PasTel Information

Study Title	**Post-Authorisation Safety Study (PASS) TachoSil Evaluation (PasTel): Short- and long-term safety evaluation of TachoSil in paediatric population**
Study abbreviation	PasTel
Protocol version identifier	2.2
Date of current version of protocol	30 October 2025
HMA-EMA RWD Catalogue number	EUPAS1000000505
Active substance	Human thrombin / Human fibrinogen; ATC code: B02BC30
Medicinal product	TachoSil
Product reference	EMEA/H/C/000505
Procedure number	EMA/PAM/0000247840
Marketing authorisation holder(s)	Corza Medical GmbH
Joint PASS	No
Research question and objectives	The main purpose of the observational study is to collect long-term safety data on the use of fibrin sealant TachoSil during surgical procedures in paediatric population and to estimate the frequency of adverse reactions over a period of time, extending beyond TachoSil exposure, in a paediatric population of subjects who have been exposed to TachoSil. The study also aims to generate new data to confirm short-term safety of TachoSil in paediatric patients within already approved indication. ***Primary endpoint:*** 1. The proportion of subjects experiencing clinically significant local reactions including abscesses, hematoma formation or foreign body granuloma formulation, at the site of TachoSil application from the start of surgery up to 36 months post-surgery, as detected through routine imaging examinations (X-ray, ultrasound, CT, MRI or intraoperative detection or physical examination). Clinically significant reactions are defined as those that require surgical re-intervention (e.g., relaparotomy, re-laparoscopy) and/or medical treatment due to signs and symptoms, as well as an impairment of organ function, which can be attributed to the product, local application changes at the site of product application noted during surgery or limitation or impairment of organ function noted during physical examination, reported by the patient or detected by abnormal imaging findings.

	***Secondary endpoints*:** 1. The proportion of subjects experiencing clinically significant tissue adhesions detected from the start of surgery up to 36 months post-surgery, as detected through routine imaging tests such as X-ray, ultrasound, computed tomography, magnetic resonance imaging or relaparotomy or intraoperative detection or physical examination Clinically significant reactions are defined as those that, in the investigator's opinion, require surgical re-intervention (e.g., relaparotomy, re-laparoscopy) and/or medical treatment due to signs and symptoms, as well as an impairment of organ function, which can be attributed to the product, local application changes at the site of product application noted during surgery or limitation or impairment of organ function noted during physical examination, reported by the patient or detected by abnormal imaging findings . 2. Proportion of subjects experiencing at least one AESI during the perioperative period (from start of surgery until hospital discharge): • Thrombotic and embolic events • Postoperative bleeding at surgical site and at the site of application of the investigational medicinal product • Allergic reactions / Immediate hypersensitivity reactions • Other surgical related infections at the site of application of the investigational medicinal product 3. Proportion of subjects experiencing at least one AE related to the use of the study product in the period from the start of surgery up to 36 months post-surgery.
Country(-ies) of study	Poland
Author	Mirosław Kocięcki, MD, Medical Director, Corza Medical

Marketing Authorisation Holder(s)

Marketing authorisation holder(s)	Corza Medical GmbH
MAH contact person	Mirosław Kocięcki, MD, Medical Director Miroslaw.Kociecki@corza.com

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MAH/Sponsor's signature and date

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical (code)
AEs	Adverse Events
AESI(s)	Adverse Event(s) of Special Interest
APTT	Activated Partial Thromboplastin Time
CRF(s)	Case Report Form(s)
CRP	C-Reactive Protein
CT	Computed Tomography
ECC	Extra Corporeal Circulation
ECMO	Extra Corporeal Membrane Oxygenation
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
ICD	International Classification of Diseases
ICSR(s)	Individual Case Safety Report(s)
INR	International Normalized Ratio
LTFU	Loss-to-follow-up
MiECC	Minimized Systems for Extracorporeal Circulation
MRI	Magnetic Resonance Imaging
PAS	Post-Authorisation Studies
PASS	Post-Authorisation Safety Study
PI	Principal Investigator
PT	Preferred Term
Q	Quarter
SIN	Study Identification Number
SAS	Safety Analysis Set
SAE(s)	Serious Adverse Event(s)
SIN(s)	Study Identification Number(s)
SOC	System Organ Class
SOPs	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBC	To Be Confirmed
TBD	To Be Determined
TEAE(s)	Treatment-Emergent Adverse Event(s)
US	United States
WHO	World Health Organisation
X-ray	Electromagnetic radiation of a short wavelength

3. RESPONSIBLE PARTIES

The main responsible parties are presented in Table 1.

Table 1 List of all main responsible parties

Responsible Party	Name and Affiliation
Sponsor	Corza Medical GmbH Bleicherweg 10 CH-8002 Zürich Switzerland.
Approx. 4 sites (or more, if required) will conduct the Study. Initially planned sites are listed below. Current version of selected Sites will be available in Study Documents	
Study site #1 Principal Investigator(s)	Department of Paediatric Surgery and Organ Transplantation, Instytut "Pomnik - Centrum Zdrowia Dziecka", av. Dzieci Polskich 20, 04-730 Warsaw, Poland PI: Head of the Clinic: Prof. Piotr Kaliciński.
Study site #2 Principal Investigator(s)	Department of Cardiac Surgery and Intensive Cardiac Care University Children's Hospital in Krakow Str. Wielicka 265, 30-663 Kraków, Poland PI: Head of Department Prof. Tomasz Mroczek.
Study site #3 Principal Investigator(s)	Clinical Department of Cardiothoracic and Pediatric Surgery UNIVERSITY CLINICAL CENTER OF THE MEDICAL UNIVERSITY OF WARSAW Str. Żwirki i Wigury 63A, 02-091 Warsaw, Poland PI: Head of the Clinical Department Prof. Mariusz Kuśmierczyk.
Study site #4 **Study** Principal Investigator(s)	Department and Clinic of Paediatric and Adolescent Surgery and Urology, University Clinical Center Dębinki Street 7; 80-952 Gdańsk, Head of the Clinic: **Prof. Piotr Czauderna.**
Pharmacovigilance	ICON Clinical Research SRL Sky Tower, 8th Floor, 400511, 246C Calea Floreasca st, Bucharest, Romania.
CRO	Biostat sp. z o.o. str. Kowalczyka 17, 44-206 Rybnik, Poland NIP: 6423125404

4. INVESTIGATOR SIGNATURE PAGE

Protocol: PasTel, ver. 2.2

Tiltle: Post-Authorisation Safety Study (PASS); TachoSil Evaluation (PasTel): Short- and long-term safety evaluation of TachoSil in paediatric population

I understand that all documentation provided to me by the Sponsor or individuals designated by the Sponsor related to this study, which has not been previously published, will be kept strictly confidential. This documentation includes the Study Protocol, Case Report Form, and other scientific data.

This study will not commence without prior written approval from the relevant Bioethics Committee and the Office for Registration of Medicinal Products, Medical Devices, and Biocidal Products (URPL). No changes to the study protocol will be implemented without prior written consent from the Sponsor, the Bioethics Committee, and the URPL, except when necessary to eliminate an immediate hazard to the patients.

I declare that the study will be conducted in accordance with the Study Protocol, ICH GCP, and applicable legal regulations.

I have read and agree to comply with all terms and instructions contained in this protocol.

Principal Investigator

.....

Site Details

.....

Name surname:

.....

Signature:

.....

Date (Day/Month/Year):

.....

5. ABSTRACT

Title

Post-Authorisation Safety Study (PASS); TachoSil Evaluation (PasTel): Short- and long-term safety evaluation of TachoSil in paediatric population

Protocol version and date	2.2 dated 30.10.2025
Author	Mirosław Kocięcki, MD, Medical Director, Corza Medical

Rationale and background

TachoSil is a surgical patch designed to assist with stopping bleeding and sealing tissues during surgery and for suture support in vascular surgery where standard techniques are insufficient. It is composed of a collagen carrier coated with human fibrinogen and thrombin, which are applied directly to the wound surface. TachoSil has received regulatory approval in 71 countries and has been used since June 2004 for various purposes, including improving haemostasis, sealing tissues, providing suture support in vascular surgery, and preventing cerebrospinal leakage following neurological surgery. In 2010, it was also approved in the United States as an adjunct for haemostasis when standard techniques are ineffective; and in 2015, the approval was extended to include paediatric patients undergoing hepatic surgery based on two studies.

Although the effectiveness of TachoSil in achieving haemostasis appears similar between the adult and paediatric populations, the sample size of paediatric patients was small. As a result, the confidence interval for the point estimate was wide, and there was no statistical comparison between the populations. Consequently, these results were insufficient to support the registration of TachoSil for paediatric use in the European Union. Further evaluation was deemed necessary, leading to the approval of TachoSil for paediatric patients through an extrapolation approach based on relevant guidelines. During the development of the extrapolation concept, certain gaps in knowledge regarding the long-term effects of TachoSil in paediatric patients were identified. However, it was determined that the missing data could be collected through a Post-Authorisation Safety Study (PASS), given the estimated low risk of long-term effects in paediatric patients, based on the currently available data. The PASS will help address the identified gaps and provide additional information on the safety of TachoSil in the paediatric population when used in line with recently approved therapeutic indications.

Research question and objectives

The study aims to evaluate both short- and long-term safety effects of TachoSil application in paediatric patients undergoing cardiovascular, hepatic or other solid organs surgery, as well as those with injuries of blood vessels, parenchymal organs, lungs requiring the use of drugs for local haemostasis, tissue sealing, and suture support in vascular surgery where standard techniques are insufficient. Those safety effects are to be addressed in a prospective, multicentre, non-interventional, uncontrolled, observational, post-authorisation cohort study.

The main purpose of this observational study is to collect long-term or delayed safety data on the use of fibrin sealant TachoSil during surgical procedures in paediatric population, and to

estimate the frequency of adverse reactions over a period of time, extending beyond TachoSil exposure.
The study also aims to generate new data to confirm short-term safety of TachoSil in paediatric patients.

