtained before registration of infant data.

10.7 Precautions/Overdose

As with any product, allergic type hypersensitivity reactions are possible. Subjects with known history of allergic reactions after application of human fibrinogen, human thrombin and/or collagen of any origin will be excluded from the trial (exclusion criterion 4).

Drug interactions may be expected only with drugs interfering with the coagulation system like heparin, warfarin, streptokinase, urokinase or tissue-type plasminogen activator. Based on preclinical data, reduced efficacy due to interactions is not expected but cannot be totally excluded in case of high doses/concentrations of these compounds (17).

The number of TachoSil sponges to be used for a subject depends on surgical need. Overdosage has never been reported for TachoSil (17).

10.8 Coding of Adverse Events

All AEs are coded using the MedDRA terminology, current version.

10.9 Sponsor's Assessment of Expectedness

Nycomed CPV will evaluate all AEs with respect to seriousness, causality and expectedness in accordance with the Directive 2001/20/EC (8). The expectedness of an AE will be determined according to TachoSil SmPC (18).

11 Case Report Forms

Each site will receive a set of consecutively numbered Case Report Forms (CRFs) from Nycomed. The subject number corresponds to a pre-calculated randomly allocated trial treatment, either TachoSil or standard surgical treatment. The CRFs will be assembled in binders, one binder per subject. For each subject, the CRF pages for the screening visit will be assembled separately (Screening Case Report Form) with the possibility of joining them with the CRF pages for the later visits in one binder (Subject Case Report Form), in case the subject has been randomised.

11.1 Rules for Completing CRFs

Investigator must write legibly with a dark ball-point pen (blue or black) and ensure that all relevant questions are answered and that no empty data blocks exist.

If a test/assessment is not done and will not be available, indicate this by writing "ND" (Not Done) in the respective answer field in the CRF. If the question is irrelevant (e.g. not applicable) indicate this by writing "NA" (Not Applicable) in the respective answer field.

Laboratory values outside the normal range must be classified as clinically significant or not clinically significant.

The Investigator or Investigator's authorised staff must ensure that all information has been accurately transcribed and that correct dates and initials or signatures are present.

The Principal Investigator or a delegated Investigator signs the overall Affirmation Statement for each subject verifying the data in the CRF for the subject, either Screening CRF (screening failures only) or Subject CRF.

11.2 Corrections to Case Report Forms

Investigator must correct data on the CRFs by drawing a straight line through the incorrect entry and writing the correct value next to the crossed-out entry. All corrections must be initialled and dated.
Corrections necessary after the CRF has been collected from site, must be documented on the Data Clarification Form of the Sponsor.

Queries from Nycomed that are issued on the Data Clarification Form must be answered within a maximum of 14 days from the day they are delivered to the Investigator.

11.3 Discontinuation

A subject that discontinues prematurely, must – if possible – be called in for a last visit. Even if the subject is not able to attend, the “End of trial” page must be completed and the “Drug Accountability Form” must be filled in.

11.4 CRF Flow

After completion, the NCR paper CRFs (original and first copy) will be either personally collected by Monitor or dispatched by courier. The original will be sent to the CTM, who will forward them after a manual check to Data Management. The second copy will remain with Investigator. Detailed procedures will be described in the Monitoring Plan prior to site initiation.

12 Verification

12.1 Monitoring Procedure

Monitoring will be performed according to the Monitoring Plan provided by CTM. During the trial, the Monitor will visit the site before trial initiation and at 4-6 weeks intervals or more often depending on recruitment and be available for discussions by phone. The purpose of the Monitoring visits is to ensure that the CRFs are completed correctly, the protocol is adhered to and drug accountability monitored.

The following source data must be entered in official hospital records, laboratory records or similar:

1. Demographic data of the subject
2. Medical history: indication for lung lobectomy and concomitant and relevant past illnesses
3. Date of inclusion in the trial, i.e. date of informed consent obtained; screening no. and if randomised, subject no. in the trial, trial ID and sponsor name
4. In- and Exclusion Criteria
5. Visit dates
6. Adverse events including pregnancy
7. Concomitant medication
8. Drug accountability
9. Withdrawal information
10. Visit dates including period hospitalised for lung lobectomy
11. Key efficacy and safety data*

* Key efficacy data in this trial is the primary endpoint, i.e. cessation of air leakage (time of assessment of last water submersion test, time of air leakage assessments every day). Other efficacy variables may be recorded in the CRFs only. Key safety data are SAEs.

