Clinical trial results:
A Randomized Controlled Non-inferiority Study to Evaluate the Efficacy and Safety of Hemopatch Compared to TachoSil in Preventing or Reducing Postoperative Air Leaks After Pulmonary Resection.

Summary

EudraCT number	2017-003931-12
Trial protocol	CZ ES IT
Global end of trial date	09 July 2019

Results information

Result version number	v1 (current)
This version publication date	14 October 2020
First version publication date	14 October 2020

Trial information

Trial identification

Sponsor protocol code	BXU513667

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03450265
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Baxter Healthcare
Sponsor organisation address	1 Baxter Pkwy, Deerfield, United States, 60015
Public contact	Sr Clinical Project Manager, Baxter R&D Europe SPRL, 224 948-7359, Global_CORP_ClinicalTrialsDisclosure@baxter.com
Scientific contact	Sr Clinical Project Manager, Baxter R&D Europe SPRL, 224 948-7359, Global_CORP_ClinicalTrialsDisclosure@baxter.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 July 2019
Global end of trial reached?	Yes
Global end of trial date	09 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of Hemopatch compared to TachoSil in postoperative air leak duration after pulmonary resection.

Protection of trial subjects:

The DSMB reviewed safety and efficacy data from the study at the following data cutoffs (1) after 50% of subjects experienced a post-operative air leak, had been completed or withdrawn and (2) study completion.

Background therapy: -

Evidence for comparator:

In a study conducted by Filosso et al (2013)2, TachoSil sealant was found to be superior to standard stapling and suturing aerostatic techniques in reducing post-operative air leaks.

Actual start date of recruitment	25 June 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 74
Country: Number of subjects enrolled	Italy: 95
Worldwide total number of subjects	169
EEA total number of subjects	169

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	63
From 65 to 84 years	106

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	279[1]
Number of subjects completed	169

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Pre-operative Screen Failures: 19
Reason: Number of subjects	Randomized with Intra-operative Screen Failures: 91

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Subjects captured in pre-assignment period include (1) pre-operative screen failures and (2) randomized with intra-operative screen failures. Only those that completed pre-assignment were randomized as intra-operative eligible and provided study treatment.

Period 1

Period 1 title	Randomized, Intra-Operative Eligibility (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Hemopatch

Arm description:

Patients undergo elective pulmonary resection. Following resection, primary stapling and suturing will be done and air leakage will be assessed. If a specific grade-level of air leakage is present, patients will be randomized and Hemopatch applied.

Arm type	Experimental
Investigational medicinal product name	Hemopatch
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sealant matrix
Routes of administration	Soft tissue use

Dosage and administration details:

The appropriate size of the pad was selected so that it overlapped the margins of the wound surface by about 1 cm. The size of the patches used for the study was 45 x 90 mm. It was permitted to cut the pad to the desired size and shape. According to the IFU, a maximum of 7 HEMOPATCH 45 x 90 mm patches can be used in adults.

Arm title	TachoSil

Arm description:

Patients undergo elective pulmonary resection. Following resection, primary stapling and suturing will be done and air leakage will be assessed. If a specific grade-level of air leakage is present, patients will be randomized and TachoSil applied.

Arm type	Active comparator

Investigational medicinal product name	TachoSil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sealant matrix
Routes of administration	Soft tissue use

Dosage and administration details:

TachoSil was applied according to the summary of product characteristics.

Number of subjects in period 1	Hemopatch	TachoSil
Started	87	82
Completed	83	81
Not completed	4	1
Consent withdrawn by subject	1	-
Adverse event, non-fatal	1	-
Lost to follow-up	1	1
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Hemopatch
Reporting group description:	
Patients undergo elective pulmonary resection. Following resection, primary stapling and suturing will be done and air leakage will be assessed. If a specific grade-level of air leakage is present, patients will be randomized and Hemopatch applied.	
Reporting group title	TachoSil
Reporting group description:	
Patients undergo elective pulmonary resection. Following resection, primary stapling and suturing will be done and air leakage will be assessed. If a specific grade-level of air leakage is present, patients will be randomized and TachoSil applied.	

Reporting group values	Hemopatch	TachoSil	Total
Number of subjects	87	82	169
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	65.4	66.2	
standard deviation	± 10.03	± 8.72	-
Gender categorical Units: Subjects			
Female	38	29	67
Male	49	53	102

End points

End points reporting groups

Reporting group title	Hemopatch
Reporting group description:	
Patients undergo elective pulmonary resection. Following resection, primary stapling and suturing will be done and air leakage will be assessed. If a specific grade-level of air leakage is present, patients will be randomized and Hemopatch applied.	
Reporting group title	TachoSil
Reporting group description:	
Patients undergo elective pulmonary resection. Following resection, primary stapling and suturing will be done and air leakage will be assessed. If a specific grade-level of air leakage is present, patients will be randomized and TachoSil applied.	

