Title: RollOut –Pre-Rolled TachoSil in Laparoscopic Utilisation. A Non-Interventional Study

NCT Number: NCT02685007

Protocol Approve Date: 20th August 2015

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

Non-Interventional Study Protocol

Short title: **RollOut** –Pre-**Roll**ed Tach**o**Sil® in Laparoscopic **Ut**ilisation. A Non-Interventional Study

Title: **RollOut** –Pre-**Roll**ed Tach**o**Sil® in Laparoscopic **Ut**ilisation. A Non-Interventional Study

Study ID: TachoSil-4001

Sponsor:

Takeda Pharma Vertrieb GmbH & Co. KG
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D-10117 Berlin
Germany

Takeda Pharma Ges.m.b.H.
EURO PLAZA, Gebäude F
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A-1120 Wien
Austria

Study phase: Medical Affairs, Non-registration Company Sponsored (Observational)

Date of version of protocol: 20th August 2015

1 Administrative information

1.1 Contacts

A separate contact information list will be provided to each site.

Issue	Germany Contact	Austria Contact
Adverse event reporting according to section 9	PPD	
Site Management, CRO (advice on study documentation e.g. protocol, ICF CRF)		
Study coordination, Sponsor (medical advice on compound)		
Responsible Medical contact (carries overall responsibility for the conduct of the study)		

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- Guidelines for good Pharmacoepidemiology Practices (GPP)
- All relevant local laws and regulations, including, without limitation, data privacy laws, disclosure laws, and regulations.

SIGNATURES

PPD

Date

PPD

Date

PPD

Date

PPD

Date

PPD

Date

2 Summary

The aim of this NIS is to collect further knowledge on the routine use of pre-rolled TachoSil® in laparoscopic surgery, especially in the field of gynecology, urology and visceral surgery where its hemostatic and sealing properties [see Summary of Product Characteristics (SmPC)] help to reduce the rate of postoperative complications, especially of postoperative bleeding and lymph leakage.

Short Title of Study

RollOut –Pre-**Roll**ed Tach**o**Sil® in Laparoscopic **Ut**ilisation. A Non-Interventional Study

Study sites

Up to 50 German and 10 Austrian hospitals performing laparoscopic surgery, from departments of gynecology, urology and visceral surgery. The number of centres is subject to adjustment.

Objectives

- To describe ease of use and satisfaction with application of pre-rolled TachoSil® in laparoscopic procedures within approved therapeutic indication (SmPC).
- To assess whether pre-rolled TachoSil® is valuable from the surgeon's view for reducing post-surgical complications, especially bleeding and lymph leakage.
- To perform a costs analysis (length of hospital stay, avoidance of complications, cost savings etc.) based on information given by physicians and pecuniary considerations.
- To describe safety in the routine use of pre-rolled TachoSil® in laparoscopic use.

Methodology

Observational Model: Cohort, Time Perspective: Prospective

Number of patients

A sample size estimation resulted in a total number of 465 patients (please refer to Chapter 11.3). The final number of enclosed patients is determined by the number of available patients with pre-rolled TachoSil®. It is planned to include up to 105 Austrian and 360 German patients who will have laparoscopic surgery, especially in the field of gynecology, urology and visceral surgery and pre-rolled TachoSil® is used.

Diagnosis/Disease/Condition and main criteria for inclusion

Inclusion Criteria:

- Inpatients planned for laparoscopic surgery, in the field of gynecology, urology and abdominal surgery where pre-rolled TachoSil® was applied, 18 years or older.

Exclusion Criteria:

- Contraindications, such as hypersensitivity to the active pharmaceutical ingredients or to other components of pre-rolled TachoSil®, according to the current SmPC.
- Patient participates in another clinical trial.

Duration of data collection per patient

Observational period for individual patient: from surgery (V0: Baseline) until date of discharge from hospital (V1: Final visit).

Criteria for evaluation

Population descriptors

Inpatients planned for laparoscopic surgery, in the field of gynecology, urology and visceral surgery where pre-rolled TachoSil® was applied and at least 18 years of age.

Main outcome variables

Primary

- Assessment by the surgeon with respect to ease of use and overall satisfaction in the application with pre-rolled TachoSil®, using 5-Point-Likert-Scales (1 = easy/satisfied, 5 = difficult/ not satisfied)
  [Time Frame: intra- and post-surgery until hospital discharge]

Secondary

- Length of hospital stay (ICU and normal hospital station)
  [Time Frame: Date of surgery until hospital discharge]
- Pharmaco-economic evaluation as assessed by the surgeon
  [Time Frame: intra- and post-surgery until hospital discharge]
- Intra- and post-operative adverse events, especially including bleeding and lymph leakage
  [Time Frame: from study start to study end]

Health economics

Cost analysis (length of hospital/ICU stay, avoidance of complications, cost savings) based on information given by physicians and pecuniary considerations (cost per minute of surgery/day in ICU/day in normal ward)

Statistical methods

For the analysis of data the safety population (SAF) only will be considered. The safety population consists of all patients,

- who received a patient information and who had consented to the collection, transmission and evaluation of their data (Comment: this has to be documented in the CRF and it is assumed that the consent forms are available for all patients in the corresponding study center.), and
- who underwent laparoscopic surgery in the field of gynecology, urology and visceral surgery with pre-rolled TachoSil® applied during surgery as documented in the CRF.