Primary endpoint:

1. The proportion of subjects experiencing clinically significant local reactions including abscesses, hematoma formation or foreign body granuloma formulation, at the site of TachoSil application from the start of surgery up to 36 months post-surgery, as detected through routine imaging examinations (X-ray, ultrasound, CT, MRI or intraoperative detection or physical examination).

Clinically significant reactions are defined as those that, in the investigator's opinion, require surgical re-intervention (e.g., relaparotomy, re-laparoscopy) and/or medical treatment due to signs and symptoms, as well as an impairment of organ function, which can be attributed to the product, local application changes at the site of product application noted during surgery or limitation or impairment of organ function noted during physical examination, reported by the patient or detected by abnormal imaging findings .

***Secondary endpoints*:**

1. The proportion of subjects experiencing clinically significant tissue adhesions detected from the start of surgery up to 36 months post-surgery, as detected through routine imaging tests such as X-ray, ultrasound, computed tomography, magnetic resonance imaging or relaparotomy or intraoperative detection or physical examination.

Clinically significant reactions are defined as those that, in the investigator's opinion, require surgical re-intervention (e.g., relaparotomy, re-laparoscopy) and/or medical treatment due to signs and symptoms, as well as an impairment of organ function, which can be attributed to the product, local application changes at the site of product application noted during surgery or limitation or impairment of organ function noted during physical examination, reported by the patient or detected by abnormal imaging findings .

2. Proportion of subjects experiencing at least one AESI during the perioperative period (from start of surgery until hospital discharge):
    - Thrombotic and embolic events
    - Postoperative bleeding at surgical site and at the site of application of the investigational medicinal product
    - Allergic reactions / Immediate hypersensitivity reactions
    - Other surgical related infections at the site of application of the investigational medicinal product

3. Proportion of subjects experiencing at least one AE related to the use of the study product in the period from the start of surgery up to 36 months post-surgery.

Study design

This is a prospective, multicentre, non-interventional, uncontrolled, observational, post-authorisation cohort study.

Population and Inclusion/Exclusion Criteria

Inclusion/Exclusion criteria

The study population covers paediatric patients undergoing a cardiovascular, hepatic or other solid organs surgery, and polytrauma patients with injuries of blood vessels, parenchymal organs, lungs requiring the use of drugs for local haemostasis, tissue sealing when control of bleeding by standard surgical techniques (such as suture, ligature, clips or cautery) appeared to be ineffective or impractical (secondary haemostatic treatment).

Data will be collected from the following age groups:

- Infants and toddlers (>= 28 days - < 2 years) on the day of signing the ICF
- Children (>=2 years – < 12 years) on the day of signing the ICF
- Adolescents (>=12 years – less than 15 years) on the day of signing the ICF

Inclusion criteria

The following individuals are eligible to participate:

- Patients aged from >=28 days to < 15 years on the day of signing the ICF.

Important Note: According to legal regulations in Poland, patients who are 18 years of age or older cannot be treated by paediatric surgeons. Therefore, only patients who are under 18 years of age by the end of the observation period will be included in the study.

- Patients who have planned a cardiovascular, hepatic or other solid organs surgery and polytrauma patients with injuries of blood vessels, parenchymal organs, lungs qualified for elective surgery
- Patients planned to have at least one TachoSil matrix applied (intraoperatively) and without the plan of application of any other products for local haemostasis at the place of TachoSil application will be qualified for the study.

Exclusion Criteria

The following individuals are not eligible to participate:

- they have known, recognized earlier congenital disorders of haemostasis such as haemophilia type A, B,C, Marfan syndrome, Rendu-Osler-Weber disease, congenital thrombocytopathies, e.g. Glanzmann's thrombasthenia, von Willebrand disease type 1,2,3, Fanconi’s anaemia.
- they have experienced severe coagulopathy defined as: INR >2.0, platelet count (PLT)<50 000 / mm3; APTT>60 seconds in the period from 7 days before to the day of surgery.
- they are hypersensitive to the active substance(s) or to any of the product excipients.

- female patients of childbearing potential: they are pregnant or want to become pregnant or those who do not use sufficient methods of contraception such as contraceptive implant, intrauterine coil and oral hormonal contraception.
- The patient who, in the investigator's opinion, presents a known risk of being lost to follow-up during the 36-month follow-up period, based on the screening assessment.

Variables

The following core data elements are to be included in the study database: demographic data, underlying disease/type of surgery, co-morbidities, treatment-related data, relevant concomitant therapies, vital signs and laboratory values routinely performed by the site (such as blood count, C-reactive protein [CRP], International Normalized Ratio[INR], Activated Partial Thromboplastin Time [APTT], adverse events of special interest (AESIs) and other adverse events recorded during perioperative period and follow-up data.

Data sources

Variables collected for the purpose of the study will be re-transcribed from existing electronic or paper medical records maintained at site. The PasTel study involves primary data collection in which the data collected are derived from routine clinical care. Whenever the recruitment or follow-up activities of these patients, aimed to evaluate the use and safety of TachoSil exposure, falls outside of normal routine activities at study site, required data will be additionally collected by the participating study site personnel, and added to the case report forms (CRF).

Study size

Based on feasibility assessments, approximately 66 patients are expected to qualify for the study and undergo surgery. All patients who undergo surgery will be included in the analysis. An anticipated dropout rate is 10%.

Data analysis

All analyses will be performed for the study population, which will comprise all enrolled subjects who received at least 1 application of TachoSil. Study endpoints will be summarized by descriptive statistics. For primary and secondary endpoints, rate of occurrence and cumulative incidence of AEs and AESIs will be determined. Descriptive statistics may include specifically, but not exclusively, arithmetic mean, medians, standard deviations, proportions, frequency counts and 25^{th} and 75^{th} percentiles. Where applicable, 95% confidence intervals of select point estimates will be determined. Figures will be prepared to illustrate the patterns of data over time where appropriate. The number of subjects included in each analysis set will be reported. The exact methodology for statistical analysis will be detailed in the Statistical Analysis Plan (SAP).

Milestones

Milestone	Planned date
HMA-EMA RWD Catalogue number: EUPAS1000000505	Mar2025
Start of data collection	3Q 2026
End of data collection	3Q 2030
Annual study progress report/PSUR	3Q2027, 3Q2028, 3Q2029, 3Q2030
EMEA Interim study report	3Q 2028

Final report of study results	1Q 2031

6. AMENDMENTS AND UPDATES

Amendments and Updates included in PasTel Study Protocol version 2.2 dated 30.10.2025

- The HMA-EMA RWD Catalogue number (EUPAS1000000505) has been added in the protocol, under 'PasTel Information'.
- INVESTIGATOR SIGNATURE PAGE has been updated to Protocol ver.2.2.
- The Abstract has been updated with the protocol version and date, authors information, and milestones.
- The Milestones section has been adjusted with the updated dates.
- The Rationale and Background section has been updated by moving the recommendation for TachoSil application from the Variables section.
- The sections Study Design, Variables, and Data Analysis have been updated by adding 'treatment' to the list of data for AE and AESI analysis.
- A comma between 'product' and 'local' was added in the definition of 'Clinically significant reactions'.
- The Settings section has been updated by adding the note: 'in emergency situation that requires acute surgery with TachoSil application, obtaining informed consent and including the patient in the study after surgery may be considered, if legal and ethical requirements are met'
- Inclusion criteria: 'Patients aged from >=28 days to < 15 years at screening' has been updated to 'Patients aged from >=28 days to < 15 years at the day of signing the ICF'.
- In the Variables section, the evaluation of Adverse Events (AEs) and Adverse Events of Special Interest (AESIs) has been updated to include the evaluation of treatment in relation to these AEs/AESIs.
- The paragraph 'For underlying diseases and comorbidities […] the incidence and cumulative incidence of adverse events and adverse drug events will be determined' has been deleted from Data sources.
- The Variables section has been updated with data regarding the wound and application: The wound condition and application of the TachoSil matrix will be assessed and collected. The following wound data will be assessed and collected: wound location, amount of blood in the wound assessed by the surgeon. The following TachoSil matrix data will be collected: TachoSil matrix size, and application method (dry, pre-moistened).

Amendments and Updates included in PasTel Study Protocol version 2.1 dated 18.06.2025:

- Active substance, Medicinal product, Product reference at PasTel Information Table were updated with appropriate information (ATC code: B02BC30/ EMEA/H/C/000505)
- An indication in 'Research question and objectives' was changed from 'proposed indication' to 'already approved indication'.
- The primary and secondary endpoints and objectives were amended with: 'or intraoperative detection or physical examination'.
- 'Clinically significant reactions' definition was extended and clarified.

- Milestones(10.7): Justifications have been provided for the submission of a revised study protocol resulting in a postponement of the study start.
- Table 2 for Milestones (10.7) was updated with HMA-EMA RWD Catalogue number and the first study progress report (Q4 2025) was deleted, additionally other dates were adjusted according to new version of study protocol approval requirements.
- Study Design (10.01) and Data Analysis (10.08) were amended with information that Time to onset (TTO), duration, severity, outcome and relatedness to TachoSil will be analyzed for reported AEs and AESI.
- PasTel Study data collection (10.3) - Co-morbidities were amended with their evaluation for the assessment of adverse events (AEs / AESI) and the assessment was extended to all projected visits
- PasTel Study data collection (10.3) - Vital Signs and Laboratory results - the assessment was extended to all projected visits
- Data Management (10.7) was amended with clarification of the tasks and responsibilities of entities involved in conducting the study.
- AE/AR reporting provisions were updated (12.0). The study will use eCRF as the primary method for reporting adverse events.

Amendments and Updates included in PasTel Study Protocol version 2.0 dated 23.01.2025:

- Table of Contents was updated
- List of Abbreviations was updated
- Table 1 was updated(list of sites)
- Table 1 – new Study Principal was added
- The primary and secondary endpoints and objectives were clarified and timeframes for collecting them were added and adjusted in applicable sections of the Protocol
- Inclusion and Exclusion Criteria were updated to be more specific and adjusted in applicable sections of the Protocol
- Point 10.3(Variables) including Table 5 were updated to be more detailed
- Participants enrolment age adjusted to local regulations
- Protocol Investigator Signature Page was added
- Separate section for Milestones was added and Milestones of PasTel study Table (Table 2) was updated
- Point 10.4 Recommendation of TachoSil application was added
- Point 10.8 (Data Analysis) was updated to more specific
- The Section 12 was updated
- Formatting and editing of text structure and fond was performed

Amendments and Updates included in PasTel Study Protocol version 1.2 dated 07.08.2024:

1. The Sponsor's signature was included.
2. Data regarding the (principal) investigator and CRO of the study protocol in Table 1 was updated.
3. The Milestones section has been updated to include the dates for the annual study progress reports.
4. The section study size was updated.
5. The section Variables (table 6) was updated.
6. The font of the PASS protocol was changed to Arial.

Amendments and Updates included in PasTel Study Protocol version 1.1 dated 08.04.2024:

7. Data regarding the author of the study protocol and study sites in Table 1 were updated.
8. The Milestones section has been updated to include new dates for start and end of data collection, registration in the EU PAS register, annual study progress reports, interim study report and final report of study results.
9. Detailed information on post-marketing reports concerning granuloma formation has been provided in section “Rationale and Background”. It was also removed from “Study Design” section.
10. The study objectives have been expanded to include an assessment of foreign-body granuloma formation over an extended period, and protocol was updated accordingly. Additionally, tissue adhesions have been incorporated as a secondary endpoint.
11. In the Section Variables was added foreign body granuloma, an extended follow-up period, and evaluation of the severity, treatment, and outcome of adverse events and AESIS during the study.
12. The term “register holders” was removed and registry was replaced by “database” in section data management.
13. Systematic literature review and comparative analysis of literature data with study results was added in “Data Analysis” section, along with information concerning SAP.
14. “Limitation” section was updated.
15. The section “Protection of human subjects” was updated.
16. The section “Management and reporting of adverse events” was updated.
17. The section “Plans for disseminating and communicating study results” was updated.
18. The section study size was updated.

7. MILESTONES

The previously approved by EMA Study Protocol version (1.2) dated 07Aug2024 was consulted with Investigators and amended according to received recommendations. Amended document approval process resulted in milestone adjustments.

Table 2. Initially planned Milestones of PasTel Study (updated versions, if applicable, will be available in Study Documents)

Milestone	Planned date
HMA-EMA RWD Catalogue number: EUPAS1000000505	Mar2025
Start of data collection	3Q 2026
End of data collection	3Q 2030
Annual study progress report/PSUR	3Q2027, 3Q2028, 3Q2029, 3Q2030
EMEA Interim study report	3Q 2028
Final report of study results	1Q 2031

8. RATIONALE AND BACKGROUND

Background

TachoSil is a surgical patch used during surgeries to assist with stopping bleeding, sealing tissues, and suture support in vascular surgery where standard techniques are insufficient. It is a combination of a collagen matrix made from horse tendons, coated with human fibrinogen and thrombin, and it is directly applied to the wound surface. TachoSil has received regulatory approval in 71 countries and was granted marketing approval by the European Medicines Agency in June 2004. Until June 8, 2023, an estimated 11.6 million patients worldwide have been exposed to TachoSil. Its approved indications in the European Union (EU) for adults include supportive treatment in surgery, improvement of haemostasis, tissue sealing, suture support in vascular surgery when standard techniques are insufficient and sealing of the dura mater to prevent postoperative cerebrospinal leakage following neurological surgery. In 2010, TachoSil was also approved in the United States as an adjunct to haemostasis when standard surgical techniques fail; in 2015, the indication was expanded to include use in children.

As of March 2023, after positive opinion from the European Medicines Agency, TachoSil has been approved in European Union for supportive treatment in surgery, for improvement of haemostasis, to promote tissue sealing and for suture support in vascular surgery in children from 1 month old to 18 years old, where standard techniques are insufficient.

Rationale

Overall, the safety data of TachoSil generally reflect the type of post-operative complications related to the surgical settings in which the trials were conducted and the underlying disease of the patients. Data from the eight controlled clinical studies conducted by the MAH has been pooled into an integrated dataset. In the integrated analyses, 997 patients were treated with TachoSil, and 984 patients were treated with comparator treatment. Due to practical reasons (comparison to standard surgical and standard haemostatic treatment), blinding was not possible in the TachoSil trials. Therefore, the studies were performed as open-label studies [1].

Paediatric use of TachoSil in the United States was accepted based on two studies including paediatric patients undergoing hepatic surgery, TC-2402-040-SP and TC-019-IN. Study TC-2402-040-SP was a pivotal study, which was a basis for the approval of the paediatric indication by FDA in 2015. This was a randomised, open-label, multicentre study that compared the efficacy and safety of TachoSil *versus* Surgicel (standard US-licensed haemostatic agent), for the secondary treatmentof local bleeding after hepatic resection in adult (aged 17 years or older) and paediatric (new-born to 16 years) patients. Twenty paediatric subjects were recruited to TachoSil arm. Eight of them were randomised to TachoSil arm and were included in Full Analysis Set (FAS) (compared to 114 adults randomised to TachoSil group). Other 12 were included in paediatric extension part to those receiving TachoSil (no comparator was involved in this extension phase). All 20 patients were included in Safety Analysis Set (SAS).
Primary efficacy endpoint was the intraoperative haemostasis at target bleeding site within 3 minutes of application of allocated trial treatment. In the paediatric FAS, the proportion of subjects who achieved haemostasis within 3 minutes after TachoSil application was 87.5% (95% CI: 47.3 -99.7%). In SAS (all paediatric patients), haemostasis at 3 minutes after TachoSil application was achieved by 17 out of 20 (85.0%) paediatric patients. In adult

population, haemostasis at 3 minutes after TachoSil application was achieved in 92 adult patients (80.7%).

Although no statistical comparison for both populations is available, the results in the paediatric population were numerically similar to those in the adult patients and were also consistent with a single-arm paediatric study TC-019-IN, non-randomised and non-comparative, with only descriptive statistics. Therein, 13 out of 16 (81.3%, 95% CI: 61.8-100%) TachoSil-treated children (median age 15 months, range 2 – 147, months) achieved haemostasis at 3 minutes (primary efficacy endpoint).

Table 3 Summary of results from both paediatric populations studied in TC-2402-040-SP and TC-019-IN. Adult population from study TC-2402-040-SP included for comparison, FAS – full analysis set, SAS – safety analysis set, CI – confidence interval.

Proportion of patients achieving haemostasis within 3 minutes from application			
TC-2402-040-SP			**TC-019-IN**
Adults (FAS n=114)	*Children*		Children n=16
	FAS n=8	SAS n=20	
80.7% 95% CI, 72.3 – 87.5	87.5% 95% CI, 47.3 – 99.7	85% 95% CI, 62.1 – 96.8	81.3% 95% CI, 61.8 – 100.0

The applicant furthermore provided a pooled analysis based on the paediatric patients from the above two mentioned studies TC-019-IN and TC-2402-040-SP. A total of 45 paediatric subjects were included in the paediatric study pool: 36 in the TachoSil group (8 randomised and 12 from the extension part from study TC-2402-040-SP, as well as 16 patients enrolled in TC-019-IN) and 9 in the comparator group (from study TC-2402-040-SP, all randomised).

The majority of subjects in both treatment groups experienced TEAEs that were considered mild or moderate in intensity, all of which were considered not related to study treatment. Incidence of severe adverse events was approximately the same across treatment groups and only 20 of 272 total adverse events were considered severe.

SAEs were reported by 17 of 36 subjects in the TachoSil group and 4 of 9 subjects in the Comparator group. No subjects in either treatment group experienced an SAE that was considered related to study treatment.

Events of special interest were presented for the paediatric study pool in comparison to the comparator Surgicel. More thrombotic/embolic events and postoperative bleedings were seen in the TachoSil-group. Tissue adhesions were similar. Immunogenicity testing and viral serology was not performed in paediatric subjects up to 6 months of age, nor for subjects enrolled in the paediatric extension part. Immunogenicity was tested in 2 children treated with TachoSil and 2 children treated with Surgicel. Only 1 paediatric subject had a 1-month follow-up test, which was negative for antibodies.

Table 4 Overall Summary of subjects with events of special interests by treatment studies TC-2402-040-SP and TC-019-IN, paediatric population

Medical Category	TachoSil N=36 n (%)	Comparator N=9 n (%)	Total N=45 n (%)
Thrombotic and embolic events	**2 (5.6)**	**0**	**2 (4.4)**
SAEs	2 (5.6)	0	2 (4.4)
Postoperative bleeding at surgical site	**16 (44.4)**	**3 (33.3)**	**19 (42.2)**
SAEs	5 (13.9)	0	5 (11.1)
Immunological events	**4 (11.1)**	**1 (11.1)**	**5 (11.1)**
SAEs	1 (2.8)	0	1 (2.2)
Abscess and other surgical related infections	**2 (5.6)**	**3 (33.3)**	**5 (11.1)**
SAEs	0	1 (11.1)	1 (2.2)
Tissue adhesions	**8 (22.2)**	**2 (22.2)**	**10 (22.2)**
SAEs	4 (11.1)	1 (11.1)	5 (11.1)

Studies in cardiovascular surgery were not performed, since it was considered not feasible, due to anticipated low enrolment and the heterogeneous nature of bleed sites that would be studied. No post-marketing requirements or commitments for clinical purposes, except from routine post-marketing surveillance, were recommended.

Despite the similarity in haemostasis rates between the target (paediatric) and reference (adult) populations, the small sample size of paediatric patients, wide confidence interval, and the absence of statistical comparison were considered insufficient to support the registration of TachoSil for paediatric use in the EU. Thus, an extrapolation approach was used following relevant guidelines, such as the *Reflection paper on the use of extrapolation in the development of medicines for paediatrics* (EMA/189724/2018) [2] and the *Structured guidance on the use of extrapolation* (EMA/CHMP/13622/2022) [3]. During the development of the extrapolation concept, gaps in knowledge regarding the long-term and delayed effects of TachoSil in the paediatric population were identified. However, it was deemed that the missing data could be collected post-approval through a Post-Authorisation Safety Study (PASS) since the currently available data indicate a very low risk of long-term effects in paediatric patients. This assumption is based on the fact that TachoSil has already been used in paediatric patients in the United States since 2015, and in the EU off-label, with no significant safety concerns reported in the Marketing Authorisation Holder's safety database for paediatric patients. Therefore, a PASS was proposed to address the identified gaps and gather additional safety information.

All enrolled patients will be followed for up to 36 months after surgery to monitor long-term treatment-related events and their clinically significant consequences. Duration of follow-up period was selected in order to evaluate in particular the risks of foreign-body granuloma formation. According to product's SmPC [1], in animal studies, TachoSil biodegrades after administration to a wound surface with few remnants left after 13 weeks. 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 (implying the possible maximum duration of TachoSil exposure). The degradation was associated with infiltration of granulocytes and formation of resorptive granulation tissue encapsulating the degraded remnants of TachoSil. No evidence of local intolerability has been observed in animal studies. From the experience in humans there have been isolated cases where remnants were observed as coincidental findings with no signs of functional impairment. Ten Individual Case

Safety Reports of granuloma occurrence after application of TachoSil were identified by MAH. Analysis of these ICSRs indicated, that most granuloma cases was reported in adult patients (n=6). Three cases concerned the unknown age, however the medical history of two of them may suggest that probably adult individuals were involved. One paediatric granuloma case was reported in 4 years old girl (case No. 2006-AT-000625). TachoSil was used to treat diffuse bleedings and to seal the anastomosis (number of sponges was unspecified). Five weeks later the patient was operated again, due to intense abdominal pain and intestinal invagination. During the operation it was discovered that TachoSil had not been resorbed, and a collar of compact tissue had developed at the site where TachoSil was initially applied. The compact tissue consisted of granulocytes and foreign body cells and was resected. The patient recovered on an unspecified date.

A case-study was published, presenting a 3-year-old girl who developed muscle weakness in the upper and lower extremities caused by foreign body granuloma mimicking malignancy in the cervical spinal cord after dural repair done via TachoComb during her neonatal period (case No. 2010-TR-000100). Despite substantial differences in composition of TachoComb and TachoSil, a collagen patch of equine origin, which is the same in both products, was considered the causative factor. The histopathological findings showed granulomatous foreign body reaction against the TachoComb used for dural repair [4]. Periodic safety update reports (PBRERS/PSUSA) have been searched for reports regarding foreign body granuloma (EVDAS search was not appropriate due to early date of occurrence< 2010), retrieving 1 event in the cumulative tabulation in PSUR 6 (2008, no further details provided), and 1 case presented with details in PSUR No. 5 (case number 101884;2007). Four granuloma events have been reported cumulatively based on the data presented in summary tabulations in the last PSUR from 2020.

Intracranial foreign body granulomas of the spinal cord, usually caused by haemostatic agents, have been rarely reported. A retrospective review of 288 consecutive neurosurgical procedures using TachoComb revealed no similar complications throughout the first two postoperative weeks. 45 patients died in the first three years due to primary malignant tumour. Autopsies revealed complete absorption of the fleece within the first three month [5].

Although foreign body reaction resulting in granuloma may be a very rare reaction, it still may have severe impact and should be considered as a potential risk associated with the use of TachoSil. Considering the above, an observation period up to 36 months was adopted for long-term safety monitoring.

This protocol has been prepared according to the relevant EMA guidelines and recommendations [6] [7] [8].

Recommendation of TachoSil application

Prior to application the wound area should be cleansed, e.g., from blood, disinfectants, and other fluids. After removal of the conventional, flat TachoSil from the sterile package it should be pre-moistened in saline solution and then applied immediately.

The yellow, active side of the matrix is applied to the bleeding/leaking surface and held against it with a gentle pressure for 3-5 minutes. This procedure enables an easy adhesion of TachoSil to the wound surface.

Alternatively, e.g., in case of stronger bleeding, TachoSil may be applied without pre-moistening, while also pressing gently to the wound for 3-5 minutes.

Pressure is applied with moistened gloves or a moist pad. Due to the strong affinity of collagen to blood, TachoSil may also stick to surgical instruments, gloves or adjacent tissues covered with blood. This can be avoided by cleansing surgical instruments, and gloves and adjacent tissues before application. It is important to note that failure to adequately clean adjacent tissues may cause adhesions. After pressing TachoSil to the wound, the glove or the pad must be removed carefully. To avoid TachoSil from being pulled loose it may be held in place at one end, e.g. with a pair of forceps.

9. RESEARCH QUESTIONS AND OBJECTIVES

The study aims to evaluate long-term safety effects of TachoSil application in paediatric population, as well as short-term outcomes in terms of safety of TachoSil in paediatric patients undergoing cardiovascular, hepatic or other solid organs surgery and polytrauma with injuries of blood vessels, parenchymal organs, lungs requiring the use of drugs for local haemostasis, tissue sealing or suture support in vascular surgery where standard techniques are insufficient. These scientific questions are to be addressed in a prospective, multicentre, non-interventional, uncontrolled, observational, post-authorisation cohort study.

The main purpose of this observational study is to collect long-term or delayed safety data on the use of fibrin sealant TachoSil during surgical procedures in paediatric population, and to estimate the frequency of adverse reactions, including the formation of foreign-body granuloma, over a period of time, extending beyond TachoSil exposure, in a paediatric population of subjects who have been exposed to TachoSil. The study also aims to generate new data to confirm short-term safety of TachoSil in paediatric patients.

9.1 PRIMARY OBJECTIVES

1. To evaluate the occurrence of clinically significant local reactions at the site of TachoSil application, as detected through routine imaging (X-ray, ultrasound, CT, MRI) or intraoperative detection or physical examination.

9.2 SECONDARY OBJECTIVES

1. To determine the occurrence of tissue adhesions, as detected through routine imaging (X-ray, ultrasound, CT, MRI) or intraoperative detection or physical examination.
2. To determine the occurrence of AESIs reported during the perioperative period, including:
    - Thrombotic and embolic events.
      Postoperative bleeding at surgical site and at the site of application of the investigational medicinal product.
    - Allergic reactions / Immediate hypersensitivity reactions.
    - Other surgical related infections at the site of application of the investigational medicinal product.
3. To determine the occurrence of adverse events related to the use of the study product in the period from the start of surgery up to 36 months post-surgery.

10. RESEARCH METHODS

10.1 STUDY DESIGN

This is a prospective, multicentre, non-interventional, uncontrolled, observational, post-authorization cohort study aimed at investigating the short- and long-term safety of TachoSil application.

The study will enrol patients undergoing cardiovascular, hepatic or other solid organs surgery, as well as those with injuries of blood vessels, parenchymal organs, lungs requiring the use of drugs for local haemostasis, tissue sealing, and suture support in vascular surgery where standard techniques are insufficient and where TachoSil was used as a secondary haemostatic treatment. The cohort will include patients identified by participating investigators (prospective enrolment). Patients who meet specified inclusion/exclusion criteria and their legal representatives will receive comprehensive information about the study orally and in written form, tailored to their understanding. The investigator will obtain their voluntary, personally signed, and dated informed consent before collecting any study-related information.

Short-term safety data, including adverse events (AEs) and adverse events of special interest (AESIs), will be collected prospectively from the time of informed consent signature, during hospital stay, and until hospital discharge. Time to onset (TTO), duration, severity, outcome, treatment and relatedness to TachoSil will be analyzed for reported AEs and AESI.

All enrolled patients will be followed for up to 36 months after surgery to monitor long-term treatment-related events and their clinically significant consequences.

To minimize stress for patients and caregivers associated with the study and the surgical intervention itself, the number and frequency of follow-up visits during the observation period will align with the routine follow-up procedures of the clinical sites.

Primary endpoint:

1. The proportion of subjects experiencing clinically significant local reactions including abscesses, hematoma formation or foreign body granuloma formulation, at the site of TachoSil application from the start of surgery up to 36 months post-surgery, as detected through routine imaging examinations (X-ray, ultrasound, CT, MRI or intraoperative detection or physical examination).

Clinically significant reactions are defined as those that, in the investigator's opinion, require surgical re-intervention (e.g., relaparotomy, re-laparoscopy) and/or medical treatment due to signs and symptoms, as well as an impairment of organ function, which can be attributed to the product, local application changes at the site of product application noted during surgery or limitation or impairment of organ function noted during physical examination, reported by the patient or detected by abnormal imaging findings

***Secondary endpoints*:**

1.The proportion of subjects experiencing clinically significant tissue adhesions detected from the start of surgery up to 36 months post-surgery, as detected through routine imaging tests such as X-ray, ultrasound, computed tomography, magnetic resonance imaging or relaparotomy or intraoperative detection or physical examination.

Clinically significant reactions are defined as those that, in the investigator's opinion, require surgical re-intervention (e.g., relaparotomy, re-laparoscopy) and/or medical treatment due to signs and symptoms, as well as an impairment of organ function, which can be attributed to the product, local application changes at the site of product application noted during surgery or limitation or impairment of organ function noted during physical examination, reported by the patient or detected by abnormal imaging findings.

2.Proportion of subjects experiencing at least one AESI during the perioperative period (from start of surgery until hospital discharge):

- Thrombotic and embolic events
- Postoperative bleeding at surgical site and at the site of application of the investigational medicinal product
- Allergic reactions / Immediate hypersensitivity reactions
- Other surgical related infections at the site of application of the investigational medicinal product

3.Proportion of subjects experiencing at least one AE related to the use of the study product in the period from the start of surgery up to 36 months post-surgery.

10.2 SETTINGS

The study will include approx. 4 sites or more, if required (Table 1). Estimated total number of recruited patients is 66. Based on feasibility assessments, approximately 66 patients are expected to qualify for the study and undergo surgery. All patients who undergo surgery will be included in the analysis. An anticipated dropout rate is 10%. Finally, number of subjects eligible for analysis: sample size is expected to be at least 60. The prospective recruitment of patients, by enrolling patients who have planned surgery and meet enrolment criteria will last for 12 months from the study start. All recruited patients will be followed up to 36 months after the date of the surgery.

Note: in emergency situation that requires acute surgery with TachoSil application, obtaining informed consent and including the patient in the study after surgery may be considered, if legal and ethical requirements are met.

The study population is paediatric patients undergoing a cardiovascular, hepatic or other solid organs surgery and polytrauma with injuries of blood vessels, parenchymal organs, lungs requiring the use of drugs for local haemostasis, tissue sealing when control of bleeding by standard surgical techniques (such as suture, ligature, clips or cautery) appeared to be ineffective or impractical.

Data will be collected from the following age groups :

- Infants and toddlers (>= 28 days - < 2 years) on the day of signing the ICF
- Children (>=2 years – < 12 years) on the day of signing the ICF
- Adolescents (>=12 years – less than 15 years) on the day of signing the ICF

Patient age analysis will be conducted throughout the study to ensure a proportional number of participants in each of the three age groups (if possible, approx. 33% per group). Ensuring an adequate number of participants in each age group will ensure that data are collected across a broad paediatric population to assess short- and long-term safety evaluation.

Inclusion/Exclusion criteria

The study population covers paediatric patients undergoing a cardiovascular, hepatic or other solid organs surgery, and polytrauma patients with injuries of blood vessels, parenchymal organs, lungs requiring the use of drugs for local haemostasis, tissue sealing when control of bleeding by standard surgical techniques (such as suture, ligature, clips or cautery) appeared to be ineffective or impractical (secondary haemostatic treatment).

Data will be collected from the following age groups:

- Infants and toddlers (>= 28 days - < 2 years) on the day of signing the ICF
- Children (>=2 years – < 12 years) on the day of signing the ICF
- Adolescents (>=12 years – less than 15 years) on the day of signing the ICF

Inclusion criteria

The following individuals are eligible to participate:

- Patients aged from >=28 days to < 15 years onthe day of signing the ICF.

Important Note: According to legal regulations in Poland, patients who are 18 years of age or older cannot be treated by paediatric surgeons. Therefore, only patients who are under 18 years of age by the end of the observation period will be included in the study.

- Patients who have planned a cardiovascular, hepatic or other solid organs surgery and polytrauma patients with injuries of blood vessels, parenchymal organs, lungs qualified for elective surgery
- Patients planned to have at least one TachoSil matrix applied (intraoperatively) and without the plan of application of any other products for local haemostasis at the place of TachoSil application will be qualified for the study.

Exclusion Criteria

The following individuals are not eligible to participate:

- they have known, recognized earlier congenital disorders of haemostasis such as haemophilia type A,B,C, Marfan syndrome, Rendu-Osler-Weber disease, congenital thrombocytopathies, e.g. Glanzmann's thrombasthenia, von Willebrand disease type 1,2,3, Fanconi's anaemia.

- they have experienced severe coagulopathy defined as: INR >2.0, platelet count (PLT)<50 000 / mm3; APTT>60 seconds in the period from 7 days before to the day of surgery.
- they are hypersensitive to the active substance(s) or to any of the product excipients.
- female patients of childbearing potential: they are pregnant or want to become pregnant or those who do not use sufficient methods of contraception such as contraceptive implant, intrauterine coil and oral hormonal contraception.

The patient who, in the investigator's opinion, presents a known risk of being lost to follow-up during the 36-month follow-up period, based on the screening assessment.

The study period will be divided into enrolment phase and follow-up phase. Both study phases can last simultaneously.

Enrolment phase: The duration of this study phase is set to be 12 months, starting from the commencement of the study at each individual site. The center will be able to start recruiting patients after obtaining, accepting and signing all necessary documents to conduct an observational study in accordance with the regulations of Polish law. The Sponsor will communicate the study start date to the sites through email and telephone contact. Patient enrolment will be carried out amongst those scheduled for upcoming surgeries.

Patients who are scheduled to undergo cardiovascular, hepatic, or other solid organ surgeries, as well as polytrauma with injuries to blood vessels, parenchymal organs, or lungs, will be identified by the designated Investigator during their routine visit to the study site. During this visit, the Investigator will discuss the study details with the patient and/or their legal representative and ask for their willingness to participate. If the patient meets the remaining inclusion/exclusion criteria, including the intraoperative application of at least one TachoSil patch, they will be enrolled in the study. It's important to note that the participating sites will use TachoSil as part of their routine clinical practice in the specified indications mentioned above. TachoSil itself is not considered an intervention in the study; its application during surgery is one of the inclusion criteria. The day on which informed consent is obtained will be considered a screening visit.

For all enrolled patients, they will continue following the routine procedures of the study site leading up to the day of surgery and throughout their hospital stay until discharge. The Investigator will perform safety assessments during the perioperative period, which includes the time from the day of surgery until discharge. These assessments will involve monitoring adverse events (AEs), adverse events of special interests (AESIs), vital signs(blood pressure, heart rate, temperature), and the analysis of relevant clinical laboratory variables as part of the routine procedure (morphology, INR, APTT).

Follow-up phase: The study phase is scheduled to last for up to 36 months following the date of surgery for each enrolled patient. There are six planned follow-up visits: one at 1 month (± 15 days) after surgery, another at 3 months (± 15 days), a third at 6 months (± 15 days), and a fourth, fifth and sixth visits at 12, 24 and 36 months (± 30 days) post-surgery, respectively. However, to minimize stress for patients and caregivers associated with the study and the surgical intervention itself, the number and frequency of follow-up visits during the observation period can be align with the routine follow-up procedures of the clinical sites.

The follow-up visits can be conducted in person at the study site if such visits are routinely performed, or they can take the form of telephone interviews with the patient and/or patient

legal representative conducted by the Investigator. In both cases eCRF should be completed with all collected and required by Protocol data.

Patients have the right to discontinue their participation in the study at any time and for any reason, whether specified or unspecified.

Furthermore, a patient/legal representative (if applicable) may be withdrawn from the study if the Investigator determines that the patient no longer meets any of the inclusion/exclusion criteria.

Lost-to-follow-up (LTFU)

To ensure the smooth progress of the PasTel study, it is crucial to minimize the occurrence of lost-to-follow-up (LTFU). Loss-to-follow-up refers to patients and/or their legal representative who, at some point during the study, cannot be reached for further follow-up procedures, resulting in an unknown status and the inability to collect important long-term information, including adverse events. On the other hand, “dropout” refers to patients who voluntarily withdraw from the study, with their health status known upon departure.

To minimize lost-to-follow-up, the following follow-up process will be implemented: If a study participant (or their legal representative) does not respond to the initial telephone contact, up to two reminder calls will be made. If there is still no response after three phone calls, the participant will be sent an email or certified letter. The overall objective is to keep the loss-to-follow-up rate below 10 %. Based on the Corza Medical experience and Feasibility analysis, it is anticipated that the final LTFU will be approximately 10 %.

10.3 VARIABLES

For underlying disease and co-morbidities, diagnoses will be defined using Polish adaptation of ICD-10 codes. The exposure/dose will be defined as the number of patches of TachoSil applied during surgery. Concomitant medication will be coded according to the current version of World Health Organization (WHO) Drug Dictionary and Anatomical Therapeutic Chemical (ATC) coding. All adverse events reported during the study will be coded by System Organ Class (SOC) and preferred term (PT) using current version of MedDRA.

For the determination of the exposure, size and number of TachoSil patches will be used as a measure of dose. This method of exposure determination was used in previous clinical studies with TachoSil and is considered adequate to determine the dose of TachoSil used in a clinical setting during surgery. Duration of drug exposure is not considered relevant since TachoSil is a degradable medicinal product, and once applied it remains embedded in the wound until it degrades on its own. A detailed algorithm of exposure calculation will be provided in the study SAP.

For primary and secondary endpoints, rate of occurrence and cumulative incidence of AEs and AESIs will be determined: Time to onset (TTO), duration, severity, outcome, treatment and relatedness to TachoSil will be analyzed for reported AEs and AESI

The PasTel study is a prospective observational study with data collected from routine standard care practices. Data mentioned below will be re-transcribed from medical records and recorded in the eCRF.