Primary: Duration of postoperative air leakage

End point title	Duration of postoperative air leakage
End point description:	
Duration was calculated as date/time of end of air leak minus date/time of end of surgery. Number of subjects included only subjects with a calculable post-operative air leak duration. The predicted mean for post-operative air leak duration was produced by an ANOVA with post-operative air leak duration as the response variable and with site, final air leak grade, type of surgery performed, and treatment as fixed effects.	
End point type	Primary
End point timeframe:	
Day 1 to Day 30	

End point values	Hemopatch	TachoSil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	81		
Units: Days				
arithmetic mean (confidence interval 95%)	3.5 (1.7 to 5.4)	2.7 (0.8 to 4.7)		

Statistical analyses

Statistical analysis title	Stats
Comparison groups	Hemopatch v TachoSil
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.4275
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	0.81

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	2.82

Notes:

[1] - Based on published data a non-inferiority margin was calculated. In order to show non-inferiority, the upper limit of the 95% two-sided CI around the difference in predicted means needed to be below 1.2 days.

Secondary: Number of Subjects with Intra-operative Treatment Failure

End point title	Number of Subjects with Intra-operative Treatment Failure

End point description:

A subject was considered a treatment failure if rescue treatment occurred. Rescue treatment could include any surgical technique or sealant (fibrin or non-fibrin), except TachoSil in subjects randomized to TachoSil.

End point type	Secondary

End point timeframe:

Day 1

End point values	Hemopatch	TachoSil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	82		
Units: Subjects	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Prolonged Air Leaks > 5 days

End point title	Number of Subjects with Prolonged Air Leaks > 5 days

End point description:

Prolonged air leaks prolong the need for chest tube, which is associated with pain, reduced mobility and may lead to further complications. Air leak control and reducing its occurrence can have positive outcomes for the subjects including those being mobilized from bed sooner post-surgery, achieving correct and efficient respiratory function, as well as shortening the time until chest tube removal and the overall length of hospital stay.

End point type	Secondary

End point timeframe:

Day 1 to Day 30

End point values	Hemopatch	TachoSil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	82		
Units: Subjects	14	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects achieving Hemostasis After Application of Product

End point title	Number of Subjects achieving Hemostasis After Application of Product

End point description:

Hemostasis is the act of restricting or stopping blood flow from a damaged vessel or organ.

End point type	Secondary

End point timeframe:

Day 1

End point values	Hemopatch	TachoSil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	82		
Units: Subjects	87	82		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects having the need for additional procedures

End point title	Number of Subjects having the need for additional procedures

End point description:

Type of procedures include chest drainage, re-operation, respiratory assistance, and blood transfusion.

End point type	Secondary

End point timeframe:

Day 1 to Day 30

End point values	Hemopatch	TachoSil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	82		
Units: Subjects	12	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Chest Tube Removal

End point title	Time to Chest Tube Removal

End point description:

Calculated as date/time of chest tube removal minus date/time of end of surgery.

End point type	Secondary

End point timeframe:

Day 1 to Day 30

End point values	Hemopatch	TachoSil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	82		
Units: Days				
arithmetic mean (standard deviation)	5.73 (± 7.067)	5.13 (± 5.731)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time in surgery

End point title	Time in surgery

End point description:

Calculated as date/time of last skin suture minus date/time of first skin incision.

End point type	Secondary

End point timeframe:

Day 1

End point values	Hemopatch	TachoSil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	82		
Units: Minutes				
arithmetic mean (standard deviation)	155 (± 77.7)	164 (± 67.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Length of Stay in Hospital

End point title	Length of Stay in Hospital
End point description: Calculated as (date of hospital discharge minus date of hospital admission) + 1.	
End point type	Secondary
End point timeframe: Day 1 to Day 30	

End point values	Hemopatch	TachoSil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	82		
Units: Days				
arithmetic mean (standard deviation)	8.52 (± 6.075)	8.01 (± 5.815)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Unplanned Interventions

End point title	Number of Unplanned Interventions
End point description: Additional procedures.	
End point type	Secondary
End point timeframe: Day 1 to Day 30	

End point values	Hemopatch	TachoSil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	82		
Units: Interventions				
median (inter-quartile range (Q1-Q3))	1 (1 to 2)	1 (1 to 3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment Emergent Adverse Events of Special Interest

End point title	Number of Subjects with Treatment Emergent Adverse Events of Special Interest

End point description:

Pre-defined post-operative adverse events of special interest (AESIs) up to 30 ± 3 days after surgery: may include pneumothorax, bronchopleural fistula, emphysema (subcutaneous and mediastinal), pleural effusions, post-operative respiratory failure, empyema, and allergic reactions in reasonable temporal relationship with the product application.

End point type	Secondary

End point timeframe:

Day 1 to Day 30

End point values	Hemopatch	TachoSil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	82		
Units: Subjects				
Post-operative Respiratory Failure	0	2		
Bronchopleural Fistula	0	1		
Pneumothorax	1	5		
Subcutaneous Emphysema	4	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patches used

End point title	Number of patches used

End point description:

Intra-operatively.