The original signed and dated Informed Consent Form must be kept in the Investigators File.

Essential documents must be filed in the Investigator File on an ongoing basis.

If source data are electronic, these must be printed, signed and dated by Investigator and stored in the Investigator File.

Monitor will perform source data verification (SDV) and ensure that the CRFs are forwarded to the Nycomed Medical Department or their representatives after Affirmation Statement Page is filled in by Investigator or the Principal Investigator, respectively. Completed CRFs (original and one copy) must be either personally collected by the Monitor or dispatched by courier.

In order to perform proper SDV, Monitor must have direct access to source documents, e.g. hospital records, original laboratory records and Informed Consent Forms. SDV will be done for all subjects. The above list of data will be verified 100% for all subjects except for medical history that will be verified 100% for approximately 20% of the subjects. If discrepancies are identified, data verification will be extended.

Monitor must continuously check the list of laboratory normal ranges for any changes. If any changes occur, Investigator should provide Monitor with the new list of laboratory normal ranges, signed and dated by Head of Laboratory and giving the date when the changes were implemented. Likewise, the Monitor must check and ensure updating of the “Log of Staff List”.

Subsequent to each monitoring visit, the Monitor must complete a written report, which must be reviewed by Trial Manager and afterwards forwarded to CTM for further review and approval.

12.2 Audit from Quality Assurance Unit

The International Clinical Quality Assurance Unit at Nycomed may audit the trial to ensure that trial procedures and data comply with the principles of GCP, protocol and Nycomed

standard operating procedures (SOPs), and that data are correct and complete. Audits will be performed according to current SOPs.

12.3 Inspection from Competent Authority

Investigator must be aware that representatives from the Competent Authorities may wish to inspect the data and the associated subject records. The Investigator must make the records available, and should notify Nycomed of the inspection.

13 Data Management

Data Management will be performed by NNIT A/S, a duly assigned Contract Research Organisation (CRO). A Data Handling Plan (DHP) including a database annotation will be finalised before any data are entered into the database. The annotation describe mapping of CRF fields to the database fields and the fields in the final Statistical Datasets to be delivered.

The Trial Data Manager must provide a Data Validation Plan (DVP) before any data cleaning. The DVP must describe all logical and qualitative checks used to clean the database and to assure accurate and consistent data in the database.

All plans must be approved by the CTM, the Trial Statistician and the Trial Data Manager.

The subject will be identified in the database only by subject identification number (screening number and/or subject number), site name and Trial ID (TC-021-IM).

All data related to the subject will be entered into the database either directly from the CRF or (partly) as electronic transfer. All recorded concomitant medication will be entered into the database. The data cleaning, including logical checks and query processes will be handled by NNIT A/S. All data handling will be documented in a Data Handling Report. The clean database will be transferred to the Trial Statistician as either ASCII files or SAS® ver. 8.2 compatible datasets.

Concomitant illnesses and AEs will be coded according to MedDRA current version, concomitant medication according to WHO Drug Dictionary current version. No coding will be done for medication related to the surgical intervention, i.e. pre-medication, anaesthesia and post-operative medication. Coding must be done before forwarding the CRFs to the Trial Data Manager.

SAEs will be reported to and handled by Central Pharmacovigilance (CPV), Nycomed.

13.1 Data Collection

The Investigator must enter the information required by the protocol into the paper based CRFs. The Monitor will review the CRFs for completeness and accuracy, and instruct site personnel to make any required corrections or additions. The original CRF and one copy will be collected by the Monitor; one copy will be retained at the investigational site.

13.2 Database Management and Quality Control

Data items from the CRFs are entered into the trial database using double data entry with electronic verification. Subsequently, Data Management staff systematically checks the entered data, using error messages printed from validation programs and database listings. Errors or omissions will be entered on Data Clarification Forms (DCFs), which will be returned to the investigational site for resolution. A copy of the signed DCF must be kept with the investigator's copy of the CRF, and once the original is received at NNIT A/S, the resolutions will be entered into the database. Quality control audits of all key safety and efficacy data in the database will be made before database lock.

When the database is declared complete and accurate, the database will be locked. Any changes to the database after that time can be made only by joint written agreement between the CTM, the Trial Statistician and the Trial Data Manager.