The SAF is used for summaries of demographic and baseline characteristics, all safety related variables and all summaries of effectiveness data. No per-protocol- set analysis will be done.

All data collected will be analyzed descriptively. In general, numerical continuous or 'quasi'-continuous data will be summarized with standard descriptive statistics including number of patients with valid data, arithmetic mean, standard deviation, minimum, median and maximum. For categorical variables tables of frequencies (absolute and relative frequencies) will be presented. The percentages are based on the number of patients in column heading unless otherwise stated. The number of patients with missing values is included in the calculation of the percentages.

Statistical analyses will be performed using validated statistical software (e.g. SAS®, SAS Institute Inc.). All statistical details including calculated variables and proposed format and content of tables will be detailed in a separate document, the statistical analysis plan (SAP). The SAP will be provided by the CRO CCI and finalized before study database lock.

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APPENDICES

1. SmPC, TachoSil® sealant matrix, German language 09/2014

List of Abbreviations and Definition of Terms

AE:	Adverse Event
ADR:	Adverse Drug Reaction
CA:	Competent Authority
CCSI:	Core Company Safety Information
CRF:	Case Report Form
CRO:	Contract Research Organisation
CV:	Curriculum Vitae
GCP:	Good Clinical Practice
GPP:	Good Pharmacoepidemiology Practices
ICH:	International Conference on Harmonisation
ICU:	Intensive care unit
IDS:	International Drug Safety
IEC:	Independent Ethics Committee
IRB:	Institutional Review Board
NIS:	Non-interventional study
PP:	Per Protocol
PSUR:	Periodic Safety Update Report
SAE:	Serious Adverse Event
SAF:	Safety Population
SAP:	Statistical Analysis Plan
SADR:	Serious Adverse Drug Reaction
SmPC:	Summary of Product Characteristics

3 Introduction

TachoSil® consists of a collagen sealant matrix coated with human fibrinogen and human thrombin for use as a local haemostatic and tissue sealing. This fixed combination is applied directly to the wound surface. Upon contact with blood, body fluids, or physiological saline, the components of the coating dissolve and diffuse into the wound surface. Thrombin converts fibrinogen into fibrin, mimicking the final stage of the coagulation cascade, and forming a cross-linked fibrin clot, which holds the collagen matrix tightly to the wound surface providing local haemostasis and tissue sealing. The active side of the coating sealant matrix is marked in yellow.

Extensive experience on the use of TachoSil® in open invasive surgery[5] and its relevant results in respect to reduction of time to hemostasis[5,7,8], change in length of hospital stay[5,9,10] and decrease in postoperative complications[5,9,11] encouraged surgeons to apply TachoSil® in minimal invasive (laparoscopic) surgery as well[6]. As laparoscopic techniques require the application of TachoSil® through a trocar, surgeons started preparing TachoSil® themselves raising the need to develop a pre-rolled form which was approved by the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) in September 2014.

No clinical trials using pre-rolled TachoSil have been performed. This real-world observational study is conducted to obtain an overview on the ease of use of pre-rolled TachoSil® in laparoscopic use, especially when performing gynaecological, urological and visceral surgery. Additionally, users' satisfaction with the product will be evaluated to confirm procedural advantages of the pre-rolled form in laparoscopic use.

4 Study Objectives

- To describe ease of use and satisfaction with application of the pre-rolled TachoSil® in laparoscopic procedures within approved therapeutic indication (SmPC).
- To assess whether pre-rolled TachoSil® is a valuable tool from the surgeon's view for reducing post-surgical complications, especially bleeding and lymph leakage.
- To perform a costs analysis (length of hospital stay, avoidance of complications, cost savings etc.) based on information given by physicians and pecuniary considerations (Euro)
- To describe safety in the routine use of pre-rolled TachoSil® in laparoscopic surgery.

5 Study Administrative Structure

5.1 Study Sites

Up to 50 German hospitals and 10 Austrian hospitals performing laparoscopic surgery, including departments of gynecology, urology and visceral surgery. Sponsor/CRO will keep a record of the individuals responsible for each participating Study Site, the Site Responsibles.

5.2 Sponsor Personnel

Sponsor will keep a record of all relevant sponsor personnel. Sponsor will be in charge of relevant document submission to Regulatory Authorities and Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs).