End point type	Secondary

End point timeframe:

Day 1

End point values	Hemopatch	TachoSil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	82		
Units: Patches				
median (inter-quartile range (Q1-Q3))	1 (1 to 1)	1 (1 to 1)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Day 1 to Day 30

Adverse event reporting additional description:

Treatment Emergent AE/SAE's were reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Hemopatch

Reporting group description:

Patients undergo elective pulmonary resection. Following resection, primary stapling and suturing will be done and air leakage will be assessed. If a specific grade-level of air leakage is present, patients will be randomized and Hemopatch applied. Treatment-Emergent AE's reported. Non-serious AE's reflect frequency threshold.

Reporting group title	TachoSil

Reporting group description:

Patients undergo elective pulmonary resection. Following resection, primary stapling and suturing will be done and air leakage will be assessed. If a specific grade-level of air leakage is present, patients will be randomized and TachoSil applied. Treatment-Emergent AE's reported. Non-serious AE's reflect frequency threshold.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: There were no treatment emergent non-serious Adverse Events with 5% or more frequency.

Serious adverse events	Hemopatch	TachoSil	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 87 (19.54%)	6 / 82 (7.32%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	2	0	
Injury, poisoning and procedural complications			
Postoperative respiratory failure			
subjects affected / exposed	0 / 87 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 87 (1.15%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	1 / 87 (1.15%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 87 (1.15%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 87 (1.15%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 87 (1.15%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 87 (1.15%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchopleural fistula			
subjects affected / exposed	0 / 87 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chylothorax			
subjects affected / exposed	0 / 87 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			

subjects affected / exposed	1 / 87 (1.15%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung hernia			
subjects affected / exposed	1 / 87 (1.15%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 87 (0.00%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary air leakage			
subjects affected / exposed	5 / 87 (5.75%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 87 (2.30%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Subcutaneous emphysema			
subjects affected / exposed	3 / 87 (3.45%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 87 (2.30%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Renal failure			
subjects affected / exposed	1 / 87 (1.15%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Pneumonia			
subjects affected / exposed	1 / 87 (1.15%)	3 / 82 (3.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 87 (1.15%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Hemopatch	TachoSil	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 87 (0.00%)	0 / 82 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 August 2017	• Addition of hemostasis as a secondary endpoint • Addition of reference that for target sites that are dry, the tissue can be moistened with Sodium Bicarbonate solution. • Removal of HbA1c test from End of Study Visit
26 October 2017	• Sample size was decreased to account for correct assumptions. It was originally assumed that 35% of subjects were expected to not experience a post-operative air leak, which was corrected to 5%. Originally it was planned to screen 326 subjects to randomize and treat 240 subjects. This was updated to screen 278 subjects to randomize 166 subjects. The cap of randomized subjects following the interim analysis was originally 300 subjects, which was updated to 250 subjects.
02 November 2017	• Changed digital CT drainage to CT drainage system to allow for both traditional and digital drainage systems. • Addition of stratification according to approach to surgery used (open or VATS). • Removal of reference to X-Rays which was performed according to hospital standards at the discretion of the investigator.
13 February 2018	• Alignment of study scheme with updates to study procedure. • Clarification that CT will be managed as per standard of care. • Removal of restriction of oral measurement to take temperature • Addition of a description of surgery and air leak monitoring • Clarification of the exclusion criterion of florid infection as active and removing chronic steroid use as an exclusion criterion. • Removal of capping strategy on randomization and 2:1:1 allocation of randomized subjects across surgery typed (lobectomy: segmentectomy: wedge resection). • Addition of fibrinogen to the clinical laboratory tests • Laboratory tests were moved from Visit 4 (Day 4) to Visit 3 (Day 3).
02 May 2018	• Clarification that Visit 4, Visit 5, and Visit 6 were only to be done if the subjects had not yet been discharged. • A note that duration of post-operative air leak was to be monitored and recorded as well as time to CT removal. If these 2 events were at different times, this was required to be documented to ensure accuracy and efficiency. If post-operative air leak persisted, subjects may have been discharged with a Heimlich valve only after observing for at least 5 days post-operatively, indicating these subjects had PAL.
07 January 2019	• Update to description of the analysis sets. For all efficacy analyses, the FAS was used as the primary analysis, while the PPS was used as supportive analysis. There were 2 main reasons for this change. Firstly, the sample size calculation did not indicate any stipulation to allow for extra recruitment of subjects to account for subjects falling out of the primary analysis set due to protocol deviations. As such, to achieve the correct sample size for the primary analysis, the FAS was used. Secondly, the nature of PPS was such that it had an inherent bias for the treatment groups as it attempted to create a 'perfect' subset of the population for whom the medical device was administered. To prevent such a bias from influencing the results, the FAS was preferred for the primary analysis set. • Clarification that appropriate rules to restart the study were outlined in the Data Safety Monitoring Board charter.
12 June 2019	Sponsor's Legal Representative and Medical Monitor were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported