25 February 2016
EMA/216119/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

TachoSil

International non-proprietary name: human thrombin / human fibrinogen

Procedure No. EMEA/H/C/000505/II/0057

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	adverse drug reaction
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BDRM	Blinded Data Review Meeting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CRO	Contract Research Organisation
CONSORT	Consolidated Standards of Reporting Trials
CSF	cerebrospinal fluid
CSR	clinical study report
CT	computerized tomography
DSMB	data safety monitoring board
eCRF	electronic case report form
EMA	European Medicines Agency
ESI	events of special interest
EU	European Union
FAS	full analysis set
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
ICH	International Conference on Harmonisation
IMP	investigational medical products
ITT	intent to treat
MRI	magnetic resonance imaging
NIHSS	National Institute of Health Stroke Score
OR	odds ratio
PIL	patient information leaflet
PP	per protocol
PT	preferred term
RMP	risk management plan
SAE	serious adverse event
SmPC	Summary of Product Characteristics
TASALL	TachoSil against Liquor Leak
TEAE	treatment-emergent adverse event

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Takeda Austria GmbH submitted to the European Medicines Agency on 9 October 2014 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I

Extension of indication to add the use of TachoSil as suture line sealing in dura mater closure where standard techniques are insufficient. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are proposed to be updated. The MAH also took the opportunity to make minor editorial corrections to the SmPC. An updated RMP version 6 was provided as part of the application.

The requested variation proposed amendments to the Summary of Product Characteristics and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 30 May 2013 (EMEA/H/SA/2546/1/2013/II). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Greg Markey

Timetable	Actual dates
Submission date	9 October 2014
Start of procedure	24 October 2014
CHMP Rapporteur Assessment Report	16 December 2014
CHMP Co-Rapporteur Assessment Report	12 December 2014
PRAC Rapporteur Assessment Report	19 December 2014
Committees comments on PRAC Rapp Advice	N/A
PRAC Rapporteur Updated Assessment Report	N/A
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	9 January 2015
CHMP comments	11 January 2015
Rapporteur Revised Assessment Report	15 January 2015
1st Request for supplementary information (RSI)	22 January 2015
CHMP Rapporteur Assessment Report	20 April 2015
PRAC Rapporteur Assessment Report	20 April 2015
Committees comments on PRAC Rapp Advice	N/A
PRAC Rapporteur Updated Assessment Report	N/A
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	7 May 2015
CHMP comments	13 May 2015
2nd Request for supplementary information (RSI)	21 May 2015
PRAC Rapporteur Assessment Report	24 August 2015
CHMP Rapporteur Assessment Report	24 August 2015
Committees comments on PRAC Rapp Advice	N/A
PRAC Rapporteur Updated Assessment Report	N/A
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	10 September 2015
CHMP comments	17 September 2015
An Oral explanation took place on	22 September 2015
3rd Request for supplementary information (RSI)	24 September 2015
CHMP Rapporteur Assessment Report	3 February 2016
PRAC Rapporteur Assessment Report	29 January 2016
Committees comments on PRAC Rapp Advice	N/A
PRAC Rapporteur Updated Assessment Report	N/A

Timetable	Actual dates
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	N/A
CHMP comments	18 February 2016
Rapporteur Revised Assessment Report	N/A
CHMP Opinion	25 February 2016

2. Scientific discussion

2.1. Introduction

In neurosurgery, cerebrospinal fluid (CSF) leakage is considered to be one of the most challenging and potentially dangerous complications. Among the envelopes which contain and protect the neural structures, the dura mater is the only one that can be surgically repaired. Watertight closure of the dura is the first line of protection from postoperative CSF leakage, which can lead to other serious complications such as meningitis and delayed wound healing. (1)

Fibrin sealants -generally containing two major components, fibrinogen and thrombin - manufactured from pooled human plasma have been used in surgery since the 1970s both for haemostatic purposes but also for sealing, reinforcement of sutures and tissue adhesion (2, 3, 4).

TachoSil is a sealant matrix coated with two active substances human thrombin and human fibrinogen. TachoSil is currently approved for use in adults for supportive treatment in surgery for improvement of hemostasis, to promote tissue sealing, and for suture support in vascular surgery where standard techniques are insufficient. The current tissue sealing label is based on study data for the sealing efficacy and safety in lung and cardiovascular surgery, demonstrating tight sealing against physiological pressures in the lung and the arterial circulation.

The Applicant is seeking to expand the indication in neurosurgery to include supportive sealing of the dura mater to prevent postoperative cerebrospinal leakage following neurological surgery , and thereby, to remove the warning currently included in Section 4.4 concerning lack of data for use in neurosurgery.

Study TC-2402-038-SP, or TachoSil against Liquor Leak (TASALL), is a recently completed study evaluating the use of TachoSil for the prevention of postoperative CSF leaks in skull base surgery.

The effect of TachoSil in preventing cerebrospinal fluid (CSF) leakage is primarily attributed to the fibrinogen/thrombin components. The mechanism of action of TachoSil is based on the interaction of the thrombin and fibrinogen components leading to the deposition of a local fibrin clot with pronounced adhesive properties, thus gluing the patch to the dural membrane.

The current indication of TachoSil is proposed to be extended by adding:
TachoSil is indicated in adults for supportive treatment in surgery for improvement of haemostasis, to promote tissue sealing, for suture support in vascular surgery where standard techniques are insufficient, and for supportive sealing of the dura mater to prevent postoperative cerebrospinal leakage following neurological surgery.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, some relevant data from the original application are summarised here:

A neurosurgery study was performed in rabbits in which TachoSil (named TachoComb S in this report) was compared to TachoComb H (SR5130; corresponding histopathology report SR5130a). In this study, the skull as well as the dura mater were opened and 6 cortical brain wounds were created in each animal. The wounds were treated with the test items and the bleeding time was measured. After hemostasis was achieved, arterial hypertension was induced and wounds were observed for rebleeding. Animals were necropsied 3 and 7 days after treatment.

Hemostasis was achieved with TachoSil and TachoComb H significantly faster ($p<0.001$) than in controls; there was no difference in bleeding times between the 2 products. Both TachoSil and TachoComb H prevented rebleeding during severely increased arterial pressure.

High-resolution magnetic resonance images showed similar edema formation in all animals. Histology revealed that TachoSil and TachoComb H did not induce any specific morphological changes in the brain tissue. Comparison of the histological findings in the animals sacrificed on Day 3 and Day 7 showed evidence of degradation of the fleece, as the mean level of degradation increased from 1 to 1.3 (0=absent; 1=slight; 2=moderate; 3=marked; 4=severe). The lysis of the fibrin clot was not further described. No adhesions with the surrounding tissues were reported.

TachoSil did not induce any specific histological or neuroradiological changes in rabbit brain tissue following 3 and 7 days of implantation.

The non-clinical data are rather limited, especially in regard to the longer term effect of TachoSil in neurosurgical procedures and the potential for adhesions. However, data from the clinical studies, in which subjects were followed up for 6 months, did not reveal any issues in regard to neurotoxicity.

TachoSil undergoes biodegradation by (1) phagocytosis and infiltration of granulation tissue and (2) degradation of the fibrin clot by endogenous fibrinolysis. The biodegradation of TachoSil was investigated macroscopically and microscopically in minipigs.

In a study in female Goettingen minipigs, the biodegradation of TachoSil was compared to that of TachoComb H after application onto a defined liver and spleen lesion (study SR28/2008). Small remnants were observed 3 months after administration of either TachoSil or TachoComb H.

A further single dose study (SR R-CP1363) investigated the toxicity and biodegradation of TachoSil in minipigs over 12 months following application to liver wounds. The use of TachoSil had no effect on local and systemic safety over 12 months. Complete degradation of TachoSil was seen in some animals 12 months after its administration to a liver wound, whereas small remnants were still observed in others.

Safety pharmacologic aspects for TachoSil are based on the results obtained from nonclinical studies with TachoSil and its predecessor products.

As the active constituents of TachoSil, ie, human fibrinogen and human thrombin are well established in clinical use, formal studies addressing clinical pharmacology are not applicable.

2.2.1. Discussion on non-clinical aspects

The mechanism of action of TachoSil follows the principles of physiological fibrin clot formation. Upon contact with a bleeding or leaking wound surface or by the presence of physiological saline, the coating of the

collagen patch dissolves and the subsequent thrombin-fibrinogen reaction initiates the last step of the coagulation cascade: Fibrinogen is converted by the action of thrombin into fibrin monomers which spontaneously polymerize to a fibrin clot. Subsequently endogenous factor XIII, activated by thrombin, covalently cross links the fibrin to create a firm and stable network.

Pharmacodynamic and safety pharmacologic aspects for TachoSil are based on the results obtained from non-clinical studies with TachoSil and its predecessor products.

TachoSil is for epilesional use only and thus pharmacokinetic investigations do not apply.

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.2. Conclusion on the non-clinical aspects

Currently available non-clinical data are adequate to support use of TachoSil in the extension of the indication for supportive sealing of the dura mater to prevent postoperative cerebrospinal leakage following neurological surgery.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1: Overview of Clinical Efficacy Studies with TachoSil in Neurosurgery

Study	Study dates	Design	Objectives	Subjects	Treatment regimen	Endpoints
TC-2402-038 SP TachoSil® versus current practice in dura sealing techniques for the prevention of post-operative cerebrospinal fluid (CSF) leaks in patients undergoing skull base surgery: An	April 2011-June 2013	Open-label, randomized, controlled, parallel-group, multicentre, phase 3 (therapeutic confirmatory) study comparing TachoSil versus Current Practice as an adjunct in sealing the dura mater.	Primary Objective: To demonstrate superiority of TachoSil compared to current practice as an adjunct in sealing the dura mater. Secondary	TachoSil: 361 Current Practice: 365	TachoSil: 1 to 4 patches (large or medium) vs Current Practice	Primary: Occurrence of clinically evident verified postoperative CSF leaks, a clinically evident pseudomeningocele or study treatment failure and was defined as an event that occurred no later than 8 weeks after surgery.

open-label, randomised, controlled, multi-centre, parallel-group efficacy and safety trial.			Objective To evaluate the safety of TachoSil as an adjunct in sealing the dura mater.			

2.4. Clinical efficacy

2.4.1. Main study(ies)

Study TC-2402-038-SP (TASALL - TachoSil® Against Liquor Leak)

TachoSil versus current practice in dura sealing techniques for the prevention of post-operative cerebrospinal fluid (CSF) leaks in patients undergoing skull base surgery: An open-label, randomised, controlled, multi-centre, parallel-group efficacy and safety trial.

Methods

This was an open-label, randomized, controlled, parallel-group, multicenter, phase 3 (therapeutic confirmatory) study comparing TachoSil versus Current Practice as an adjunct in sealing the dura mater.

Patients were evaluated for pre-operative eligibility at the Screening visit up to 5 days before randomisation. Final eligibility (randomisation) of patients was dependent on the fulfilment of intra-operative eligibility criteria.

During surgery, immediately prior to application of primary dura closing techniques (primary suture of the dura, duraplasty, or both), eligible patients were randomly assigned in a 1:1 ratio to either TachoSil or current practice. The randomised trial treatment was applied intra-operatively and dosing of randomised trial treatment (quantity, size of patch, amount [e.g. mL]) was according to the choice of technique and the size of the dura opening. TachoSil was applied during surgery as an adjunct to the closure of the dura, as a single layer or a sandwich (double layer), and was not removed after application. If used the sandwich technique the first layer of TachoSil was applied on the inside of the dura. The primary suture of the dura or duraplasty was then performed prior to the second application of TachoSil. The second layer of TachoSil was applied on the outside of the dura.

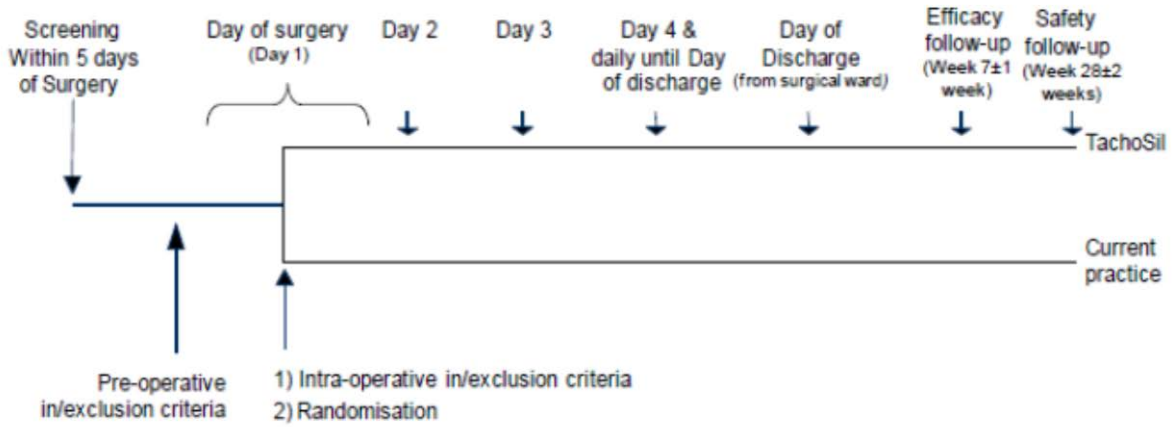
In case of insufficient dura sealing after the first application of TachoSil (both for single layer and for the second TachoSil application in sandwich application), a second application of TachoSil could have been applied on top of the first application on the outside of the dura.

The sealing efficacy was evaluated post-operatively as clinically evident CSF leaks and clinically evident and non-clinically evident pseudomeningoceles. Sealing efficacy was collected post-operatively until the Efficacy Follow-up (Week 7 ± 1 week). Non-clinically evident pseudomeningoceles were evaluated by computed tomography (CT) or magnetic resonance imaging (MRI) scans performed prior to surgery (up to 4 months) and any day prior to discharge and according to local practice from Day of Discharge until Safety Follow-up (Week 28 ± 2 weeks).

Safety data were collected from when the patient signed the Informed Consent Form until the Safety Follow-up (Week 28 ± 2 weeks). Any visits to out-patient physicians (e.g. General Practitioners, specialists, physiotherapists), hospital staff and hospitals were documented on the Patient Card with which the patient was provided at the time of informed consent, thus empowering the trial staff to investigate and classify/document relevant events appropriately.

The National Institute of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS) and Glasgow Coma Scale (GCS) patient assessments were conducted at Screening, Day 2, Day of Discharge, Efficacy Follow-up and Safety Follow-up. Home readiness was assessed daily from Day 4 until Day of Discharge from the surgical ward.

Figure 1 Outline of Clinical Trial Design



An independent Data Safety Monitoring Board was set-up to monitor the safety data during the conduct of the trial. The trial was not to be stopped prematurely based on efficacy reasons.

Study participants

- ***Study participants***

The study population consisted of subjects undergoing elective skull base surgery. A total of 778 subjects were enrolled in the study at 35 sites across 10 countries. Of these 778 subjects, a total of 726 subjects were randomly assigned to trial treatment, with 361 and 365 subjects randomized to TachoSil and Current Practice group, respectively.

The main inclusion and exclusion criteria are presented below, and are as per Version 6.0 of the trial protocol onwards.

Pre-Operative Inclusion Criteria

1. The patient was 18 years or older

2. The patient was to undergo non–trauma-related neurosurgery for pathology of the skull base resulting in opening and closing of the dura mater. Dura substitution was allowed

3. A CT or MRI scan of the head had been performed within 4 months before surgery

Intra-Operative Inclusion Criteria

4. The Surgical Wound Classification Class was class I (Clean surgical wound. Clean wound definition: uninfected surgical wounds in which no inflammation was encountered and the respiratory, alimentary, genital, or uninfected urinary tracts were not entered. In addition, clean wounds were primarily closed, and if necessary, drained with closed drainage) (Garner et al, 1986))

5. The surgical approach/procedure was consistent with skull base surgery, , i.e. one of the following:

a) Lateral approach to the foramen magnum: far lateral, extreme lateral, anterolateral, posterolateral

b) Approach to the jugular foramen: infratemporal, juxta condylar, transjugular

c) Approach to the cerebello pontine (CP) angle and petrous apex: retrosigmoid

d) Approach to the middle fossa: subtemporal (± petrous apex drilling), pterional approach (any fronto temporal approach ± orbitozygomatic deposition)

e) Approach to the anterior fossa: subfrontal (uni or bilateral)

f) Approach to the midline posterior fossa

Pre-Operative Exclusion Criteria

1. The patient had evidence of an infection within 5 days of surgery indicated by any one of the following: fever >101ºF/38.5°C, white blood cells (WBC) <3.5/GL or >13.0/GL (if patient was on steroid treatment >20.00/GL), positive urine culture, positive blood culture, positive chest X-ray

2. The patient had a known coagulopathy

3. A history of allergic reactions after application of human fibrinogen, human thrombin and/or collagen of any origin

4. The patient had been subject to neurosurgery involving opening of the dura mater within the last 3 months before Screening

5. The patient was anticipated to undergo any additional neurosurgery involving opening of the dura mater that may have affected the efficacy evaluation (e.g. re-operation or anticipation to undergo several neurosurgeries) before the Efficacy Follow-Up (Week 7 ± 1 week)

6. The patient was anticipated to undergo any additional neurosurgery involving opening of the dura mater that may have affected the safety evaluation (e.g. re-operation or anticipation to undergo several neurosurgeries) before the Safety Follow-up (Week 28 ± 2 weeks)

Intra-Operative Exclusion Criteria

7. The surgical approach/procedure was consistent with any transcranial or transfacial or combination of transcranial – transfacial approaches with wide defect in the skull base, i.e. any of the following:

a) Trans basal approach

b) Total petrosectomy

c) Trans facial approach

d) Trans sphenoidal approach

e) Endoscopic procedures

f) Trans oral approach (and any extension: Le Fort, mandibulotomy)

8. The surgical approach was consistent with one of the following approaches

a) Translabyrinthine approach

b) Retrolabyrinthine approach

c) Transcochlear (limited transpetrosal) approach

9. The arachnoid membrane and the CSF containing system remained intact during surgery

10. The patient had more than 1 dura opening (not including dura openings from extraventricular or lumbar drains)

11. TachoSil, fibrin or polymer sealants had been used during the current surgery prior to randomisation

Treatments

TachoSil was applied during surgery as an adjunct to the closure of the dura, as a single layer or a sandwich (double layer).To avoid selection bias random allocation was performed prior to application of primary dura closing techniques. Reason for this decision was to allow the sandwich technique.

This study allowed the treating surgeon to apply a number of standard dura closing techniques alone or in combination. Non-investigational medicinal products included all trial treatments with medicinal products or medical devices utilised by the individual surgeon to seal the dura, including fibrin sealants, polymer sealants and any artificial dura substitutes.

Objectives

Primary Objective

To demonstrate superiority of TachoSil compared to current practice as an adjunct in sealing the dura mater.

Secondary Objective

To evaluate the safety of TachoSil as an adjunct in sealing the dura mater.

Outcomes / endpoints

The primary endpoint was the occurrence of clinically evident, verified postoperative CSF leaks, a clinically evident pseudomeningocele, or study treatment failure defined as an event that occurred no later than 8 weeks after surgery. The primary endpoint was considered to have been reached if a clinically evident verified CSF leak or clinically evident pseudomeningocele had occurred post-operatively until Efficacy Follow-up (Week 7 ± 1 week), or if trial treatment failure had occurred upon dura closure.

Verification of CSF leaks was to be done by performing a glucose (glucose level of CSF is one-third lower than in serum), alternatively a β-2 transferrin test.

The secondary endpoint was defined as the presence of nonclinically evident pseudomeningocele, ie, CSF accumulation found by CT or MRI scanning, postoperatively until Day of Discharge without occurrence of the primary endpoint.

The occurrence of clinically evident verified post-operative CSF leaks or a clinically evident pseudomeningocele chosen as part of the primary endpoint are generally considered adequate to allow an assessment of the efficacy of the dura sealing.

Sample size

Anticipating a control group leak rate of 17%, a TachoSil group leak rate of 8.5% and a drop-out rate of 5% and a type I error of 0.05 (2-sided) it was calculated that an asymptotic chi-square test with 726 patients (363 per group) would provide 90% power to detect such a response difference.

Based on the assumptions made, the trial was sufficiently powered. However, the discrepancy between the anticipated leak rate in the control group (according protocol: based on feedback from neurosurgeons) and the observed leak rate in the trial is astonishing.

Randomisation

Patients were randomised in an 1:1 (TachoSil : current practice) ratio by means of an Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS). Permuted block randomisation (with varying block length) was applied.

Blinding (masking)

The trial was planned as an open label trial.

Statistical methods

In general data were summarised by means of descriptive statistics (continuous data: number of patients, mean, standard deviation (SD), median, lower quartile (25%), upper quartile (75%), minimum and maximum; categorical data: absolute and relative frequencies). Treatment effects were described by means of point estimates (e.g. odds ratio, difference of proportions) including their 95% confidence intervals. To describe time to event data, Kaplan-Meier plots were used.

A logistic regression model (factors treatment and pooled centre) was used to compare both treatment groups with regard to the primary endpoint (occurrence of clinically evident verified post-operative CSF leaks, clinically evident pseudomeningocele or trial treatment failure up to the efficacy follow-up visit (week 7±1)). The null-hypothesis of no treatment effect was to be rejected in case of a (2-sided) p-value < 0.05. The primary analysis was based on the Full Analysis Set of all randomized subjects. This analysis was replicated for the Per Protocol Population. Graphical methods were applied to assess the homogeneity of treatment effects across centres.

Missing primary endpoint values were in general accounted for as non-leaks: It was assumed that an event of the primary endpoint was likely to prompt the patient to contact the investigator. If a patient died after randomisation and before the efficacy follow-up visit (week 7±1) and death could be definitively explained by reasons other than the indication then this was also defined as a non-leak.

To assess the impact of missing value on the primary analysis the following approaches were used in addition:

1. All drop outs counted as leaks

2. 50% of drop outs counted as leaks, i.e. 50% of the patients who dropped out were randomly assigned counting as a leak and 50% were assigned counting as a non-leak (stratified by treatment group).

3. Assuming identical leak rates for drop outs and completers, i.e. patients who dropped out were randomly assigned as counting to be a leak or not a leak using this rate (stratified by treatment group).

Additional analyses were performed to assess the impact of potentially predictive variables on the primary outcome, to compare TachoSil to each of 2 current practice subgroups (fibrin and polymer sealants and other methods of dura closure) and to assess the treatment effect across surgical approaches (i.e. interaction between surgical approaches and treatment group) was analysed

The same approach as for the primary endpoint was applied to analyse the secondary endpoint (presence of non-clinically evident pseudomeningocele post-operatively until day of discharge without occurrence of the primary endpoint).

Only the primary endpoint was to be tested in a confirmatory manner. Thus no multiplicity adjustment was necessary.

All treatment emergent AEs (TEAE) were summarised by providing the number of patients, the proportion of patients with an event, and the number of events, using preferred term (PT) grouped by system organ class (SOC). In addition TEAEs were summarised by seriousness, severity and relationship to trial treatment and trial procedure.

Laboratory data were standardised to account for the differences between local laboratories by relocating each original, locally recorded value to the corresponding value on the chosen reference range. Absolute laboratory values and changes from baseline were summarised by parameter and visit.