Screening Visit

The following data will be collected:

Patient data:

- Informed consent signature date
- Assessment of patient eligibility
- Demographic data collection (birthdate, age, gender)
- Medical history – underlying disease (date of initial diagnosis, disease name, use of treatments related to medical history)
- Comorbidities and their evaluation for the assessment of adverse events (AEs / AESI)
- Adverse Events evaluation including treatment of AEs
- Concomitant Medication
- Vital signs (as per each site's standard of care as blood pressure, body temperature, and heart rate), if available
- Laboratory data (as per each site's standard of care such as: blood count, C-reactive protein [CRP], International Normalized Ratio[INR], Activated Partial Thromboplastin Time [APTT]), if available

Surgery

- Data to be collected:
    - type and date and time of surgery
    - patient's discharge details
- Adverse Events evaluation including treatment of AEs
- Adverse Events of Special Interest evaluation including treatment of AESIs
- Comorbidities and their evaluation for the assessment of adverse events (AEs / AESI)
- TachoSil usage related data:
    - exposure/dose/application time (size and number of patches applied)
    - repeated application
    - treatment not effective/other treatment required
    - Batch number, expiration date and size of all TachoSil matrices used
    - The wound condition and application of the TachoSil matrix will be assessed and collected. The following wound data will be assessed and collected: wound location, amount of blood in the wound assessed by the surgeon. The following TachoSil matrix data will be collected: TachoSil matrix size, and application method (dry, pre-moistened).
- Concomitant medication(except drugs used for anaesthesia)
    - Specific treatments, such as: ECMO (extracorporeal membrane oxygenation), hypothermia, ECC (extracorporeal circulation), MiECC (minimal invasive systems for extracorporeal circulation),
- Vital signs (as per each site's standard of care as blood pressure, body temperature, and heart rate), if available
- Laboratory data (as per each site's standard of care such as: blood count, C-reactive protein [CRP], International Normalized Ratio[INR], Activated Partial Thromboplastin Time [APTT]),if available

Hospital Discharge Data

At the time of discharge following information should be collected and enter into eCRF:

- Concomitant therapies updates
- Adverse Events evaluation including treatment of AEs
- Adverse Events of Special Interest evaluation including treatment of AESIs
- Comorbidities and their evaluation for the assessment of adverse events (AEs / AESI)
- Granuloma occurrence and Tissue adhesions and other clinically significant events for the endpoint
- Vital signs (as per each site's standard of care as blood pressure, body temperature, and heart rate), if available
- Laboratory data (as per each site's standard of care such as: blood count, C-reactive protein [CRP], International Normalized Ratio[INR], Activated Partial Thromboplastin Time [APTT]),if available

Follow-up Visits/Contacts

At the time of Follow Up Visits/Contacts following information should be collected and enter into eCRF:

- Concomitant therapies updates
- Adverse Events evaluation including treatment of AEs
- Adverse Events of Special Interest evaluation including treatment of AESIs
- Comorbidities and their evaluation for the assessment of adverse events (AEs / AESI)
- Granuloma occurrence and Tissue adhesions and other clinically significant events for the endpoint
- Vital signs (as per each site's standard of care as blood pressure, body temperature, and heart rate), if available
- Laboratory data (as per each site's standard of care such as: blood count, C-reactive protein [CRP], International Normalized Ratio[INR], Activated Partial Thromboplastin Time [APTT]),if available

Follow-up visits will be scheduled at 1, 3, 6, 12, 24 and 36 months post-surgery.

Study premature discontinuation details (any time from surgery till end of the study)

- Reason for premature discontinuation
- If possible, the following information to be collected: Adverse Events, Adverse Events of Special Interest, Comorbidities and their evaluation for the assessment of adverse events (AEs / AESI), Granuloma occurrence and Tissue adhesions and other clinically significant events for the endpoint
- Vital signs (as per each site's standard of care as blood pressure, body temperature, and heart rate), if available
- Laboratory data (as per each site's standard of care such as: blood count, C-reactive protein [CRP], International Normalized Ratio[INR], Activated Partial Thromboplastin Time [APTT]),if available

Table 5 PasTel Study data collection schedule

Collected data (if available)	**Screening**	**Surgery**	**Hospital Discharge Data** (collected during perioperative period defined as standard practice discharge from the hospital after the surgery at the site)	**Follow-up Visits/Contacts (months[2])**						**Study premature discontinuation details** (any time from surgery till end of the study
				1	**3**	**6**	**12**	**24**	**36**	
				Visit window: +/- 15 days			Visit window: +/- 30 days			
Informed consent	•									
Demographic Data	•									
Inclusion/Exclusion Criteria	•	•								
Underlying disease	•									
Type and date of surgery		•								
Patient's discharge details			•							
Co-morbidities and their evaluation for the assessment of adverse events (AEs / AESI)	•	•	•	•	•	•	•	•	•	•
Concomitant medication	•	•	•[1]	•	•	•	•	•	•	•
Specific treatments, such as: ECMO (extracorporeal membrane oxygenation), hypothermia, ECC (extracorporeal circulation), MiECC (minimized systems for extracorporeal circulation)		•								
TachoSil usage details		•								

Adverse Events evaluation including treatment of AEs	•	•	•	•	•	•	•	•	•	•
Granuloma occurrence and Tissue adhesions and other clinically significant events for the endpoint[4]		•	•	•	•	•	•	•	•	•
AESIs evaluation including treatment of AESIs		•	•	•	•	•	•	•	•	•
Vital signs[3]	•	•	•	•	•	•	•	•	•	•
Laboratory values[3]	•	•	•	•	•	•	•	•	•	•
Reason for premature discontinuation										•
1 - except drugs used for anaesthesia 2 – 1 month is defined as 30 days 3 – applicable during the follow period only if available 4 – The wound condition and application of the TachoSil matrix will be assessed and collected. The following wound data will be assessed and collected: wound location, amount of blood in the wound assessed by the surgeon. The following TachoSil matrix data will be collected: TachoSil matrix size, and application method (dry, pre-moistened).										

10.4 DATA SOURCES

The study will utilize a data collection system implemented by the Sponsor, targeting patients who meet the eligibility criteria. Variables collected for the purpose of the study will be re-transcribed from existing electronic and/or paper medical records maintained at site. The PasTel study involves primary data collection in which the data collected are derived from routine clinical care. In instances where patient recruitment or follow-up activities specific to evaluating the safety of TachoSil exposure, extend beyond the regular routine activities at the study site, additional data will be collected by personnel at the participating study site. This primary data collection will be incorporated into the case report forms (CRFs)

10.5 STUDY SIZE

Approx.4 or more, if required, paediatric surgery centres will participate in the PasTel study.

Based on feasibility assessments, approximately 66 patients are expected to qualify for the study and undergo surgery. All patients who undergo surgery will be included in the analysis. An anticipated dropout rate is 10 %.

The recruitment will be conducted until the planned number of patients is reached. All patients available in the study population will be considered for the analysis.

10.6 DATA MANAGEMENT

CRO Team will be responsible for the eCRF data management after receipt the data from the Investigators.

Pharmacovigilance Team will be responsible for safety data collection, processing and reporting.

The study will utilize existing databases known as “patient clinical records”. Each database may have different processes for managing and extracting data, following the standard practices established by the respective study site.

Once the Investigators have re-transcribed the relevant data, it will be transferred to electronic-based case report form (CRF). To maintain patient confidentiality, a unique dummy study identification number (SIN) will be assigned to each enrolled patient before delivering the data to Corza Medical. Corza Medical will receive the data without any identifiable patient information. At Corza Medical, the SINs will be used for linking the data at an individual level. This means that the researchers at Corza Medical will have access to data where individuals cannot be directly identified. After receiving the data from the Investigators, Corza Medical, in cooperation with entities involved in conducting the study, will process the data.

Computer software will be utilized for data management, including creating the analysis database and performing statistical analyses to generate tables, graphics, and statistical models. An audit trail will be maintained, documenting the entire data processing journey from the raw data obtained from the study sites to the final statistical tables and graphs in the reports. The source code for data management and analysis will be retained for inspection for a period of 15 years after the end of the study. The study may be subject to inspection by independent representatives appointed by the Sponsor, EMA representatives, the scientific committee, or competent authorities.

10.7 DATA ANALYSIS

All analyses will be performed for the study population, which will comprise all enrolled subjects who received at least 1 application of TachoSil. Study endpoints will be summarised by descriptive statistics. For primary and secondary endpoints, rate of occurrence and cumulative incidence of AEs and AESIs will be determined. Time to onset (TTO), duration, severity, outcome, treatment and relatedness to TachoSil will be analyzed for reported AEs and AESI.

Descriptive statistics of all endpoints may include specifically but not exclusively, arithmetic mean, medians, standard deviations, proportions, frequency counts and 25^{th} and 75^{th} percentiles. Where applicable, 95% confidence intervals of select point estimates will be determined. Figures will be prepared to illustrate the patterns of data over time where appropriate. The number of subjects included in each analysis set will be reported.

A qualitative comparison of results collected during the study with an existing literature data will be performed, particularly focusing on the incidences, time to onset, severity, and outcomes of AESIs and SAEs, with existing literature. Literature searches in databases like PubMed, Embase and Cochrane Library will be conducted to identify relevant studies. The search will use specific keywords and criteria related to TachoSil, adverse events, and study

populations.- Studies selected for comparison will be based on relevance, quality, and up to date results. Key data from the selected studies, such as incidences, time to onset, severity, and outcomes of AESIs and SAEs, will be extracted. A standardized form will be used to ensure consistent data collection. A narrative synthesis will be provided, discussing similarities and differences in the findings. Both our study and the selected literature will undergo a critical appraisal to assess the quality and risk of bias, which will be considered in the interpretation of the results. The discussion will highlight the similarities and differences in the findings to provide context for the study's outcomes. Additionally, the Clinical Study Report will include a description of the methodology utilized, including search keywords, inclusion and exclusion criteria for relevant studies, and data collection form used in the analysis.

Statistical Analysis Plan (SAP) will be developed subsequently to the protocol. The SAP will be finalized prior to database lock to ensure the integrity of the analysis. It will outline detailed statistical methods, including but not limited to, the statistical models to be used for comparative analyses, the handling of missing data, and the approach for subgroup analyses. The SAP will also specify the statistical software to be used for these analyses.

10.8 QUALITY CONTROL

The study will be conducted according to the protocol and in compliance with relevant regulations and guidelines (ICH-GCP and local law). Any modifications to the protocol must be approved by the study principal investigator and the study Sponsor. These revisions will be properly documented as protocol amendments and shared with ethics committees and study sites. After finalizing the protocol amendments, they will be submitted to the Ethics Committee, Office for Registration of Medicinal Products, Medical Devices and Biocides (URPL) and the European Medicines Agency (EMA) for approval.

Corza Medical will act as the database holder for the retrieved data and will also be responsible for securely storing and eventually destroying the data after the study concludes. The study will adhere to the standard operating procedures established by Corza Medical or an entity involved in conducting the study. These procedures encompass internal quality audits, secure and confidential data storage practices, document archiving methods, programming quality control procedures, standards for writing analysis plans, and the requirement for senior scientific review.

All work conducted will be subjected to rigorous quality control and documentation procedures to ensure accuracy and thoroughness in the final report, as well as reproducibility of the analyses. If the data do not allow for the planned analysis or if additional analyses are needed, the report(s) will include any missing or supplementary information along with the corresponding explanations. Key study documents such as the protocol, statistical analysis plan, and study reports will undergo quality control review, senior scientific review, and editorial review.