14 Analysis Datasets

The Intention to treat population (ITT) will be defined as all subjects that are randomised and given trial treatment. The safety population will be identical to the ITT population.

Subjects will be excluded from the Per Protocol (PP) population for the following reason:

- Any major protocol violation judged to obscure the evaluation of TachoSil efficacy.

The decision to exclude a subject from the PP population resides with the CTM, the Data Manager and the Trial Statistician in collaboration. The decision is taken before database lock and will be documented in the database release document with reason(s) for exclusion.

15 Statistical Considerations

International Medical Affairs, Nycomed will be responsible for statistics. A Statistical Analyses Plan (SAP) will be finalised before any site is initiated.

15.1 Sample Size Calculation

The sample size calculation is based on the primary endpoint, duration of post-operative air leakage. The H_0 hypothesis to be tested is that the survivor functions in the two treatment groups are equal. The alternative hypothesis H_1 states that the survivor functions differ between the treatments. The H_0 hypothesis will be tested with a log-rank test.

The sample size calculation is based on the results from an earlier trial with TachoSil (trial ID: TC-013-IN) with similar objective and design as the present (2). In the subgroup of subjects entering the TC-013-IN trial with intra-operative air leakage grade > 0 the median duration of post-operative air leakage was 1 day for subjects treated with TachoSil and 2 days for subjects allocated to the standard treatment group, which is the minimal relevant difference between treatments to be identified. A number of trials (10.000) were simulated. Each trial was generated by selecting subjects from the above defined subpopulation in TC-013-IN using random sampling with replacement. Equal number of subjects was chosen from each of the two treatment groups. In each trial the log-rank test was performed to assess the difference between treatments. The percentage of trials with the log-rank test showing statistical significance based on α=5% was used as power estimate. The results of the simulations are shown in the table below:

Total number of subjects	Power
200	82%
250	90%
300	94%

Given the results of the simulations, a total sample size of 300 subjects, equally allocated to treatment groups, is chosen.

15.2 Statistical Methods

All tests are two sided at a significance level of 5%.

15.3 Efficacy Analysis

The primary efficacy endpoint, duration of post-operative air leakage, will be analysed for the ITT population using life table analysis. From evening on day of operation and onwards presence of post-operative air leakage will be evaluated using Sentinel Seal Dual Chamber system and provocation by coughing, see Section 8.1.2. Since air leakage is recorded at nominal time points, i.e. evening on day of operation, 1st shift at day after operation etc., the

actual time points of sealing are not observed. It may be attributed to one of the time intervals Day $0_{operation}$- Day $0_{evening}$, Day $0_{evening}$ - Day $1_{morning}$, Day $1_{morning}$ - Day $1_{evening}$, etc.. Subjects who do not obtain absence of air leakage will be censored at the day of the last assessment.

For subjects where duration of post-operative air leakage cannot be assessed because the last assessments of air leakage is missing, the duration of post-operative air leakage will be censored at the time of the last available assessment. A sensitivity analysis will be performed where missing values in the TachoSil treatment group will be assigned the maximum measured duration of post- operative air leakage in the treatment group, and in the standard treatment group the assigned value will be the last measurement. In both treatment groups the values will be right censored. The Log-rank test of equality over treatments will be performed controlling for centre, and the survival curves will be estimated and presented by centre using the life table method. The primary efficacy analysis will be repeated for the PP population as a secondary analysis.

An exploratory parametric survival analysis of the primary endpoint, which takes account of the interval censoring, will be performed using an accelerated failure time model with treatment and centre effect included. In this analysis the actual time points of air leakage assessment will be used.

The secondary endpoint, reduction in intra-operative air leakage intensity, will be analysed for the ITT population. Subjects will enter with a rating of 1 or 2 and have ratings 0, 1 or 2 after first treatment. The reduction will be tested by a Wilcoxon test.
The primary and secondary and descriptive variables (Section 6.1.3) will be summarised by descriptive statistics.
There will be no imputation of missing values for the secondary endpoints.

15.4 Safety Analysis

Adverse events will be tabulated by treatment, system organ class, high level term, severity and relation. The tabulation will correspond to the Nycomed Full ICH Report Guideline.

As decentralised laboratories are used, laboratory test values will be normalised by means of the Z-values method (20). Laboratory values from the day after surgery and from the discharge visit will be plotted against the values from the screening visit for each treatment.