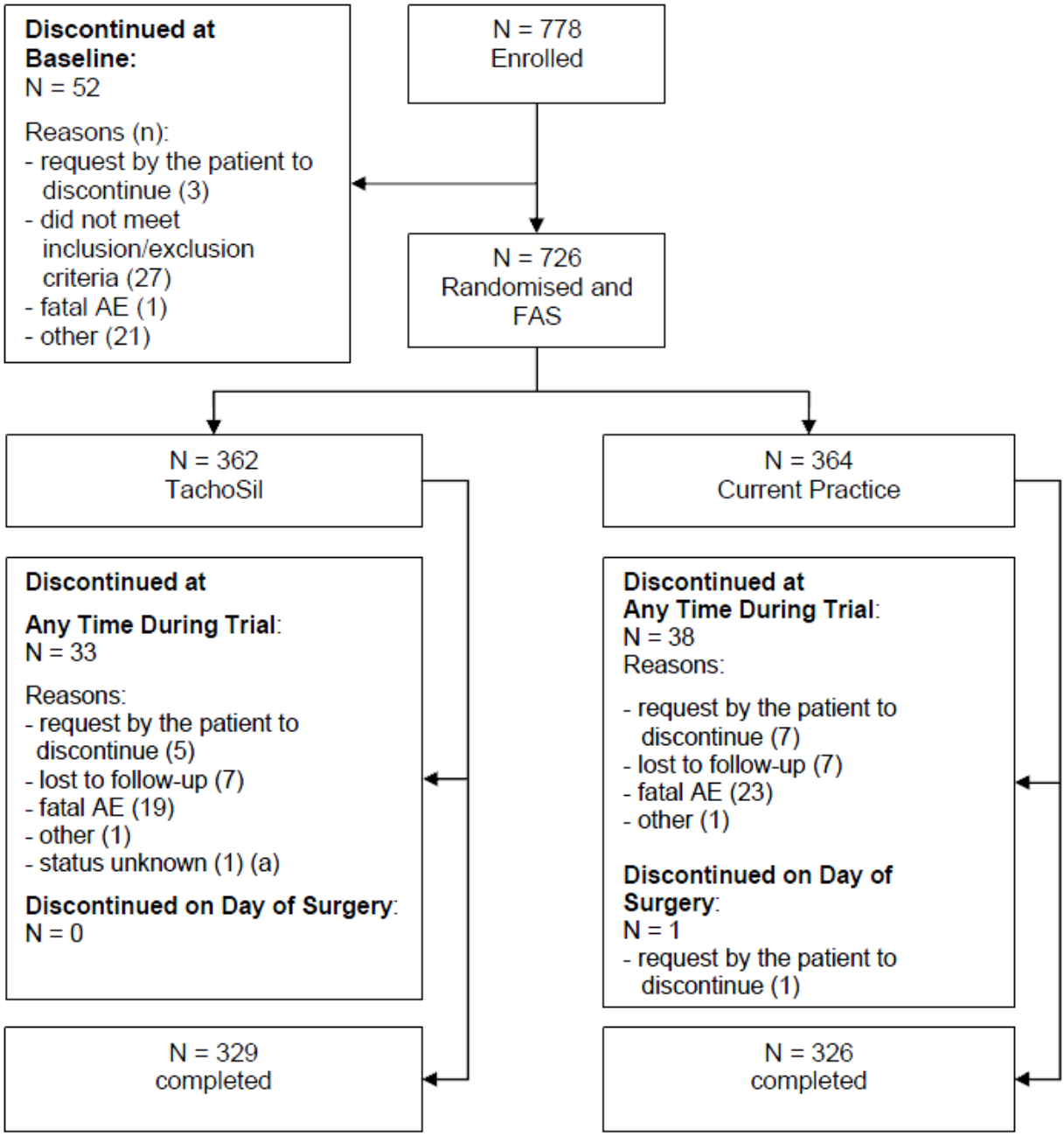
Vital signs data were summarised and presented by treatment group for each parameter and visit.

In general the statistical methods applied are considered adequate.

Results

Participant flow

Figure 2 Subject Disposition



AE, adverse event; FAS, full analysis set.
(a) One subject's data for the final follow-up visit and End of Trial CRF page is missing; completion status could not be confirmed.

The eligibility of subjects according to protocol-defined inclusion and exclusion criteria was evaluated prior to surgery. Discontinuations at Baseline (prior to randomization) are expected to have affected both treatment arms equally, thus introducing no selection bias. No discontinuations occurred after randomization and prior to surgery.
The reasons for discontinuation were varied and did not show any clear pattern.

Recruitment

Studied Period: 28 April 2011 (first patient enrolled) to 27 June 2013 (last patient completed)

Conduct of the study

The original protocol (dated 27 July 2009) was amended as follows: Substantial Amendments 1, 2, 3, 4, 5 and 6: dated 21 September 2009, 14 October 2010, 16 November 2010, 25 November 2011 (Version 2.0), 25 November 2011 and 19 October 2012, respectively. The inclusion and exclusion criteria were updated during the trial

A large number of substantial amendments were made to the protocol during the course of the study. Most were not likely to have introduced significant variability into the study, and were made to clarify the protocol. Limited transpetrosal surgical approaches (translabyrinthine, retrolabyrinthine, transcochlear) were specifically excluded in amendment 4.

Baseline data

The mean age of the patients was 53.1 years (range 18-87 years). The majority of patients were white or Caucasian (98.6%) and the most common ethnicity was non-Hispanic and non-Latino (80.4%). A higher proportion of male patients was randomly assigned to the Current Practice group (42.2%) than to the TachoSil group (35.5%) – see table

Table 2 Demographic Characteristics of Patients (FAS)

Characteristic	TachoSil (N=361)	Current Practice (N=365)	Total (N=726)
Age, years			
n	361	365	726
Mean	53.1	53.2	53.1
SD	13.80	14.22	14
Median	54	54	54
Range	18, 87	18, 81	18, 87
Age group, n (%)			
18-65 years	288 (79.8)	293 (80.3)	581 (80)
>65 years	73 (20.2)	72 (19.7)	145 (20)
Sex, n (%)			
Male	128 (35.5)	154 (42.2)	282 (38.8)
Female	233 (64.5)	211 (57.8)	444 (61.2)
Race, n (%)			
White/Caucasian	355 (98.3)	361 (98.9)	716 (98.6)
Asian	1 (0.3)	0	1 (0.1)
Black or African American	3 (0.8)	2 (0.5)	5 (0.7)
American Indian or Alaska Native	1 (0.3)	1 (0.3)	2 (0.3)
Other	1 (0.3)	1 (0.3)	2 (0.3)
Ethnicity, n (%)			
Hispanic or Latino	55 (15.2)	62 (17)	117 (16.1)
Non-Hispanic and Non-Latino	295 (81.7)	289 (79.2)	584 (80.4)
Unknown	11 (3)	14 (3.8)	25 (3.4)
Height, cm			
Mean	167.4	168.5	168
SD	9.44	9.18	9.32
Median	167	168	168
Range	145, 194	142, 200	142, 200
Weight, kg			
Mean	73.6	75.2	74.4
SD	14.40	16.79	15.65
Median	72	75	73
Range	41, 119	43, 180	41, 180

Characteristic	TachoSil (N=361)	Current Practice (N=365)	Total (N=726)
BMI, kg/m^2			
Mean	26.20	26.42	26.31
SD	4.44	5.10	4.79
Median	25.61	26.03	25.83
Range	15.6, 41.1	15.3, 57.5	15.3, 57.5
Fertility status, n (%)[1]			
Fertile	74 (20.5)	74 (20.3)	148 (20.4)
Post-menstrual	140 (38.8)	111 (30.4)	251 (34.6)
Surgically sterile	19 (5.3)	26 (7.1)	45 (6.2)
Not applicable	128 (35.5)	154 (42.2)	282 (38.8)

BMI, body mass index; FAS, full analysis set; N, total number of patients in the group; n, the number of patients within the analysis set; SD, standard deviation.

Percentages are based on the number of patients in the FAS.

1. Prior to Protocol Amendment 4, Version 2.0 dated 25 November 2011, "Fertile" was classified as "menstrual" and "post-menstrual" was classified as "post-menopausal".

The mean age of the patients was 53.1 years (range 18-87 years). The majority of patients were white or Caucasian (98.6%) and the most common ethnicity was non-Hispanic and non-Latino (80.4%).

Baseline characteristics were generally similar across the 2 treatment groups based on evaluation of demography, medical history, concomitant illness, concomitant medication, leak rate predictive variables, surgery times and intra-operative variables.

The proportion of females in the study was substantially larger than that of males: 444 (61.2%) of the 726 enrolled subjects were female (TC-2402-038-SP CSR Table 14.1.3.1). Females represented 64.5% of the TachoSil arm and 57.8% of the Current Practice arm. This preponderance is largely due to the fact that the most common primary indication for surgery was benign meningioma (CSR Appendix 16.2, Listing 16.2.4.1.2), which occurs more frequently in females. Benign meningioma was identified as the primary indication in 130 female subjects (17.9% of the 726 enrolled) and 47 male subjects (6.5%). The next largest gender imbalance was seen in intracranial aneurysm, which represented the primary indication in 66 female (9.1%) and 19 male subjects (2.6%).

Baseline variables considered predictive of leak rate are summarised below.

Table 3 Predictive Variables for Efficacy Outcome (FAS)

Predictive Variable	**TachoSil (N=361)**	**Current Practice (N=365)**	**Total (N=726)**
	n (%)		
Evidence of hydrocephalus[1]			
Yes	7 (1.9)	6 (1.6)	13 (1.8)
No	354 (98.1)	359 (98.4)	713 (98.2)
Previously received chemotherapy[2]			
Yes	14 (3.9)	10 (2.7)	24 (3.3)
No	347 (96.1)	355 (97.3)	702 (96.7)
Previously received radiotherapy			
Yes	18 (5.0)	14 (3.8)	32 (4.4)
No	343 (95.0)	351 (96.2)	694 (95.6)
Air cells opened			

Yes	81 (22.4)	69 (18.9)	150 (20.7)
No	280 (77.6)	296 (81.1)	576 (79.3)
Gap in suture line after primary suture			
Yes	105 (29.1)	102 (27.9)	207 (28.5)
No	256 (70.9)	263 (72.1)	519 (71.5)
Length of dura incision (mm)[3]			
Mean	83.9	86.0	84.9
SD	47.15	47.49	47.30
Median	75.0	78.0	75.0
Range	10, 250	10, 220	10, 250
Age centred (years; mean age=53.1)			
Mean	-0.07	0.06	0.00
SD	13.797	14.218	14.001
Median	0.86	0.86	0.86
Range	-35.1, 33.9	-35.1, 27.9	-35.1, 33.9
Passive/active drainage or shunt			
Yes	68 (18.8)	72 (19.7)	140 (19.3)
No	293 (81.2)	293 (80.3)	586 (80.7)

FAS, full analysis set; N, total number of patients in the group; n, the number of patients within the analysis set; SD, standard deviation.

1. Evidence of hydrocephalus in screening computed tomography or magnetic resonance imaging scan.
2. Patients had received treatment within 5 years prior to the Day of Surgery (Day 1).
3. If duraplasty was applied alone it was counted as missing.

Surgery times (skin incision to randomisation time, time from randomisation time to dura closure start, dura closure start to dura closure completion time, dura closure completion time to skin closure time and time from skin incision to skin closure) were similar in the 2 treatment groups.

Intra-operative variables (dura incision length, dura incision shape, side of surgery, closure of skull and cranioplasty type) were generally similar across both treatment groups.

For the primary suture, the proportion of patients for whom only sutures were used was higher in the TachoSil group (63.2%) than in the Current Practice group (45.5%). The proportion of patients for whom suture and duraplasty were used was lower in the TachoSil group (35.7%) than in the Current Practice group (49.6%). Dura closure variables (dura application) were otherwise generally similar across both treatment groups.

Post-operative variables were generally similar across both treatment groups. The mean (SD) length of stay as an in-patient in the original hospital was 11.0 (13.60) days in the TachoSil group (range 1-49 days) and 16.2 (15.12) days in the Current Practice group (range 2-61 days). The proportion of patients who visited a General Practitioner or out-patient specialist, were re-admitted to hospital, or who had a surgical re-intervention were similar in the TachoSil and Current Practice groups.

Only a small proportion (5%) of patients had received prior radiotherapy to the head within the past 5 years.

Numbers analysed

Table 4 Data Sets Analysed

	TachoSil	Current Practice	Total
Analysis population	**n (%)**	**n (%)**	**n**
All Patients Enrolled			778
FAS	361 (99.7)	365 (100.3)	726
PP	333 (92.0)	325 (89.3)	658
SAF	362 (100)	364 (100)	726

FAS, full analysis set; n, the number of patients within the analysis set; PP, per-protocol analysis set; SAF, safety analysis set.

The enrolled total includes all patients enrolled in the trial, including those who were not randomly assigned.