A quality control process will be implemented to ensure the accuracy and completeness of data collected in the electronic Case Report Form (eCRF) and data collected by the Sponsor during the literature review process. In terms of data collected in the eCRF, this process will involve verifying that all mandatory variables are collected and performing cross-checks for data consistency and correctness by the Data Management team. Any discrepancies, missing data, or errors identified within the eCRF data will be verified and resolved in collaboration with the site or Investigator. For data collected outside the eCRF and managed directly by the Sponsor, a parallel quality control process will be applied. If any required information is found

to be missing or incorrect, the Biostatistician will coordinate directly with the Sponsor to secure the necessary corrections or additional data.

These measures ensure that all data, regardless of its source, adheres to the study's quality and completeness standards.

The programs for Data Management and Statistics will be developed by the Data Manager(s) and Biostatistician(s), with independent quality control checks conducted by another Data Manager and Biostatistician to ensure accuracy. All processes related to Data Management and Statistics leading to the dissemination of study results will undergo rigorous quality control checks, including verification of programs, result tables, and written text. These checks will be documented in accordance with the CRO's Standard Operating Procedures (SOPs).

10.9 Limitations of the Research Methods

One of the strengths of PasTel study is a prospective observational study design, which allows for the collection of data over time. This design is suitable for examining the short- and long-term safety of TachoSil application and can provide valuable insights into the outcomes of the treatment. The study is an observational cohort study, which means that it does not involve any interventions or experimental procedures. This design allows for the examination of the treatment's safety in a real-world setting, reflecting the routine clinical practice. The study aims to recruit a substantial number of patients, which can enhance the generalizability of the findings and provide more robust results. The study includes a specific population of paediatric patients undergoing cardiovascular, hepatic, or other solid organ surgeries, as well as polytrauma with certain injuries. This targeted approach ensures that the study focuses on patients who are likely to benefit from TachoSil application, allowing for a more accurate assessment of its safety in the intended population. Additionally, the PasTel study follows patients up to 36 months after surgery, enabling the examination of both short- and long-term safety outcomes. This duration allows for the identification of potential adverse events or complications that may occur over an extended period.

Despite these strengths, PasTel study has also some limitations. The study does not include a control group for comparison. Without a control group receiving an alternative treatment or a placebo, it may be challenging to attribute observed outcomes solely to the TachoSil application. The absence of a control group limits the ability to establish causality or make direct comparisons. PasTel study relies on patient self-reporting during follow-up visits, which may introduce recall bias or incomplete data. Depending on the method of follow-up (in-person or telephone visits), the accuracy and reliability of the information collected may vary. Confounding by indication is also very common in observational studies (e.g., cohort studies). It can occur in relation to either beneficial outcomes or harmful outcomes and can result in either an increase or a reduction in the apparent risk of the outcome. However, careful study design, e.g., including a range of different indications for the same exposures, enables the relationship between the exposure and the outcome in relation to each of the individual indications to be analysed separately. A consistent outcome across all indications will suggest that the outcome is indeed due to the exposure, since it is unlikely that each different indication would cause the same outcome.

The study design may be prone to selection bias, primarily due to its non-interventional, observational nature and specific inclusion/exclusion criteria. By focusing only on paediatric patients undergoing certain types of surgery and requiring specific haemostatic treatments, the study might not represent the broader paediatric population undergoing various surgical

procedures. Additionally, excluding patients with congenital disorders of haemostasis or severe coagulopathy could further skew the results, as these patients might exhibit different safety profiles or adverse event rates. These selective criteria can impact the generalizability of the study findings to all paediatric surgical patients.

Finally, participants have the option to withdraw from the study at any time, which could lead to attrition bias if those who withdraw differ systematically from those who remain. Additionally, discontinuation may result in incomplete data for some patients, potentially affecting the overall study findings.

11. PROTECTION OF HUMAN SUBJECTS

The study will be conducted in full compliance with the General Data Protection Regulation (GDPR) to ensure the highest standards of privacy and data protection for individuals. In addition to following the ENCePP Code of Conduct and the Guidelines for Good Pharmacoepidemiology Practices (GPP), the study will strictly adhere to the principles set forth in the Declaration of Helsinki. All treatment centres participating in the study will be provided with informed consent forms that are in line with these principles.

Patients and/or their legal representatives will be contacted during the follow-up phase of the study, and their treatment will not be affected by the study. It is crucial to note that written informed consent will be required from patients or their legal guardians, and these consent forms will be securely stored at the respective treatment centres. The Sponsor will only receive pseudonymized data, including Subject Identification Numbers (SINs), and will not have access to patient-level data at any stage of the study. The Sponsor's employees are bound by professional secrecy and are fully informed about their responsibilities under local legislation.

Regarding the storage of informed consent forms, they will be retained at the treatment centres and managed according to local patient privacy regulations of each participating country. For paediatric patients who reach legal adulthood during the course of the study, direct collection of signed informed consent forms will be implemented, allowing these individuals to personally consent to their continued participation in the study.

Furthermore, rigorous processes ensuring data security will be employed during data extraction, storage, and back-up. The data and all study documents will be maintained until the Sponsor provides written notification that records may be destroyed. The study will be registered in ENCePP's European Union electronic Register of Post-Authorisation Studies (EU PAS register) to ensure transparency and ethical conduct throughout the research process.

12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS / ADVERSE REACTIONS

Definitions

An adverse event (AE) is defined as any untoward medical occurrence in a patient administered TachoSil treatment and which did not necessarily have a causal relationship with this treatment.

For this study, reporting of Adverse Events begins when the patient signs the Informed Consent Form to participate in the study.

The following are not recorded as an AE if recorded at Screening:

- A pre-planned procedure, unless the condition for which the procedure was planned had worsened since baseline.

Treatment-emergent AEs (TEAEs) are defined as AEs with an onset after the start of surgery (date and time of elective surgery start).

Complications to pre-planned procedures are recorded as AEs. Furthermore, postoperative nausea, vomiting, or pain that the investigator considered common and expectable postoperative findings, treated or untreated, are not recorded as AEs. Postoperative nausea, vomiting, or pain considered by the investigator as either uncommon, unexpected, or both, are recorded as AEs. Any worsening in severity or frequency of a baseline concomitant illness or any new illness diagnosed during the study conduct are recorded as AEs.

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

- results in death. Death itself is not an AE but rather the outcome of an AE, which is to be described using medical terminology. When Death is the only reported event, this will be considered as an event.
- is life-threatening. Life-threatening referred to an event in which the patient is at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it had been more severe.
- requires inpatient hospitalization or prolongation of existing hospitalization. Inpatient hospitalization includes an overnight admission, even if the duration of hospitalization is shorter than 24 hours.
- results in persistent or significant disability/incapacity.
- is a congenital anomaly/birth defect.
- is medically important. Medical judgment is exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalization but could jeopardize the patient or could require intervention to prevent one of the other outcomes listed in the definition above are considered as serious.

A non-serious AE is defined as any AE that does not meet the SAE criteria above.

An adverse reaction is defined as any untoward and unintended response to a TachoSil treatment that is considered to have a causal relationship with the treatment.

A suspected unexpected serious adverse reaction (SUSAR) is defined as a serious adverse reaction, the nature or severity of which is not consistent with the applicable product information.

An abnormal laboratory value or vital sign is defined as any abnormality/change from Screening that suggests a disease and/or organ toxicity and is of a severity that requires active management, i.e., change of dose, discontinuation of trial treatment, medical treatment, more frequent follow-up, or diagnostic investigation.

Adverse events of special interest (AESIs) occurring in the course of treatment (from start of the surgery until hospital discharge) will include:

- Thrombotic and embolic events
- Postoperative bleeding at surgical site
- Allergic reactions or/ immediate hypersensitivity reactions
- Abscess and other surgical related infections
- Tissue adhesions.

During follow-up period of up to 36 months after surgery date, patients will be monitored for adverse events during follow-up visits, which will also include the evaluation of the risks of foreign-body granuloma formation.

Classification of adverse events

Severity is a clinical observation and describes the intensity of the event as one of the following:

- Mild: Transient symptoms, no interference with the patient's daily activities
- Moderate: Marked symptoms, moderate interference with the patient's daily activities
- Severe: Considerable interference with the patient's daily activities.

Causality describes the relationship of the event to the TachoSil treatment as one of the following:

- Related: A reasonable temporal relationship between the TachoSil treatment and the AE where there is no other obvious explanation for the occurrence of the AE
- Not related: There is evidence for an alternative explanation(s) for the AE, e.g., the AE is explained by one or more of the following: a) the patient's medical condition (medical history, disease progress or indication), b) a concomitant medication for which the event was labelled, or c) AE occurrence prior to the TachoSil treatment.

Outcome of the event is described as one of the following:

- Recovered: Fully recovered or the condition had returned to the level observed at screening
- Recovering/Resolving: Condition is improving, and patient is expected to recover from the event
- Recovered with sequelae: As a result of the AE, the patient suffered persistent and significant disability/incapacity (e.g., became blind, deaf or paralyzed)
- Not recovered
- Fatal
- Unknown.

Reporting of adverse events

Throughout the conduct of the study, the Principal Investigator and investigators will be responsible for collecting and reporting adverse events to the Sponsor (Corza Medical). They are responsible for the timely identification, documentation, and reporting of all AEs, AESIs and adverse reactions (ARs) observed during the study. The principal investigator will ensure that all investigators are thoroughly trained in these procedures and understand their responsibilities.

The management of the follow-up of AEs and ARs, including reporting to the sponsor, is a critical component of the study. Investigators are required to provide comprehensive follow-up information on each AE and AR, ensuring detailed documentation of the event's evolution, management, and resolution. This information must be communicated to the sponsor promptly as per the reporting timelines outlined in the protocol. All events that met the definition of an AE and will occur in the period from the patient signing the ICF and until the final follow-up visit (at 36 month ± 30 days) will be recorded. During follow-up phase of the study, at each contact between the study site and the patient (visit or phone), the patient will be asked no leading questions about AEs, e.g., “Have you experienced any problems since our last contact?”