Changes in laboratory test values from screening to day after surgery, and from screening to day of discharge will be compared between treatments by means of the Mann-Whitney test.

Laboratory parameters, vital signs, and results of chest X-ray will be summarised by descriptive statistics.

Shift tables and lists will be produced of abnormal laboratory safety variables.

15.5 Interim Analysis

No interim analysis is planned.

15.6 Safety Committee/Person

No safety committee/person is foreseen as the trial is not blinded.

16 Trial Termination

16.1 Planned End of Trial

End of trial is defined as last subject last visit or last subject completed follow-up period.

Nycomed will ensure that end of trial notification is submitted to Competent Authorities (CA) and Ethics Committee (EC) for each trial site and for the complete trial.

16.2 Premature Termination or Suspension of a Trial

If the trial is prematurely terminated or suspended for any reason, the Investigator/Institution must promptly inform the trial subjects and should assure appropriate therapy and follow-up of the subjects.
If the Investigator terminates or suspends a trial without prior agreement of the Sponsor, the Investigator must inform the Institution where applicable. The Investigator/Institution must promptly inform Nycomed and should provide Nycomed with a detailed written explanation of the termination or suspension.

If Nycomed terminates or suspends a trial, the Investigator must promptly inform the Institution where applicable.

In both cases Nycomed will promptly inform the Competent Authority and Ethics Committee and provide them, with a detailed written explanation of the termination or suspension.

If the Competent Authority or Ethics Committee terminates or suspends its approval/ favourable opinion of a trial, Nycomed must inform the Principal Investigators and Institutions and provide them with a detailed written explanation of the termination or suspension.

17 Responsibilities

Nycomed will be responsible for centralized archiving of all CRFs and Investigator Files from the sites. At the close out visits, the Investigators will be informed about the archive procedures.

18 Reports and Publications

Clinical Trial Report. Nycomed will prepare a full Clinical Trial Report, which will describe the results obtained and will comply with the ICH-guidelines (7, 19, 21). The Co-ordinating Investigator will sign the Clinical Trial Report on behalf of all Investigators. Neo-antigenicity analysis and reporting will be done separately, i.e. not as part of the Clinical Trial Report for TC-021-IM.

Publication. Nycomed acknowledges the Investigator's rights to publish results from this trial. Any such scientific paper, presentation, communication, or other information concerning the investigation described in this protocol, must be submitted to Nycomed prior to submission for publication/presentation for comments. These will be given within one month from receipt of the manuscript.

Nycomed is free to use the data from this trial as basis for a publication. Nycomed is allowed on own initiative to write publication(s), in case Investigator has not submitted manuscript(s) to Nycomed 6 months after completion of the Clinical Trial Report.
In any such publication, all sites that included minimum 15 randomised subjects will qualify as contributors. The last author of the publication will be the Co-ordinating Investigator, who will also assign his co-author. Each qualified site may provide one co-author; these will be listed in descending order according to the number of randomised subjects from their site. Nycomed may provide one co-author that will be listed (second) last. All other participating Investigators will be acknowledged according to the rules of the journal of publication. Sites with less than 15 randomised subjects will be acknowledged in a footnote as contributing

sites of this TC-021-IM trial. An Investigator can be mentioned in the manuscript only if he/she gives permission.

The manuscript(s) will be submitted for comments to all (co)-authors that must respond within 2 months. In the event of disagreement of the text, the opinion of authors and Nycomed will be fairly and sufficiently represented.

The Co-ordinating Investigator will be the first to announce TC-021-IM data at any relevant meeting.

No Publication Committee is foreseen.

Nycomed has the right to use the results from this trial for registration purpose and internal presentation and after publication for promotion.

Investigators are not allowed to disclose or publish any information concerning patent applications, manufacturing processes, or formulation information about the investigational product (TachoSil) to others without permission from Nycomed.

19 Retention of Clinical Trial Documentation

The Investigator must arrange archiving of the Investigator File, CRF copies and source data. The Investigator must keep these documents in a secure place protected from fire and theft. The following documents must be archived:

- until at least 2 years after the last approval of a marketing application in an ICH region or
- until there are no pending or contemplated marketing applications in an ICH region or
- until at least 2 years have elapsed since the formal discontinuation of the clinical development of the trial product.

The documents should, however, be archived for a longer period if required by the applicable Competent Authorities or if agreed with Nycomed. It is the responsibility of Nycomed to inform the Investigator/Institution when these documents no longer need to be archived.