A patient was considered enrolled if they were given a patient identification number and had given informed consent. Percentages are based on all patients enrolled by received treatment, with the number of patients in the SAF as the denominator. The summaries for all enrolled, PP and SAF are presented by treatment received. The summaries for FAS are presented by randomised treatment. One patient (Patient ES3860004) was randomised to current practice but received TachoSil. This results in a percentage greater than 100% for the FAS in the Current Practice group.

Outcomes and estimation

Primary Efficacy Variable

Table 5 Analysis of Incidence of Clinically Evident Verified Post-Operative CSF Leaks, Clinically Evident Pseudomeningocele or Treatment Failure at Efficacy Follow-up (FAS)

Treatment	n/N (%)	Exact Binomial 95% CI	Pairwise Comparison TachoSil - Current Practice		
			Odds Ratio (SE)	Wald 95% CI	*P* value
TachoSil	25/361 (6.9)	(4.5, 10.1)	-	-	-
Current Practice	30/365 (8.2)	(5.6, 11.5)	0.82 (0.23)	(0.47, 1.43)	0.485

CI, confidence interval; CSF, cerebrospinal fluid; FAS, full analysis set; N, total number of patients in group; n, the number of patients within the analysis set; SE, standard error.

Percentages are based on the number of patients with incidence of clinically evident post-operative CSF leaks, clinically evident pseudomeningocele or treatment failure in the FAS.

The proportion of patients with incidence of clinically evident post-operative CSF leaks, clinically evident pseudomeningocele or treatment failure (n) was analysed by using a logistic regression model with treatment and pooled centre as covariates.

P values were 2-sided.

A total of 6.9% (25/361) of subjects in the TachoSil group and 8.2% (30/365) of subjects in the Current Practice group (full analysis set [FAS]) had clinically evident, verified postoperative CSF leaks, clinically evident pseudomeningocele, or were treatment failures at efficacy follow-up.

The primary analysis of the incidence of clinically evident verified post-operative CSF leaks, clinically evident pseudomeningocele or treatment failure (FAS) showed an estimated OR of 0.82 (95% CI: 0.47, 1.43, P=0.485). The proportion of patients in the TachoSil group without clinically evident verified post-operative CSF leaks, clinically evident pseudomeningocele or treatment failure was therefore not superior to the Current Practice group for the FAS. A significant centre effect was found (P=0.046); this effect appeared to be driven by a higher leak rate in Russia. Care must be taken when interpreting the centre effect, however,

given the small sample size of the Russian subgroup. Similar results were obtained when all CSF leaks (including non-verified leaks) were included in the analysis: 27 (7.5%) patients in the TachoSil group and 34 (9.3%) patients in the Current Practice group had clinically evident post-operative CSF leaks, clinically evident pseudomeningocele or treatment failure (OR: 0.78, 95% CI: 0.46, 1.33, P=0.360); however, the centre effect was not statistically significant (P=0.066).

The proportion of patients with clinically evident post-operative CSF leaks, clinically evident pseudomeningocele or treatment failure was analysed by demographic subgroup category for the FAS. For verified CSF leaks, the estimated OR was 0.43 for male patients and 1.38 for female patients, implying a greater likelihood of a female TachoSil patient experiencing a CSF leak (compared with a female Current Practice patient) and conversely a lower likelihood of a male TachoSil patient experiencing a CSF leak. The 95% CIs for both OR estimates included 1 and no statistically significant difference between treatments could be concluded for either gender. (summarised in Section 14, Table 14.2.3.3 study report)

The proportion of patients with incidence of clinically evident post-operative CSF leaks, clinically evident pseudomeningocele or treatment failure by 2 Current Practice subgroups (fibrin and polymer sealants and other methods of dura closure): For the analysis of the primary endpoint by Current Practice subgroup, the estimated OR for the Fibrin and Polymer Sealant subgroup compared with TachoSil was 0.91 (95% CI: 0.4, 2.0, P=0.820). For the Other Dura Closure Methods subgroup compared with TachoSil, the estimated OR was 1.47 (95% CI: 0.8, 2.8, P=0.241).

Of the 87 patients in the Current Practice group who had suturing alone, 8 (9.2%) patients had clinically evident post-operative CSF leaks, pseudomeningocele or treatment failure. Of the 361 patients in the TachoSil group, 25 (6.9%) had clinically evident post-operative CSF leaks, pseudomeningocele or treatment failure. The estimated OR for suturing alone compared with TachoSil was 1.29 (95% CI: 0.6, 3.0, P=0.559).

Secondary Efficacy Variable

The primary analysis of the incidence of non-clinically evident post-operative pseudomeningocele (FAS) showed an estimated OR of 1.01 (95% CI: 0.43, 2.36, P=0.979). No difference between the TachoSil and Current Practice groups could be concluded.

Table 6 Analysis of Incidence of Non-Clinically Evident Post-Operative Pseudomeningocele (FAS and PP)

Treatment	n/N (%)	Exact Binomial 95% CI	Pairwise Comparison TachoSil - Current Practice		
			Odds Ratio (SE)	Wald 95% CI	*P* value
FAS					
TachoSil	11/361 (3.0)	(1.5, 5.4)	-	-	-
Current Practice	11/365 (3.0)	(1.5, 5.3)	1.01 (0.44)	(0.43, 2.36)	0.979
PP					
TachoSil	11/333 (3.3)	(1.7, 5.8)	-	-	-
Current Practice	11/325 (3.4)	(1.7, 6.0)	0.98 (0.42)	(0.42, 2.28)	0.954

FAS, full analysis set; N, total number of patients in group; n, the number of patients within the analysis set; PP, per-protocol analysis set; SE, standard error.

Percentages are based on the number of patients with incidence of non-clinically evident pseudomeningocele in the FAS or PP.

The proportion of patients with incidence of non-clinically evident pseudomeningocele (n) was analysed by using a logistic regression model with treatment as covariate. Pooled centre was removed from the model.

P values were 2-sided.

In the TachoSil arm of study TC-2402-038-SP, 1 of the 11 nonclinically evident postoperative pseudomeningoceles reported as a secondary efficacy measure occurred in the postdischarge period. The remaining 10 occurred before discharge. In the Current Practice arm, 2 of the 11 nonclinically evident postoperative pseudomeningoceles occurred in the postdischarge period, and 9 occurred before discharge.

In the TachoSil arm, 26 scans were conducted in the post-discharge period. The time range of the scans (between 2 to 250 days after discharge) showed no particular trend. Only 1 of the 26 scans was positive for non-clinically evident postoperative pseudomeningoceles. One subject had 2 scans at different times and both were negative. Another subject with positive pre-discharge scan findings on Day 8 remained positive for non-clinically evident postoperative pseudomeningoceles on a repeat scan on post-discharge Day 98.

In the Current Practice arm, 27 scans were conducted in the post-discharge period. The time range of the scans was 1 to 179 days after discharge and showed no particular trend. Four of the 27 scans were positive for non-clinically evident postoperative pseudomeningoceles.

Exploratory Analyses

A total of 34 (9.4%) subjects in the TachoSil group and 38 (10.4%) subjects in the Current Practice group (FAS) had either the primary endpoint or nonclinically evident pseudomeningocele. The exploratory analysis of the combined endpoint (FAS) showed an estimated OR of 0.88 (95% CI: 0.54, 1.44, p=0.609).

For the analysis of the primary endpoint by Current Practice subgroup, the estimated OR for the Fibrin and Polymer Sealant subgroup compared with TachoSil was 0.91 (95% CI: 0.4, 2.0, p=0.820). For the Other Dura Closure Methods subgroup compared with TachoSil, the estimated OR was 1.47 (95% CI: 0.8, 2.8, p=0.241).

Table 7 Exploratory Analyses of Combined Endpoints and Current Practice Subgroups

Outcome Variable	Treatment	n/N (%)	Exact Binomial 95% CI	Pairwise Comparison TachoSil vs Current Practice		
				Odds Ratio	Wald 95% CI	p-value
Combined Primary and Secondary Endpoint Events (a)	TS	34/361 (9.4)	(6.6, 12.9)			
	CP	38/365 (10.4)	(7.5, 14.0)	0.88	0.54, 1.44	0.609
Primary endpoint – TS vs	TS	25/361 (6.9)	(4.5, 10.1)			
Fibrin/polymer sealant (b)	CP	10/171 (5.8)	(2.8, 10.5)	0.91	0.4, 2.0	0.820
Other sealing methods (b)	CP	20/194 (10.3)	(6.4, 15.5)	1.47	0.8, 2.8	0.241

Source: Study TC-2402-038-SP Tables 14.2.6, 14.2.16.
CP=Current Practice, TS=TachoSil.
(a) Percentages are based on the number of subjects with incidence of the primary endpoint or nonclinically evident pseudomeningocele (combined endpoint) in the FAS. The proportion of subjects with incidence of the primary endpoint or nonclinically evident pseudomeningocele (n) was analyzed by using a logistic regression model with treatment and pooled center as covariates. An OR <1 implied a smaller likelihood of a TachoSil-treated subject to experience the primary endpoint or nonclinically evident pseudomeningocele (combined endpoint).
(b) Percentages are based on the number of subjects with incidence of clinically evident postoperative CSF leaks, clinically evident pseudomeningocele or treatment failure in the FAS. The proportion of patients with incidence of clinically evident postoperative CSF leaks, clinically evident pseudomeningocele or treatment failure (n) was analyzed by using a logistic regression model with treatment and pooled center as covariates. An OR >1 implies a smaller likelihood of a TachoSil treated subject to experience clinically evident postoperative CSF leaks, clinically evident pseudomeningocele, or treatment failure.
Note: All p-values are two-sided.

For the primary suture, the proportion of patients for whom only sutures were used was higher in the TachoSil group (63.2%) than in the Current Practice group (45.5%). The proportion of patients for whom suture and duraplasty were used was lower in the TachoSil group (35.7%) than in the Current Practice group (49.6%). Dura closure variables (dura application) were otherwise generally similar across both treatment groups.

A subgroup analysis of the primary endpoint by TachoSil application type (sandwich or single layer) is shown in Table 8. The odds ratio values do not provide support for use of the double-layer (sandwich) technique.

Table 8 Subgroup Analysis of Primary Endpoint by Method of TachoSil Application: Study TC-2402-038-SP

Treatment/ Comparison	Primary Endpoint (a) (n/N)	Incidence Rate, % (95% CI)	Odds Ratio (95% CI)	P-value
Current Practice	30/365	8.22 (5.4, 11.04)	-	-
TachoSil sandwich	12/114	10.53 (4.89, 16.16)	-	-
Sandwich-Current Practice	-	2.31 (-3.99, 8.61)	1.0713 (0.51, 2.24)	0.8552
TachoSil single layer	13/247	5.26 (2.48, 8.05)	-	-
Single layer-Current Practice	-	-2.96 (-6.92, 1.01)	0.6313 (0.32, 1.25)	0.1845

(a) Subjects with incidence of clinically evident postoperative CSF leaks, clinically evident pseudomeningocele, or treatment failure.

The first analysis of the primary endpoint only includes the verified leaks. However, including the non-verified leaks does not change the picture of a very low number of events in both treatment groups.

The company had expected an event rate of 5-6% in the TachoSil group, however they had assumed a much higher (15-20%) event rate in the current practice group than found in this study.

The proportion of patients for whom only sutures were used was higher in the TachoSil group than the Current Practice group whereas the proportion of patients for whom suture and duraplasty were used was lower in the TachoSil group than in the Current Practice group. It was discussed that the current practise group was too broad and probably the dura closure was more thorough than in a normal clinical setting. But this isn't verified and it can be supposed that if a surgeon carefully performs the dura closure such results would be obtained.