The investigator will record all AEs on the standard AE Form (electronic CRF). The investigator will record only 1 AE per form.

For SAE/s, the SAE Form (electronic CRF or paper SAE Form if eCRF is out of order) will also be completed. The investigator will have to record the diagnosis if available. If no diagnosis is available, the investigator will record each sign and symptom as individual AEs. The investigator will evaluate the seriousness, severity, outcome, and causality of AEs.

The Investigator will report all ICSRs to Pharmacovigilance via eCRF and the Sponsor will be notified. Paper version reporting might be used only when the system is not available. Once the system becomes available, the Investigator should enter the data from the paper form to eCRF. SAE/AESI should be reported within 24 hours after obtaining knowledge of the event. The CIOMS report will be prepared on the basis of the appropriate electronic CRF form.

All adverse events, or special situations will be reported as such to the sponsor. All adverse events collected throughout the study, both aggregate findings and individual reports, will be summarized in the study report. Data collected on other products not included in the programme/protocol design must also be collected and reported as spontaneous ICSR but may not be included in the study report.

In general, the reporting of serious valid ICSRs is required as soon as possible, but in no case later than 15 calendar days after initial receipt of the information by the national or regional pharmacovigilance centre of a competent authority or by any personnel of the marketing authorisation holder, including medical representatives and contractors. This applies to initial and follow-up information. Where a case initially reported as serious becomes non-serious, based on new follow-up information, this information should still be reported within 15 days; the reporting time frame for nonserious reports should then be applied for the subsequent follow-up reports.

Non-serious valid ICSRs shall be reported to EMA by the sponsor within 90 days from the date of receipt of the reports.

The sponsor's responsibilities in AE reporting include the timely collection, analysis, and reporting of AE and AR data to regulatory authorities. The sponsor is also responsible for ensuring the dissemination of this information to all participating study sites, ensuring that all parties are aware of any new safety concerns.

The selected CRO will train all study site personnel involved in the management and reporting of AEs/ARs. This training will cover the recognition of AEs/ARs, documentation standards, reporting procedures.

13. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Corza Medical and the principal investigator will report the results in a study report. The completed study will be summarized in a final report that accurately and completely presents the study objectives, methods, results, limitations of the study, and interpretation of the findings. The report will be delivered to the sponsor and the responsible parties. The final study report may be used for the discussions with the competent authorities as required.

The MAH will submit the final study report to the European Medicines Agency (EMA) no later than one year following the conclusion of the study. The MAH will also provide annual study progress reports to the EMA. These reports will either be submitted as standalone documents or included within the Periodic Safety Update Reports (PSURs), as appropriate. The progress reports will detail the study's ongoing status, including enrolment updates, preliminary findings (if available), and any significant developments or modifications. Alongside the next scheduled PSUR, the MAH will submit an interim report of the study. This report will provide an update on the study's progress and preliminary findings from the data collected to date.

Following the study report, an abstract of the study findings will be made available to the public through the EU PAS register. According to the ENCePP Code of Conduct [9], the principal investigator is responsible for publication of the results. The main results of the study will be published, whether positive or negative, including results from a possibly prematurely terminated study. In no way shall the interpretation and presentation of the results be aimed towards any commercial, financial or personal interests. The sponsor is entitled to view the final results and interpretations prior to submission for publication in the EU PAS register, and to comment these without unjustifiably delaying the publication. The principal investigators may ask the ENCePP Secretariat to delay the publication of this abstract for a limited period due to pending response from the peer-review process.

Study results will be considered for academic publication. In addition, communication in appropriate scientific meetings will be considered. Upon the first acceptance of the final manuscript of a publication detailing the study results, the MAH will submit this manuscript to the EMA within two weeks of acceptance. This ensures that the EMA is promptly informed of the study findings as they are prepared for dissemination to the wider scientific and medical community.

The MAH recognizes the importance of these communications in maintaining regulatory compliance and contributing to the body of scientific knowledge. Therefore, all reports and publications will be prepared with due diligence, ensuring accuracy, completeness, and compliance with relevant guidelines and regulations.

14. REFERENCES

[1] TachoSil EPAR Product Information, available on https://www.ema.europa.eu/en/documents/product-information/tachosil-epar-product-information_en.pdf, downloaded 03.08.2023

[2] *Reflection paper on the use of extrapolation in the development of medicines for paediatrics* (EMA/189724/2018)

[3] Structured guidance on the use of extrapolation (EMA/CHMP/13622/2022)

[4] Ekici MA, Ekici A, Per H, Tucer B, Kurtsoy A. Foreign body granuloma mimicking upper cervical spinal mass after dural repair with Tachocomb [correction of Tachocomp]: a case report. Pediatr Neurosurg. 2010 Aug;46(2):133-7.

[5] Reddy M, Schöggl A, Reddy B, Saringer W, Weigel G, Matula C. A clinical study of a fibrinogen-based collagen fleece for dural repair in neurosurgery. Acta Neurochir (Wien). 2002 Mar;144(3):265-9; discussion 269.

[6] Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies (Rev 3). EMA/813938/2011 Rev 3*

[7] Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies. EMA/623947/2012

[8] ENCEPP CONSIDERATIONS ON THE DEFINITION OF NON-INTERVENTIONAL TRIALS UNDER THE CURRENT LEGISLATIVE FRAMEWORK (“CLINICAL TRIALS DIRECTIVE” 2001/20/EC)

[9] The ENCePP Code of Conduct. For Scientific Independence and Transparency in the Conduct of Pharmacoepidemiological and Pharmacovigilance Studies. EMA/929209/2011

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Date	Title
1	TBD	List of sites declaring willingness to participate in PasTel Study
2	TBD	Feasibility Questionnaire

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is “Yes”, the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer ‘N/A’ (Not Applicable) can be checked and the “Comments” field included for each section should be used to explain why. The “Comments” field can also be used to elaborate on a “No” answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
PASS TachoSil Evaluation (PasTel): Short- and long-term safety evaluation of TachoSil in paediatric population

EU PAS Register® number: HMA-EMA RWD Catalogue number: EUPAS1000000505
Study reference number (if applicable): TBD

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[2]	☒	☐	☐	6
1.1.2 End of data collection[3]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Progress report and interim reports are not planned for this study.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8 & 9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

No hypothesis is to be tested in this study.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.3

[2] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[3] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☒	☐	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in the case of primary data collection)	☒	☐	☐	11

Comments:

In most cases measures of association require both, exposed and not exposed study groups. In current study design, simple measures of associations can be used to assess e.g., strength and direction between two variables, such as exposure and occurrence of an adverse event(s) (correlation coefficients) or relationship between categorical variables, e.g., how proportions of one variable differ by levels of another categorical variable (Chi-square or Fisher exact test).

Currently, analysis plan is briefly described and includes simple descriptive statistics for evaluation of adverse events of TachoSil use (rate of occurrence or cumulative incidence). Final version of analysis plan will be determined after completion of feasibility questionnaires by all Investigators. At the time of filling this checklist, feasibility evaluation was not completed.

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2
	4.2.2 Age and sex	☒	☐	☐	9.2
	4.2.3 Country of origin	☐	☒	☐	
	4.2.4 Disease/indication	☒	☐	☐	9.2
	4.2.5 Duration of follow-up	☒	☐	☐	9.2
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

The study will be conducted in Poland, and it is expected that patients of Polish origin will make up the majority of the study population, however country of origin is not particularly considered an important factor in this study

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.1 & 9.3

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.1
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Exposure categorization according to time window is not considered relevant since TachoSil is a degradable medicinal product, and once applied it remains embedded in the wound until it degrades on its own.

The study, by design, does not involve comparator.

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8 & 11
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	11
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

The study aims to evaluate adverse events and AESIs during perioperative periods and adverse events during 36 months period following surgery. Methods of assessing AEs are provided in section 11 and follow standard clinical practices.

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.9
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Individuals recruited to this study do not differ systematically from the population of interest, in fact it is the same population, therefore selection bias is not considered relevant.

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

TachoSil is a fibrin sealant and has the same action despite the indication (type of surgery) for which it is used. Effect modification is all about stratification and occurs when an exposure has a different effect among different subgroups. Therefore, effect modifiers are not relevant for this study.

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3
	9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
	9.2.2 Outcomes? (e.g. date of occurrence, multiple events, severity measures related to event)	☒	☐	☐	9.3
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3
	9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.6

Comments:

It should be noted that information available from data sources (medical records maintained at site) is to be determined after completion of feasibility questionnaires by all Investigators. At the time of filling this checklist, feasibility evaluation was not completed.

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☐	☒	☐	9.7
10.2	Is study size and/or statistical precision estimated?	☐	☒	☐	9.7
10.3	Are descriptive analyses included?	☒	☐	☐	9.7
10.4	Are stratified analyses included?	☐	☒	☐	9.7
10.5	Does the plan describe methods for analytic control of confounding?	☐	☒	☐	9.7
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	9.7

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	9.7
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	9.7

Comments:

Analysis plan is briefly described and includes simple descriptive statistics for evaluation of adverse events of TachoSil use. Final version of analysis plan will be determined after completion of feasibility questionnaires by all Investigators. At the time of filling this checklist, feasibility evaluation was not completed.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	
11.2 Are methods of quality assurance described?	☐	☒	☐	
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☒	☐	

Comments:

Individuals recruited to this study do not differ systematically from the population of interest, in fact it is the same population, therefore selection bias is not considered relevant.

At the time of filling this checklist, feasibility evaluation was not completed.

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☒	☐	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☐	☒	☐	

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Mirosław Kocięcki

Date: 2025-10-31 | 14:28 CET

Signature: DocuSigned by: Mirosław Kocięcki D3B17DF8CDE3441...

ANNEX 3. ADDITIONAL INFORMATION