Nycomed will maintain the documentation pertaining to the trial as long as the trial product is on the market and the Clinical trial report will be maintained 5 years hereafter.

20 Indemnity Statement

To the extent Nycomed is legally liable, Nycomed accepts liability for any harmful effects suffered by a subject arising from administration of our trial product (TachoSil) or trial procedures in this trial.

Nycomed does not undertake liability in the event of negligence, cross-negligence or wilful misconduct by the clinics or Investigators conducting clinical trials or by persons for whom the said clinic or Investigators are responsible.

21 References

1. World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. Helsinki 1964, amended in Tokyo 1975, Venice 1983, Hong Kong 1989, South Africa 1996, Edinburgh 2000.

2. An open, randomised, prospective, multicentre, parallel-group phase III trial to compare efficacy and safety of TachoComb S versus standard surgical treatment in subjects undergoing lobectomy for lung cancer and requiring treatment of air leakage after primary stapling. Nycomed Clinical Trial Report, trial ID: TC-013-IN, 1 - 56, 2002.

3. Nycomed Clinical Trial Report. Trial ID-PHTC009. A randomised, three parallel-group, open, multicentre study to evaluate efficacy and safety of the haemostatic and tissue sealant TachoComb H versus argon beamer versus no immediate secondary haemostatic treatment in patients undergoing liver resections. 2004.

4. Nycomed Clinical Trial Report. Trial ID-TC-014-IN. An open, randomised, prospective, multicentre, parallel-group phase III trial to compare efficacy and safety of TachoComb S and argon beamer in patients undergoing liver resection. 2004.

5. Nycomed Clinical Trial Report. Trial ID-TC-016-IN. An open, randomised, prospective, multicentre, parallel-group trial to compare efficacy and safety of TachoComb S and argon beamer coagulator in subjects undergoing liver resection (II). 2004.

6. Guideline on the clinical investigation of plasma derived fibrin sealant / haemostatic products. CHMP/BPWG/1089/00. The European Medicines Agency, 2004.

7. ICH Harmonised Tripartite Guideline for Good Clinical Practice, E6.

8. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official Journal of the European Communities L/21/34 1.5.2001.

9. Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the Protection of Individuals with Regard to the Processing of Personal Data and on the Free Movement of Such Data.

10. Financial Disclosure by Clinical Investigators. Federal Register: 31 December 1998 (Volume 63, Number 251), 21CFR Part 54.

11. Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use. April 2004.

12. Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial. April 2004.

13. Investigator´s Brochure - TachoSil. Edition 04, October 2005.

14. The CONSORT Statement (JAMA, April18, 2001-Vol 285,No.15:1987-1991).

15. Macchiarini P., Wain J., Almy S, Dartevelle P., Experimental and clinical evaluation of a new synthetic, absorbable sealant to reduce air leaks in thoracic operations. J Thoracic Cardiovasc Surg Vol 117, Number 4 (1999): 751 - 758.

16. Annex 13/2003/94/EC, Volume 4. Good manufacturing practices Annex 13. Manufacture of investigational medicinal products, July 2003.

17. TachoSil™ Product Monograph, September 2004.

18. TachoSil Summary of Product Characteristics, 8 June 2004.

19. ICH topic E9. Note for guidance on statistical principles for clinical trials. Step 4, consensus guideline, 1998.

20. Chuang-Stein C., Summarizing laboratory data with different reference ranges in multi-center clinical trials. Drug Information Journal, Vol. 26 (1992): 77-84.

21. ICH topic E3. Note for guidance on structure and content of clinical study reports. Step 4, consensus guideline (CHMP/ICH/135/95), 1995.

22. Harlow & Lane: Antibodies, a laboratory manual. Cold Spring Harbor Laboratory, 1988. ISBN 0-87969-314-2.

23. Crowter: The ELISA Guidebook, Methods in Molecular Biology, volume 149, 2001. Humana Press. ISBN 0-89603-728-2.

APPROVALS

Protocol Amendment

Title:

TC-021-IM Amendment 02

ID:

TC-021-IM

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

Name **Reason for signature**	**Outcome** **Date for signature**
David Becedas correctness and completeness	Approved 15.Nov.2006 13:45:17

Document ID: C00009125

Version: 1.0

Non-substantial Protocol Amendment No. 02

Short title: TachoSil® versus standard surgical treatment for air leakage in pulmonary lobectomy

Title: An open, randomised, prospective, multi-centre, parallel-group trial to compare efficacy and safety of TachoSil® versus standard surgical treatment in patients undergoing pulmonary lobectomy for lung malignancy and requiring treatment for air leakage.