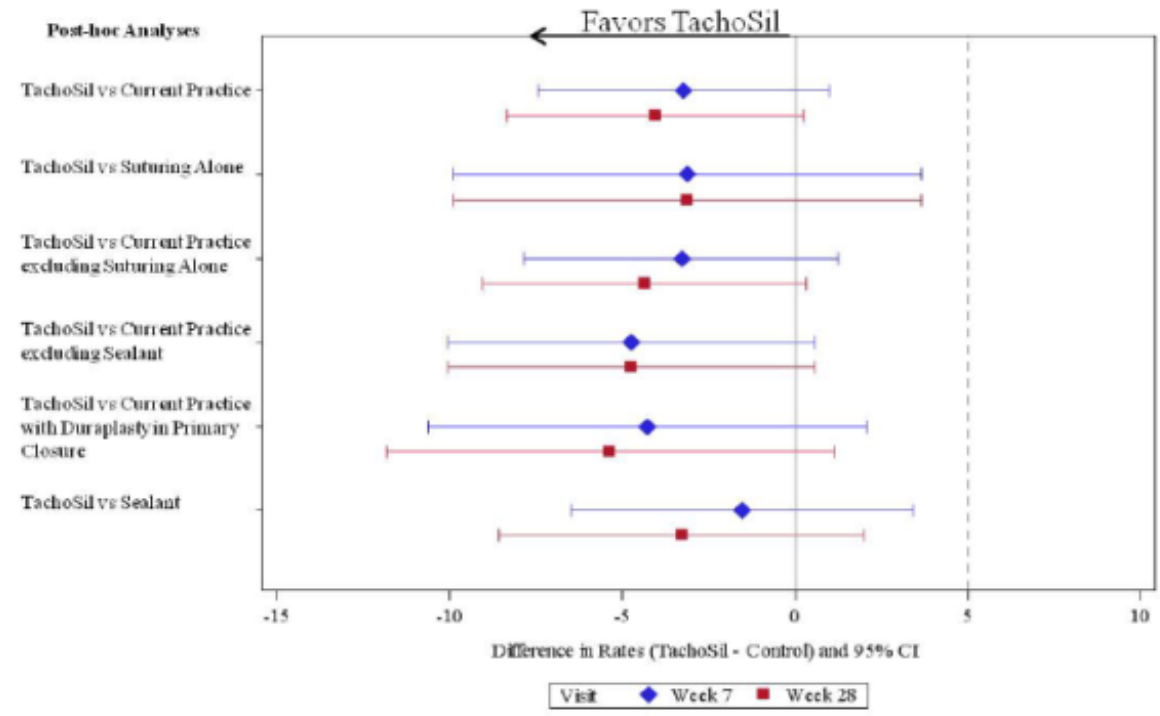
According to the subgroup analysis provided in Table 7 there is no statistically significant difference between the TachoSil and Current Practice groups for any surgical approach.

A total of 8.2 % (30/365) of subjects in the Current Practice group and 6.9% (25/361) of subjects in the TachoSil group had clinically evident, verified postoperative CSF leaks, clinically evident pseudomeningocele, or were treatment failures at efficacy follow-up.

The subgroup analysis of the primary endpoint showed an estimated OR of 1.07 (95% CI: 0.51, 2.24, P=0.855) for TachoSil sandwich and 0.63 (95% CI: 0.32, 1.25, P=0.1845) for TachoSil single-layer.

Therefore, the proportion of patients treated with double-layer technique was therefore not superior to the the single-layer group.

The use of rescue treatment was very low in both treatment groups (5 [1.4%] patients in each group).



Source: Appendix 1 Analyses Tables 3.1: TachoSil vs Current Practice; 3.2: TachoSil vs suturing alone; 3.3: TachoSil vs Current Practice excluding suturing alone; 3.4: TachoSil vs Current Practice excluding sealant; 3.5: TachoSil vs Current Practice with duraplasty in primary closure; 3.6: TachoSil vs sealant.
Note: Stippled line indicates applied noninferiority margin of 5%.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 7 Summary of efficacy for trial TC-2402-038-SP

Title: TachoSil® versus current practice in dura sealing techniques for the prevention of post-operative cerebrospinal fluid (CSF) leaks in patients undergoing skull base surgery: An open-label, randomised, controlled, multi-centre, parallel-group efficacy and safety trial.				
Study identifier	TC-2402-038-SP EudraCT No. 2009-013056-71			
Design	Open-label, randomized, controlled			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		28.04.2011 – 27.06.2013 not applicable not applicable	
Hypothesis	Superiority			
Treatments groups	TachoSil		TachoSil, intra-operative, n = 362	
	CP		Current practice in dura sealing, intra-operative, n = 364	
Endpoints and definitions	Primary: Post-operative cerebrospinal fluid leaks	CSF leak	Occurrence of a post-operative clinically evident CSF leak or clinically evident pseudomeningocele or treatment failure until the efficacy follow-up visit (week 7±1)	
	Secondary:	Pseudomeningocele	Occurrence of post-operative non-clinically evident pseudomeningocele until the efficacy follow-up visit (week 7±1) without occurrence of CSF leak	
Database lock	Date not provided			

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat: all patients randomized Time point per patient: efficacy follow-up visit (week 7±1)			
Descriptive statistics and estimate variability	Treatment group	TachoSil	CP	
	Number of subject	361	365	
	CSF leak (n/N, %)	25/361 (6.9%)	30/365 (8.2%)	
	95%-CI	4.5 – 10.1%	5.6 – 11.5%	
	Pseudomeningocele (n/N, %)	11/361 (3.0%)	11/365 (3.0%)	
	95%-CI	1.5 – 5.4%	1.5 – 5.3%	
Effect estimate per comparison	CSF leak	Comparison groups	CSF leak vs. CP	
		Odds ratio	0.82	
		95%-CI	0.47 – 1.43	

		P-value	0.485
	Pseudomeningocele	Comparison groups	CSF leak vs. CP
		Odds ratio	1.01
		95%-CI	0.43 – 2.36
		P-value	0.979
Notes	In line with the primary analysis, none of the additionally performed analyses indicated a superiority of TachoSil when compared to current practice.		

Analysis performed across trials (pooled analyses and meta-analysis)

The company performed a meta-analysis using high-level data from the Hutter (2014) trial. According to the documents results from "suture alone" from the TASALL trial and the Hutter trial were pooled.

The primary dural closure in the TASALL and Hutter [10] studies was defined as primary suture of the dural membrane and/or duraplasty with a dural patch, hence the techniques were the same. “Dural patch” is a general term used to describe the various types of materials used for duraplasty in the primary closure. “Dural patch” should not be confused with medicinal product like some sealants or TachoSil. The technique of duraplasty in all cases involves suturing to attach the dural patch to the edges of the residual dural membrane. The dural patch materials used in the TASALL and Hutter [10] studies were the same. They included autologous tissue (galea, muscle, pericranium) or an artificial membrane material.

Accordingly, the primary treatments consisting of suturing and duraplasty to close the dura were the same in the 2 studies.

The secondary, randomized treatment in control subjects in the Hutter study was suture [10]. This is comparable to the treatment in the subgroup of subjects receiving suturing alone in the TASALL study. Since the primary endpoint was the same in both studies (discussed in Response to the 2nd RSI; sequence 0066), it is therefore justified and appropriate to combine the 2 studies in a meta-analysis comparing TachoSil treatment with suturing alone across the 2 studies. The objective of the meta-analysis was to increase the statistical power. The similarity of the subject populations, procedures, and efficacy endpoints in both the studies ensured a robust meta-analysis. The result of the meta-analysis showed statistical superiority of TachoSil, with a leak event rate reduction of -5.6 percentage points (95% CI, -11.1%, -0.2%; p=0.035) over suturing, corresponding to a clinically relevant relative reduction of 43%.

2.4.2. Discussion on clinical efficacy

The purpose of this application was to present data in support of the efficacy of TachoSil for supportive sealing of the dura mater to prevent postoperative cerebrospinal leakage following neurological surgery based on the results obtained from neurosurgery Study TC-2402-038-SP.

Design and conduct of clinical studies

Study TC-2402-038-SP was designed as an open-label, randomized, controlled, parallel-group, multicenter, phase 3 (therapeutic confirmatory) study comparing TachoSil versus Current Practice as an adjunct in sealing the dura mater.

The inclusion and exclusion criteria are appropriate to generate an adequate patient population. Only adult patients were included in the pivotal study in neurosurgery. Just under half of the patients were enrolled using the selection criteria from an earlier version of the protocol, which differed in regard to a smaller number of allowed surgical approaches. However, this is not considered to have had a major impact on the results of the study.

The randomization procedure was comprehensible and sufficiently described. It is agreed, based on the differences in the applied treatment modalities (patch versus 'current practice') applied to the dura mater during surgery - that use of placebo or blinding is practically impossible. It was planned to show a difference in CSF leak or pseudomeningocele rates between TachoSil (8.5%) and the control group (17.0%) with a fixed sample size of 726 patients. 362 patients were randomised to treatment with TachoSil, which was applied over the suture line in a single layer, or as a double sandwich layer, inside and outside of the dura, where a sufficient overlap of the suture line was not possible with a single layer application. 364 control patients were randomised to best standard of care, at the discretion of the Investigator (eg, duraplasty, fibrin/polymer sealant, sutures alone, etc.). The use of a broad range of standard of care treatments in the control group was appropriate since there is no gold standard treatment, and since there were ethical concerns with restricting control subjects to sutures alone when CSF leakage has been shown to occur in almost 20% of cases. Together with this, the eligibility criteria were broad, and included those with previous local radiotherapy, which may predispose to CSF leakage.

There was no specified reference product in this clinical trial. The control treatment in the trial is defined as current practice, which is primary suture and in addition whatever means of dura closure is deemed necessary by the investigator (except of TachoSil treatment). This is noted, since there is no defined gold standard and in current clinical practice several alternatives are applied, e.g. fibrin glue, hydrogel, dura substitute. However, as requested by the 'European guideline on the clinical investigation of plasma derived fibrin sealant/haemostatic products' (CPMP/BPWG/1089/00), the efficacy of fibrin sealant should be investigated in comparison to standard treatment without fibrin sealant to allow for demonstration of haemostatic properties and clinical benefit of the investigational medicinal product.

To avoid selection bias random allocation was performed prior to application of primary dura closing techniques. Reason for this decision was to allow the sandwich technique.

Only adult patients were included in the pivotal study in neurosurgery. The occurrence of clinically evident verified post-operative CSF leaks or a clinically evident pseudomeningocele chosen as part of the primary endpoint are considered adequate to allow an assessment of the efficacy of the dura sealing.

Baseline characteristics were generally similar across the 2 treatment groups based on evaluation of demography, medical history, concomitant illness, concomitant medication, leak rate predictive variables, surgery times and intra-operative variables.

Efficacy data and additional analyses

The results for the primary analysis show that approximately 7% of TachoSil subjects experienced a CSF leak, a pseudomeningocele, or treatment failure during surgery, compared with 8% of control patients. Although the point estimate of the odds of failure in dural sealing was 0.82 compared with current practice (over half of whom received an adjunctive sealing technique), the confidence interval was wide (0.47 to 1.43). The sensitivity analyses for different methods of handling missing data do not change the conclusions from the primary analysis. Regarding the secondary endpoint, non-clinically evident post-operative pseudomeningocele occurred in 3% of subjects in each treatment group, giving an odds ratio of 1.01 (0.43, 2.28).

The results of the additional comparisons of TachoSil treatment and a number of treatment modalities in the Current Practice treatment arm showed that TachoSil prevented more postoperative leak events than any of the subgroups. Values for the reduction in postoperative leak events ranged from 1.53 to 4.75 percentage points at postoperative Week 7 and from 3.12 to 5.35 percentage points at Week 28, corresponding to clinically relevant relative reductions of 20% to 44% and 34% to 47%, respectively. All of these comparisons support the use of TachoSil in neurosurgery to prevent CSF leaks.

For the largest subgroup (Current Practice excluding suturing alone) in the post-hoc analysis, superiority of TachoSil was demonstrated with statistical significance at Week 28 (p=0.050).

In order to increase the statistical power, a meta-analysis of data from TASALL and the published study by Hutter et al was done and carefully discussed. This meta-analysis comparing TachoSil treatment with suturing alone showed statistical superiority of TachoSil with a reduction in leak rate of 5.6 percentage points (95% CI, -11.1%, -0.2%, p=0.035), corresponding to a clinically relevant relative reduction of 43%.

Study TC-2402-038-SP was planned to show a difference in CSF leak or pseudomeningocele rates between TachoSil (8.5%) and the control group (17.0%) with a fixed sample size of 726 patients.

In the Current Practice group, a total of 87 (23.8%) patients received suture alone/suture, 171 (46.8%) patients received sealant and 156 (42.7%) patients received duraplasty.

In the TachoSil group, a total of 241 (66.8%) patients received single layer treatment and 113 (31.3%) patients received sandwich treatment for the first application of TachoSil.

The proportion of patients without clinically evident CSF leak, clinically evident pseudomeningocele or treatment failure in the TachoSil treatment group was not different from the Current Practice treatment group (OR: 0.82, 95% CI: 0.47, 1.43 for the FAS); therefore, TachoSil was not shown to be superior to current practice as an adjunct in sealing the dura mater. The results were supported by the Per-Protocol Analysis Set and sensitivity analyses.

The first analysis of the primary endpoint only includes the verified leaks. However, including the non-verified leaks does not change the picture of a very low number of events in both treatment groups.

Furthermore, the company has presented an additional post hoc analysis which is not based on the original primary endpoint because the MAH has considered any CSF leak is clinically relevant. This method has to be taken into consideration when interpreting this subgroup analysis. The results of this further analysis are not statistically significant except one of twelve subgroup analysis (CP excluding suturing alone). At least, it can be evaluated as a positive signal for treatment efficacy. Moreover, the MAH refers to a clinically relevant relative reduction in all subgroups. But these data are presented without a confidence interval which might a hint to non-significant results. This can only be considered as a positive signal, too. Therefore, Efficacy was not conclusively demonstrated in the TASALL trial.

The company had expected an event rate of 5-6% in the TachoSil group; however they had assumed a much higher (15-20%) event rate in the current practice group than found in this study. The proportion of patients for whom only sutures were used was higher in the TachoSil group than the Current Practice group whereas the proportion of patients for whom suture and duraplasty were used was lower in the TachoSil group than in the Current Practice group. It was discussed that the current practise group was too broad and probably the dura closure was more thorough than in a normal clinical setting. The MAH believes that the main reason for the statistically nonsignificant result is the overestimation of the expected postoperative CSF leak rate. It is accepted that a number of factors leading to a lower event rate in the standard of care arm may have contributed to this, including the use of another supportive method in addition to suturing in a high proportion of patients in the current practice arm. The results in the subgroup of subjects with a gap ≥5 mm (all leak events, TachoSil single layer only) showed a leak event rate of 0% in TachoSil-treated subjects vs 19.4% in control-treated subjects at Weeks 7 and 28. But these are even more nonsignificant results. Nevertheless the overall trend in favour of TachoSil is observed.

The proportion of patients with non-clinically evident pseudomeningocele was not found to be different in the TachoSil group in comparison with the Current Practice group (OR: 1.01, 95% CI: 0.43, 2.36 for the FAS).

Moreover, results of subgroup analysis couldn't show statistically significant difference between the TachoSil and Current Practice groups.

TachoSil was applied during surgery as an adjunct to the closure of the dura, as a single layer or a sandwich (double layer). The subgroup analysis of the primary endpoint showed an estimated OR of 1.07 (95% CI: 0.51, 2.24, P=0.855) for TachoSil sandwich and 0.63 (95% CI: 0.32, 1.25, P=0.1845) for TachoSil single-layer.

Therefore, the proportion of patients treated with double-layer technique was therefore not superior to the single-layer group and is no longer part of this variation, because treatment effect could not been demonstrated.

The use of rescue treatment was very low in both treatment groups (5 [1.4%] patients in each group).

A meta-analysis of data from TASALL and the published study by Hutter et al was done and discussed at an Oral Explanation with the CHMP. This meta-analysis comparing TachoSil treatment with suturing alone showed statistical superiority of TachoSil with a reduction in leak rate of 5.6 percentage points (95% CI, -11.1%, -0.2%, p=0.035), corresponding to a clinically relevant relative reduction of 43%.

In accordance with its design the TASALL study failed to demonstrate superiority of TachoSil over current clinical practice in the claimed indication extension. Despite the failure to demonstrate superiority against control, the argument that the standard of care employed in the study produced a higher than expected success rate. It is acknowledged that the results numerically are in favour for TachoSil and when compared against subgroups, the overall trend in favour of TachoSil is observed. Finally, the previously presented meta-analysis of data from TASALL and the Hutter study showed statistical superiority over suturing alone.

2.4.3. Conclusions on the clinical efficacy

An overall trend in favour of TachoSil when compared against subgroups, is observed in the TASALL study and supported by the presented meta-analysis of data from TASALL and the published Hutter study showing statistical superiority over suturing alone.

2.5. Clinical safety

Introduction

More recent safety data continue to support the clinical use of TachoSil. Since the approval of TachoSil in the European Union, an estimated number of 3,600,000 patients have been exposed to TachoSil until 08 June 2013 under the assumption of an average use of 1 patch for each surgical procedure. Up to 08 June 2013, a total of 261 spontaneously reported ADRs were recorded. A total of 184 ADRs were considered to be serious and 77 were non-serious.

The safety of TachoSil for suture line sealing in dura mater closure is based on the results obtained from neurosurgery Study TC-2402-038-SP.

Patient exposure

In the present study TC-2402-038-SP to support the neurosurgical indication applied for, a total of 726 subjects were randomized to treatment, thereof 362 to TachoSil and 364 to control.

61% of patients required 0.25-1 patches, 33% required .125-2 patches, 4% required 2.25-3 patches, and 2% required 3.25-4 patches. In the TachoSil group, a total of 241 (66.8%) patients received single layer treatment and 113 (31.3%) patients received sandwich treatment for the first application of TachoSil.

Adverse events

Table 9 Summary of Adverse Events (SAF)

	TachoSil (N=362)		Current Practice (N=364)		Total (N=726)	
	n (%)	E	n (%)	E	n (%)	E
Adverse events	250 (69.1)	768	250 (68.7)	781	500 (68.9)	1549
Serious adverse events	94 (26.0)	158	97 (26.6)	183	191 (26.3)	341
Adverse events related to trial treatment	5 (1.4)	9	0	0	5 (0.7)	9
Serious adverse events related to trial treatment	3 (0.8)	5	0	0	3 (0.4)	5
Adverse events related to trial procedure	95 (26.2)	201	85 (23.4)	159	180 (24.8)	360
Serious adverse events related to trial procedure	30 (8.3)	38	23 (6.3)	27	53 (7.3)	65
Not related adverse events	213 (58.8)	564	204 (56.0)	622	417 (57.4)	1186
Mild adverse events	199 (55.0)	397	203 (55.8)	405	402 (55.4)	802
Moderate adverse events	131 (36.2)	237	115 (31.6)	226	246 (33.9)	463
Severe adverse events	80 (22.1)	134	80 (22.0)	150	160 (22.0)	284
Adverse events leading to death	19 (5.2)	19	24 (6.6)	24	43 (5.9)	43
Serious adverse events other than death	83 (22.9)	139	86 (23.6)	159	169 (23.3)	298

E, total number of events; N, number of patients in the SAF; n, number of patients with at least 1 event; SAF, safety analysis set; %, number of patients with at least 1 event as % of the SAF.
Not related adverse events include events not related to either trial treatment or trial procedure.

Adverse events were reported for 250 (69.1%) patients in the TachoSil group and 250 (68.7%) patients in the Current Practice group. The majority of AEs in each treatment group were considered by the Investigator to be not related to trial treatment or trial procedure. In the TachoSil group, AEs considered by the Investigator to be related to trial treatment were reported for 5 (1.4%) patients.

The types and frequencies of AEs were generally similar in the 2 treatment groups. Adverse events were most frequently reported in the nervous system disorders SOC in both treatment groups (152 [42.0%] patients in the TachoSil group and 149 [40.9%] patients in the Current Practice group). The most frequently reported AEs by PT for patients in the TachoSil group were constipation (24 [6.6%] patients), pneumocephalus (21 [5.8%] patients) and hypokalaemia (20 [5.5%] patients). The most frequently reported AEs by PT for patients in the Current Practice group were pneumocephalus (25 [6.9%] patients), pyrexia (24 [6.6%] patients) and hypokalaemia (23 [6.3%] patients). The majority of AEs were considered by the Investigator to be unrelated to trial treatment.

The proportion of patients with severe AEs was similar in the 2 treatment groups, occurring in 80 (22.1%) patients in the TachoSil group and 80 (22.0%) patients in the Current Practice group. The severe AE PTs most frequently reported for patients in the TachoSil group were hydrocephalus (8 [2.2%] patients), VIIth nerve paralysis (6 [1.7%] patients) and pneumonia (5 [1.4%] patients). The severe AE PTs most frequently reported for patients in the Current Practice group were sepsis (6 [1.6% patients]) and hydrocephalus and pneumonia (5 [1.4%] patients each).

The proportion of patients with serious AEs (SAEs) (excluding those that led to death) was similar in the 2 treatment groups. In the TachoSil group the most frequently reported were hydrocephalus (10 [2.8%] patients) and meningitis (5 [1.4%] patients). In the Current Practice group the most frequently reported were hydrocephalus (8 [2.2%] patients) and pneumonia (6 [1.6%] patients). The proportion of patients with

SAEs considered by the Investigator to be related to trial treatment: 3 (0.8%) patients in the TachoSil group and no patient in the Current Practice group.

Table 10 Summary of Adverse Events Reported for ≥5% of Patients in Either Treatment Group (SAF)

System Organ Class Preferred Term	TachoSil (N=362) n (%)	E	Current Practice (N=364) n (%)	E
Gastrointestinal disorders				
Constipation	24 (6.6)	24	12 (3.3)	12
Nausea	19 (5.2)	20	16 (4.4)	18
General disorders and administration site conditions				
Pyrexia	12 (3.3)	12	24 (6.6)	24
Metabolism and nutrition disorders				
Hypokalaemia	20 (5.5)	21	23 (6.3)	24
Nervous system disorders				
Pneumocephalus	21 (5.8)	21	25 (6.9)	26
Vascular disorders				
Hypertension	18 (5.0)	18	20 (5.5)	31

E, total number of events; N, number of patients in the SAF; n, number of patients with at least 1 event; SAF, safety analysis set; %, number of patients with at least 1 event as % of the SAF.
Adverse event terms were coded using the Medical Dictionary for Regulatory Activities, Version 16.0.
If a patient experienced multiple adverse events within the same system organ class, then the patient was listed for each preferred term but was counted only once in the total for that system organ class.

Table 11 Summary of Treatment-Related Adverse Events by Treatment (SAF)

System Organ Class Preferred Term	TachoSil (N=362) n (%)	E	Current Practice (N=364) n (%)	E
Total number of patients with at least 1 treatment-related adverse event	**5 (1.4)**	**9**	**0**	**-**
General disorders and administration site conditions				
Drug effect decreased	1 (0.3)	1	0	-
Infections and infestations				
Mastoiditis	1 (0.3)	1	0	-
Meningitis	1 (0.3)	1	0	-
Sepsis	1 (0.3)	1	0	-
Subdural empyema	1 (0.3)	1	0	
Extradural abscess	1 (0.3)	1	0	-
Nervous system disorders				
Cerebrospinal fluid leakage	1 (0.3)	1	0	-
Sensory loss	1 (0.3)	1	0	-
Vascular disorders				
Air embolism	1 (0.3)	1	0	-

E, total number of events; N, number of patients in the SAF; n, number of patients with at least 1 event; SAF, safety analysis set; %, number of patients with at least 1 event as % of the SAF.
Adverse events with missing relationship to the trial treatment were categorised as related.

In the TachoSil group, overall nine AEs have been considered by the Investigator to be related to trial treatment. The proportion of patients with at least 1 AE considered by the Investigator to be related to trial treatment was low (n=5, 1.4 %). Apart from air embolism, all AEs (i.e. Infections, Nervous system disorders) are considered to be consequences of the surgical procedure and/or the underlying disease. There were no treatment-related AEs reported for patients in the Current Practice group.

Serious adverse events and deaths

Adverse events leading to death were reported for 19 (5.2%) patients in the TachoSil group and 24 (6.6%) patients in the Current Practice group. No AEs leading to death were considered by the Investigator to be related to trial treatment. The AEs leading to death reported for more than 1 patient in the TachoSil group were cardio-respiratory arrest, pneumonia, neoplasm progression and cerebral ischaemia (2 [0.6%] patients each). AE leading to death reported for more than 1 patient in the Current Practice group was sepsis (2 [0.5%] patients).