Trial ID: TC-021-IM

Sponsor: Nycomed ApS
International Medical Affairs
Langebjerg 1, DK-4000 Roskilde, Denmark
Tel.: +45 4677 1111
Fax: +45 4675 5999

Trial phase: Therapeutic confirmatory / Phase IIIb

Co-ordinating Trial Manager: David Becedas, M. Sc. Pharm.
International Medical Affairs

Date protocol last modified: 27 October 2005
Date Amendment last modified: 07 March 2006 (Amendment 01)

PREPARED BY:

Martin Nottmeier, M. Sc. Pharm.

International Medical Affairs

Nycomed Denmark ApS

APPROVER:

Co-ordinating Trial Manager:

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For signature see separate page

Changes

Deleted text is written with ~~strikethrough~~ letters.
Added text is written in *italic* letters.

A new Co-ordinating Trial Manager has been appointed from 24 July 2006 instead of ~~Eva Nobis M. Sc.,~~ *David Becedas M. Sc. Pharm. (contact details above).*

A new Medical Safety Adviser has been appointed from 1 April 2006 instead of ~~Lusine Movsesyan M.D.,~~ *Helle Heisel White DVM, tel. +45 46771658, hhwh@nycomed.com*

A new Trial Manager/Monitor has been appointed in Austria from 15 April 2006 instead of ~~Angelika Pöltl PhD,~~ *Beate Stemberger M. Sc., tel. +43 160134206, best@nycomed.com*

A new Trial Manager/Monitor has been appointed in Belgium from 31 August 2006 instead of ~~Nadine Witters M.D,~~ *Kristof Vercruysse M. Sc., tel. + 32 24640792, kris@nycomed.com*

A new Trial Manager/Monitor has been appointed in Switzerland from 25 August 2006 instead of ~~Angelika Pöltl PhD,~~ *Carsten Cirkel, tel. + 49 6261675441, info@cirkel-consulting.com*

A new Clinical Trial Supplies Coordinator has been appointed from 1 February 2006 instead of ~~Karina Nymark M. Sc. Pharm,~~ *Annette Bested M.Sc. Pharm., tel. +45 46771784, atb@nycomed.com*

A new Safety Data Manager has been appointed from 1 April 2006 instead of ~~Berit Nautrup Andersen,~~ *Mette Rynkebjerg, tel. +45 46771634, mry@nycomed.com*

Changes

4 Introduction

For further information on efficacy and safety, see the *current version of the* TachoSil Investigator´s Brochure (13) and the *current version of the* Summary of Product Characteristics SmPC (18).

8.1.7 FOLLOW UP (1 month +/- 10 days after surgery)

The follow up visit ~~should~~ *may* be done *as an off-site phone visit or* at site.

9.4 Storage and Drug Accountability of Investigational Medicinal Product

[…] Investigator must keep and update the "Drug Accountability per Subject Form" where the use of all sponges should be accounted for. This form must be available to the Monitor for accountability checks. *Empty cartons may be discarded after monitor has performed accountability checks.* Any discrepancies must be explained in writing by the Investigator. The completed form, signed by Principal Investigator at the end of the trial, will be returned to Nycomed.

After completion of the trial, all unused TachoSil sponges ~~and empty cartons~~ must be returned to Clinical Trial Supply, International Pharmaceutical Affairs, Nycomed Denmark by using the "IMP return to CTS Form".

21 References

13. ~~Investigator´s Brochure – TachoSil. Edition 04, October 2005~~. *Current version of Investigator´s Brochure.*

18. TachoSil Summary of Product Characteristics, ~~8 June 2004~~ *current version available on EMEA's webpage: http://www.emea.europa.eu*

Reasons for changes

A follow-up visit to site was originally planned according to the original protocol to allow sampling for neo-antigenicity testing. After the neo-antigenicity test was taken out of the protocol, it is allowed to perform the Follow-up visit by telephone.

Clinical Trial Supply, Nycomed, have confirmed that empty TachoSil cartons may now be discarded at site after the monitor has performed accountability checks.