Serious AEs were reported for 94 (26%) patients in the TachoSil group and 97 (26.6%) patients in the Current Practice group.

In the TachoSil group, SAEs considered to be related to trial treatment were reported for 3 (0.8%) patients. No patients in the Current Practice group experienced SAEs that were considered by the Investigator to be related to trial treatment.

Table 12 Summary of Serious Adverse Events Other than Death Reported in ≥1% of Adult Patients in Either Treatment Group (SAF)

System Organ Class Preferred Term	TachoSil (N=362) n (%)	E	Current Practice (N=364) n (%)	E
Total number of patients with at least 1 SAE other than death	**83 (22.9)**	**139**	**86 (23.6)**	**159**
Blood and lymphatic system disorders				
Anaemia	1 (0.3)	1	4 (1.1)	4
General disorders and administration site conditions				
Pyrexia	0	-	4 (1.1)	4
Infections and infestations				
Meningitis	5 (1.4)	5	3 (0.8)	3
Pneumonia	4 (1.1)	5	6 (1.6)	7
Meningitis aseptic	0	-	4 (1.1)	4
Nervous system disorders				
Hydrocephalus	10 (2.8)	10	8 (2.2)	8
Cerebrospinal fluid leakage	4 (1.1)	4	4 (1.1)	4

E, total number of events; N, number of patients in the SAF; n, number of patients with at least 1 event; SAE, serious adverse event; SAF, safety analysis set; %, number of patients with at least 1 event as % of the SAF.

The majority of SAEs were severe. The proportion of patients with severe SAEs was similar in the 2 treatment groups (63 [17.4%] patients in the TachoSil group and 72 [19.8%] patients in the Current Practice group). Severe SAEs were most frequently reported in the nervous system disorders SOC in both treatment groups (35 [9.7%] patients in the TachoSil group and 34 [9.3%] patients in the Current Practice group). The severe SAE PTs most frequently reported in the TachoSil group were hydrocephalus (8 [2.2%] patients) and pneumonia (5 [1.4%] patients). The severe SAE PTs most frequently reported in the Current Practice group were hydrocephalus, pneumonia and sepsis (5 [1.4%] patients each).

No AE leading to death was considered by the Investigator to be related to trial treatment. The AEs leading to death were assessed by the sponsor to be due to post-operative complications or the patient's underlying disease or general condition.

It is agreed that serious adverse events as observed in the trial might be related to surgical complications and underlying medical conditions.

Laboratory findings

As expected due to the nature of the underlying disease in this patient population, several patients in each treatment group had clinically significant abnormal laboratory test results at certain visits and several patients in each treatment group had AEs related to abnormal laboratory results. Similar proportions of patients in each treatment group experienced AEs in the blood and lymphatic system disorders SOC, which comprised anaemia, thrombocytopenia, leukocytosis, leukopenia and neutropenia; none of these AEs were considered related to trial treatment.

Mean vital sign results (heart rate, systolic and diastolic blood pressure, respiratory rate, body temperature) were similar across both treatment groups and there was little change from Baseline at each time point. Several patients in each treatment group had clinically significant abnormal vital sign results at certain visits and several patients in each treatment group had AEs related to abnormal vital sign results. Similar

proportions of patients in each treatment group experienced AEs of hypertension, hypotension, tachycardia and bradycardia; none of these AEs were considered related to trial treatment.

Clinical laboratory results were generally similar in the 2 treatment groups.

Post marketing experience

The most recent PSUR was submitted to the PRAC on 11 September 2014, and covered the period June 2011 to June 2014. The Rapporteur preliminary assessment report was circulated on 10 November 2014, and the final PRAC assessment report is expected on 8 January 2015. The preliminary conclusion of the PRAC Rapporteur was that no new safety information had arisen during the reporting period which would change the benefit-risk balance for TachoSil.

2.5.1. Discussion on clinical safety

The data obtained from the clinical trial with TC-S indicate no concerns for the safety profile of TC-S when used in neurosurgery to support suture line sealing in dura mater closure. This assessment is supported by the data from studies and postmarketing experience with TachoSil.

In the present study 362 subjects were randomized to treatment with TachoSil and 364 to control. Both treatments were adjunctive to primary suture dura repair.

The most frequent AEs were constipation, pneumocephalus and, which are all commonly associated with this type of surgery. Constipation was more frequently reported in the TachoSil group.

It is agreed that serious adverse events as observed in the trial might be related to surgical complications and underlying medical conditions. No AE leading to death was considered by the Investigator to be related to trial treatment. The AEs leading to death were assessed by the sponsor to be due to post-operative complications or the patient's underlying disease or general condition.

It can be presumed that TachoSil provides a durable dura closure which lasts long enough to enable watertight closure until healing of the dura cut is completed since CSF leaks occur mostly within 30 days postoperatively according to the literature in neurosurgery.

It is not known whether recent radiation therapy affects the efficacy of TachoSil when used for dura mater sealing. This statement has been added under section 4.4. of the SmPC.

Furthermore, a previous statement on lack of data in neurosurgery is now revised following this submission.

2.5.2. Conclusions on clinical safety

TachoSil was found to be well tolerated in the context of the surgical procedures performed, with no evidence of increased frequency of AEs compared with patients treated with current practice. The numbers of AEs and SAEs were equally distributed between treatment groups and the type/nature and level were as expected considering the surgery performed and the patient co-morbidities.

The presented results are considered to be acceptable. There were no safety signals due to the use of TachoSil in neurosurgery procedures.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 6.0 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 6.1 with the following content (new text marked as underlined, deletions marked as strikethrough):

Safety concerns

Summary of safety concerns	
Important identified risks	Thrombotic and embolic events Immunological events including hypersensitivity
Important potential risks	~~Immunological events~~ Transmission of infectious agents Off label use ~~Drug-drug interactions~~ ~~Atrial fibrillation~~ ~~Pyrexia~~
Missing information	Lack of experience ~~in neurosurgery or~~ in gastrointestinal anastomosis surgery Lack of experience in pregnant or lactating women Repeated use of TachoSil

Pharmacovigilance plan

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

~~**Study / Activity Type, Title and Category (1-3)**~~	~~**Objectives**~~	~~**Safety Concerns Addressed**~~	~~**Status (Planned, Started)**~~	~~**Date for Submission of Interim or Final Reports (Planned or Actual)**~~

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
TC-018-IN An international, non-interventional, prospective, single-cohort study of the use of TachoSil in supportive treatment in surgery for improvement of hemostasis where standard techniques are insufficient (PASS, 1)	To collect information on thromboembolic events, immunological events, and drug interactions leading to thrombotic and embolic events or major bleeding	Thrombotic and embolic events, immunological events and drug interactions.	Completed	Final study report July 2008
TC-2402-038-SP A Phase III, openlabel, randomized, controlled, multicenter, parallel group, efficacy and safety trial TachoSil versus current practice in dura sealing techniques for the prevention of postoperative cerebrospinal fluid (CSF) leaks in patients undergoing skull base surgery	To demonstrate superiority of TachoSil compared to current practice as an adjunct in sealing the dura mater.	To support missing information on the use of TachoSil in neurosurgery	Completed	Final study report 20 March 2014

~~Study / Activity Type, Title and Category (1-3)~~	~~Objectives~~	~~Safety Concerns Addressed~~	~~Status (Planned, Started)~~	~~Date for Submission of Interim or Final Reports (Planned or Actual)~~
~~TC-2402-040-SP~~ ~~A randomized, open-label, controlled, parallelgroup, multicenter therapeutic confirmatory trial comparing TachoSil with Surgicel Original for the secondary treatment of local hemorrhage from the hepatic resection wound in adult and paediatric patients~~	~~Study objective:~~ ~~To compare the efficacy and safety of TachoSil as secondary hemostatic treatment in hepatic resection surgery to the standard US licensed hemostatic agent, Surgicel Original.~~ ~~Immunogenicity long-term safety follow-up objective:~~ ~~To assess immunogenicity results obtained in trial TC-2402-040 and to understand the clinical impact of the immunogenicity findings.~~	~~Immunological events and pyrexia (Potential risk)~~	~~Completed~~	~~Final study report submitted on 27 February 2014. Immunogenicity addendum submitted on 10 February 2015.~~

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Thrombotic and Embolic Events	Current approved SmPC: **4.2 Posology and method of administration** The use of TachoSil is restricted to experienced surgeons. **4.4 Special warnings and precautions for use** For local use only. Do not use intravascularly. Life threatening thromboembolic complications may occur if the preparation is applied intravascularly. **4.8 Undesirable effects, *Vascular disorders:*** Thromboembolic complications may occur if the preparation is	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	applied intravascularly.	
Immunological events including hypersensitivity	Current approved SmPC: **4.3 Contraindications** Hypersensitivity to the active substances or to any of the excipients. **4.4 Special warnings and precautions for use** As with any protein product, allergic type hypersensitivity reactions are possible. Signs of hypersensitivity reactions include hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. If these symptoms occur, the administration has to be discontinued immediately. In case of shock, the current medical standards for shock treatment should be observed. **4.8 Undesirable effects, *Immune system disorders:*** Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the application site, bronchospasm, chills, flushing, generalized urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) may occur in rare cases in patients treated with fibrin sealants/haemostatics. In isolated cases, these reactions may progress to severe anaphylaxis. Such reactions may especially be seen, if the preparation is applied repeatedly, or administered to patients known to be hypersensitive to constituents of the product. ***Investigations:*** Antibodies against components of fibrin sealant/haemostatic products may occur rarely.	None proposed.
Transmission of infectious agents	Current approved SmPC: **4.4 Special warnings and precautions for use** Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV and for the non-enveloped virus HAV.	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	The measures taken may be of limited value against nonenveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g., haemolytic anaemia). It is strongly recommended that every time that TachoSil is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.	
~~Drug-drug interactions~~	~~Current approved SmPC:~~ ~~**4.5 Interactions with other medicinal products and other forms of interactions**~~ ~~No formal interaction studies have been performed. Similar to comparable products or thrombin solutions, the sealant may be denaturated after exposure to solutions containing alcohol, iodine or heavy metals (e.g. antiseptic solutions). Such substances should be removed to the greatest possible extent before applying the sealant.~~	~~None proposed.~~
~~Atrial fibrillation~~	~~Please refer to section regarding thromboembolic events.~~	~~None proposed.~~
~~Pyrexia~~	~~Current approved SmPC:~~ ~~**4.8 Undesirable effects**~~ ~~General disorders and administration site condition: Pyrexia may occur commonly.~~	~~None proposed.~~
Off-label use (sealing)	Current approved SmPC: **4.1 Therapeutic indications** TachoSil is indicated in adults for supportive treatment in surgery for improvement of haemostasis, to promote tissue sealing, for suture support in vascular surgery where standard techniques are insufficient, and for supportive sealing of the dura mater to prevent postoperative cerebrospinal leakage following neurological surgery. **4.2 Posology and method of administration** Paediatric patients: TachoSil is not recommended for use in children below age 18 years due to insufficient data on safety and efficacy. **4.4 Special warnings and precautions for use** Specific data have not been obtained on the use of this product in neurosurgery or in gastrointestinal anastomoses [sic] surgery.	None proposed.
Lack of experience ~~in neurosurgery or~~	Current approved SmPC: **4.4 Special warnings and precautions for use**	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
in gastrointestinal anastomosis surgery	Specific data have not been obtained on the use of this product ~~in neurosurgery or~~ in gastrointestinal anastomoses [sic] surgery.	
Lack of experience in pregnant or lactating women	Current approved SmPC: **4.6 Pregnancy and lactation** The safety of TachoSil for use in human pregnancy or breastfeeding has not been established in controlled clinical trials. Experimental animal studies are insufficient to assess the safety with respect to reproduction, development of the embryo or foetus, the course of gestation and peri- and postnatal development. Therefore, TachoSil should be administered to pregnant and lactating women only if clearly needed.	None proposed.
Repeated use of TachoSil	Current approved SmPC: **4.3 Contraindications** Hypersensitivity to the active substances or to any of the excipients. **4.4 Special warnings and precautions for use** As with any protein product, allergic type hypersensitivity reactions are possible. Signs of hypersensitivity reactions include hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. If these symptoms occur, the administration has to be discontinued immediately. In case of shock, the current medical standards for shock treatment should be observed. **4.8 Undesirable effects *Immune system disorders:*** Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the application site, bronchospasm, chills, flushing, generalized urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) may occur in rare cases in patients treated with fibrin sealants/ haemostatics. In isolated cases, these reactions may progress to severe anaphylaxis. Such reactions may especially be seen, if the preparation is applied repeatedly, or administered to patients known to be hypersensitive to constituents of the product. ***Investigations:*** Antibodies against components of fibrin sealant/ haemostatic products may occur rarely.	None proposed.

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

2.7. Update of the Product information

As a consequence, sections 4.1, 4.4, 5.1 and 6.6 of the SmPC are being updated. The MAH also took the opportunity to make minor editorial corrections to the SmPC.

2.7.1. User consultation

Not applicable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The study was designed as an open-label, randomized, controlled, parallel-group, multicenter, phase 3 (therapeutic confirmatory) study comparing TachoSil versus Current Practice as an adjunct in sealing the dura mater.

Study TC-2402-038-SP was planned to show a difference in CSF leak or pseudomeningocele rates between TachoSil (8.5%) and the control group (17.0%) with a fixed sample size of 726 patients. 362 patients were randomised to treatment with TachoSil, which was applied over the suture line in a single layer, or as a double sandwich layer, inside and outside of the dura, where a sufficient overlap of the suture line was not possible with a single layer application. 364 control patients were randomised to best standard of care, at the discretion of the Investigator (eg, duraplasty, fibrin/polymer sealant, sutures alone, etc.).

The use of a broad range of standard of care treatments in the control group was appropriate since there is no gold standard treatment, and since there were ethical concerns with restricting control subjects to sutures alone when CSF leakage has been shown to occur in almost 20% of cases. Together with this, the eligibility criteria were broad, and included those with previous local radiotherapy, which may predispose to CSF leakage. The results for the primary analysis show that approximately 7% of TachoSil subjects experienced a CSF leak, a pseudomeningocele, or treatment failure during surgery, compared with 8% of control patients. Although the point estimate of the odds of failure in dural sealing was 0.82 compared with current practice (over half of whom received an adjunctive sealing technique), the confidence interval was wide (0.47 to 1.43). The sensitivity analyses for different methods of handling missing data do not change the conclusions from the primary analysis. Regarding the secondary endpoint, non-clinically evident post-operative pseudomeningocele occurred in 3% of subjects in each treatment group, giving an odds ratio of 1.01 (0.43, 2.28).

The results of the additional comparisons of TachoSil treatment and a number of treatment modalities in the Current Practice treatment arm showed that TachoSil prevented more postoperative leak events than any of the subgroups. Values for the reduction in postoperative leak events ranged from 1.53 to 4.75 percentage points at postoperative Week 7 and from 3.12 to 5.35 percentage points at Week 28, corresponding to clinically relevant relative reductions of 20% to 44% and 34% to 47%, respectively. All of these comparisons support the use of TachoSil in neurosurgery to prevent CSF leaks.

For the largest subgroup (Current Practice excluding suturing alone) in the post-hoc analysis, superiority of TachoSil was demonstrated with statistical significance at Week 28 (p=0.050).

In order to increase the statistical power, a meta-analysis of data from TASALL and the published study by Hutter et al was done and carefully discussed. This meta-analysis comparing TachoSil treatment with suturing alone showed statistical superiority of TachoSil with a reduction in leak rate of 5.6 percentage points (95% CI, -11.1%, -0.2%, p=0.035), corresponding to a clinically relevant relative reduction of 43%.

Uncertainty in the knowledge about the beneficial effects

The non-clinical data are rather limited, especially in regard to the longer term effect of TachoSil in neurosurgical procedures and the potential for adhesions. However, data from the clinical studies, in which subjects were followed up for 6 months, did not reveal any issues in regard to neurotoxicity.

Methodological issues which led to the failure of the trial to prove superiority have been adequately explained. Further analyses into the data and meta-analysis the results of a published trial showed the efficacy of TachoSil in the final agreed indication. The result of the meta-analysis showed statistical superiority of TachoSil although neither the TASALL study nor the study by Hutter demonstrate a statistically significant treatment effect on their own.

Risks

Unfavourable effects

The data obtained from the clinical trial with TC-S indicate no concerns for the safety profile of TC-S when used in neurosurgery to support suture line sealing in dura mater closure. This assessment is supported by the data from studies and postmarketing experience with TachoSil.

The clinical safety of TachoSil for use in surgical haemostasis has been demonstrated in a range of clinical studies in lung, liver, kidney and cardiovascular surgery. In addition, there is a large amount of post-marketing experience for TachoSil in surgical procedures, and the most recent PSUR, covering June 2011 to June 2014, has just been submitted. Only three adverse drug reactions are listed in the SmPC, pyrexia, hypersensitivity, and thromboembolism (if inadvertently applied intravascularly).

The total number of postoperative complications was fewer in the TachoSil group than the Current Practice/Control group (5.2% and 6.3%), ie, meningitis, empyema, and hematomas and the TASALL study has shown a lower frequency for more serious interventions, ie, hospital readmission, surgical revision/reoperation due to leak events in the TachoSil group.

Uncertainty in the knowledge about the unfavourable effects

The non-clinical data are limited, especially in regard to the longer term effect of TachoSil in neurosurgical procedures and the potential for adhesions. Clinical research into the absorption of and potential tissue reactions to TachoSil in humans is limited due to ethical reasons, since it would involve repeat intervention with open or laparoscopic surgery for follow-up observation and/or to take a biopsy sample for histological examination.

However no issues have been reported from the extensive post marketing experience so far.

Effects Table for TachoSil EMEA/H/C/505/II/57

	Effect	Short Description	Unit	Placebo/Comparator	Tachosil	Uncertainties/ Strength of evidence	References
Favourable	Efficacy of TachoSil as an adjunct in sealing the dura mater	Difference in CSF leak or pseudomeningocele rates between TachoSil (8.5%) and the control group (17.0%)	%	8,2% (n/N=30/365), Standard dura closing techniques alone or in combination (medicinal products/medical devices to seal the dura, including fibrin sealants, polymer sealants, any artificial dura substitutes)	6,9% (n/N=25/361)	Primary analysis: estimated OR of 0.82 (95% CI:0,47; 1,43; p=0,485), No statistically significant difference between treatments could be concluded. Results numerically in favour for TachoSil. Meta-analysis showed statistical superiority.	2.4.2 Response to 2nd and 3rd RSI
		Treatment effect in subgroup of subjects with gap ⩾5 mm at weeks 7 and 28		19,4%	0%	Nonsignificant results. Estimated OR of 0,14 (95% CI:0; 1,29; p=0,181)	
	Efficacy of TachoSil used as single layer or double layer	Sandwich technique: first layer inside of dura, second layer outside of dura after primary suture or duraplasty	%	8.2% (n/N=30/365)	Double layer: 10.5% (n/N=12/114) Single layer: 5,3% (n/N=13/247)	OR of 1.07 (95% CI:0.51; 2.24; p=0.86) OR of 0.63 (95% CI:0.32; 1.25; p=0.18) No support for use of double layer.	Response to 2nd RSI

	Effect	Short Description	Unit	Placebo / Comparator	Tachosil	Uncertainties / Strength of evidence	References
Unfavourable	Stability/resorption of the layer	Possibility of patch remnants, adhesions, neurotoxicity and local tolerance following dural application.				Non-clinical data limited in regard to longer term effect in neurosurgery. Clinical data, followed up for 6 months did not reveal any issues in regard to neurotoxicity.	2.2
	Postoperative complications of CSF leakage	Meningitis, Empyema, Hematoma		17 subjects; 3.5%	8 subjects; 1.7%	Reduction of postoperative complications compared to control group; Supported by results of Hutter study	Response to 3rd RSI

Benefit-Risk Balance

Importance of favourable and unfavourable effects

It is accepted that there is a need for watertight sealing of the dura mater after neurosurgical procedures, in order to prevent CSF leaks and consequent postoperative morbidity due to surgical site infections, meningitis, pneumocephalus and meningocerebral adhesions. Standard closure techniques, such as use of sutures only, have been associated with post-operative leakage in around a fifth of patients. Other techniques, such as grafting of fat, fascia, muscle, or use of fibrin/polymer sealant products have been shown effective in reducing the intra- and post-operative leakage rate.

In the TASALL trial, although the leakage rate in treated patients was low (7%), the leakage rate in control patients, who could receive any available therapy at the discretion of the Investigator, and who may consequently have been over-treated, was also low (8%). The study therefore failed to demonstrate the superiority of TachoSil over current practice. But it is accepted that a number of factors leading to a lower event rate in the standard of care arm may have contributed to this, including the use of another supportive method in addition to suturing in a high proportion of patients in the current practice arm. The results for the analysis in the subgroup of subjects with a gap ≥5 mm showed a leak event rate of 0% in TachoSil-treated subjects vs 19.4% in control-treated subjects at Weeks 7 and 28. But these are even more nonsignificant results. Nevertheless the overall trend in favour of TachoSil is observed.

In patients treated with the double-layer technique no treatment effect could be demonstrated. Therefore sandwich application is no longer part of this variation.

The safety of TachoSil in neurosurgical procedures appears acceptable, and comparable with the known safety in other surgical procedures. There were no signals of specific events occurring disproportionately in treated patients compared with control patients.

Benefit-risk balance

Overall, the potential clinical benefit for use in suture line sealing in dura mater closure where standard techniques are insufficient are considered to outweigh any unfavourable effect and so the current benefit-risk balance of TachoSil in the claimed indication is considered to be positive.

Discussion on the Benefit-Risk Balance

The purpose of this application was to present data in support of the safety and efficacy of TachoSil for supportive sealing of the dura mater to prevent postoperative cerebrospinal leakage following neurological surgery based on the results obtained from neurosurgery Study TC-2402-038-SP.

An incomplete sealing of the dura mater intraoperatively implies a risk of developing substantial postoperative complications such as a pseudomeningocele or worse: a fistula leading to postoperative cerebrospinal fluid (CSF) leakage presenting as rhinorrhea, otorrhea and/or a CSF leak through the surgical skin incision.

Considering efficacy, taking all data together, in accordance with its design the TASALL study failed to demonstrate superiority of TachoSil over current clinical practice in the claimed indication extension. Despite the failure to demonstrate superiority against control, as it appears that the standard of care employed in the study produced a higher than expected success rate. It is acknowledged that the results numerically are in favour for TachoSil and when compared against subgroups, the overall trend in favour of TachoSil is observed. Finally, the previously presented meta-analysis of data from TASALL and the Hutter study showed statistical superiority over suturing alone.

TachoSil was found to be well tolerated in the context of the surgical procedures performed, with no evidence of increased frequency of AEs compared with patients treated with current practice. The numbers of AEs and SAEs were equally distributed between treatment groups and the type/nature and level were as expected considering the surgery performed and the patient co-morbidities.

Moreover, the study presented a lower frequency of postoperative complications of CSF leakage including meningitis, empyema and hematoma in the TachoSil group compared with the control groups. This overall trend of reduction of postoperative complications of CSF leaks is supported. Therefore, this data indicates a favourable effect for TachoSil in neurosurgery.

Overall, the potential clinical benefit for use in suture line sealing in dura mater closure where standard techniques are insufficient are considered to outweigh any unfavourable effect and so the current benefit-risk balance of TachoSil in the claimed indication is considered to be positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I

Extension of indication to add the use of TachoSil for supportive sealing of the dura mater to prevent postoperative cerebrospinal leakage following neurological surgery. As a consequence, sections 4.1, 4.4, and 5.1 of the SmPC have been updated. The MAH also took the opportunity to make minor editorial corrections to the SmPC. An updated RMP version 6.1 was agreed during the procedure.

The variation leads to amendments to the Summary of Product Characteristics and to the Risk Management Plan (RMP).