5.3 Contract Research Organisation (CRO)

The CRO CCI [redacted] will be in charge of document development, monitoring, data management, Statistical Management Plan, analysis and generation of a study report. Details of the tasks and responsibilities are regulated in the study task order between the sponsor and the CRO.

The CRO will keep a record of all involved CRO personnel.

5.4 Essential Documents

The following essential documents must be received by Sponsor/CRO before the study is initiated at a site:

- Written agreement, including section of protocol agreement between Takeda and the Study Site Responsible/Hospital.
- Patient Information Sheet and Informed Consent Form in local language (notified to / approved by Independent Ethics Committees (IECs) as locally required
- Written IEC vote according to local regulations
- Authority notification according to local regulations

6 Ethics

This study is an observational study where the existence of the study has no impact on the patient except for collection of informed consent to use of the patient's data.

6.1 Ethical conduct of the Study

This study will be conducted in accordance with the protocol, the current version of the Declaration of Helsinki, Good Pharmacoepidemiology Practices (GPP), ISPE GPP guideline and any local regulations. Special attention will be paid to data protection as described in Directive 95/46/EC.

Takeda will ensure that the protocol, any amendments and the Patient Information Sheet/Informed Consent Form are submitted to the relevant Independent Ethics Committees (IECs) according to local requirements.

Takeda as the sponsor is responsible for meeting the ICH requirement for yearly updates to the IECs, if applicable.

6.2 Independent Ethics Committee

According to all relevant local regulations, the Sponsor will:

- notify or obtain approval from the relevant IEC of the protocol, any amendments and the Patient Information Sheet / Informed Consent Form

The Sponsor will submit required documents to the IEC, such as:

- notification of substantial changes of the study documents
- notification of the end-of-study
- a summary of the study results

Sponsor/CRO will keep an updated list of all submission and approval dates of all documents submitted to the IEC and will provide the Site Responsible with a copy of this list. Copies of the documents will be distributed upon request.

Authorities

Sponsor will send required documents to the competent authority (CA) and/or other national or regional authorities. Sponsor will keep an updated list of submission and approval dates and a copy of all documents submitted.

6.3 Patient Information and Written Informed Consent

The Site Study Responsible must give the patient (and if applicable, legal guardian) oral and written information about the study in a form that the patient (legal guardian) can understand, and obtain the patient's (and if applicable, the patient's assent and the legal guardian's)

written consent before collection of identifiable patient information (hereinafter referred to as personal data). Before consenting, the patient (and if applicable, legal guardian) must be left with ample time to consider and to pose questions.
Since the study is observational the consent only concerns the data collection per se and is no consent to any experimental procedure or treatment.
As patients will only be eligible for study participation in case pre-rolled TachoSil® has been applied during surgery, information regarding the study will be provided to potential participants before the surgery, but consent will be collected only after the surgery.

The patient must agree that sponsor personnel, their representatives or IEC or CA personnel (national or other) may require direct access to the patient's data / personal records which were collected, processed and stored in an anonymized form.

The patient must agree that his / her data will be processed and stored in an anonymized form for evaluation of this study and any later overviews. Data may also be transferred in anonymized form to third parties, e.g. other companies or authorities, that may be located in other countries with potentially different regulations for data.
The patient and legal guardian, if applicable, has the right to withdraw his/her consent at any time without prejudice. In the Informed Consent Form it is stated that if consent is withdrawn, any data collected before withdrawal of consent will be kept unless its deletion is actively requested by the patient. The original, signed Informed Consent Forms must be kept on the Site.
For details, see the Patient Information Sheet and Informed Consent Form.

7 Study Design and Plan

This study is a 'non-interventional study' as defined in**:** G-STND-PV-006, Directive 2001/83/EC (4) and will follow the guidelines for GPP (2). Additional applicable sponsor SOPs are: 1410A-SOP-0000001.03, DE-BE-MED-ALL-025.

This means that:

- The assignment of a patient to a particular therapeutic strategy is not decided in advance by the study protocol but falls within current practice
- No additional diagnostic or monitoring procedures shall be applied to the patients
- Epidemiological methods shall be used for the analysis of collected data

- Pre-rolled TachoSil® is prescribed in accordance with the terms of the marketing authorisation(s)
- The prescription of pre-rolled TachoSil® is clearly separated from the decision to include the patient in the study

7.1 Study Schedule

Planned Start of Study:	October 2015
Planned collection of first data point:	October 2015
Planned collection of the last data point:	November 2016
Planned End of Study:	February 2017
Planned completion of the Study Report:	May 2017

The Start of Study is defined as country specific IEC votes are available.
The End of study is defined as database lock.

Sponsor will ensure that End-of-Study notification is submitted to the concerned authorities and IEC for each site, for each country and for the complete study, as locally required.

Global Research will ensure that results are posted on “clinicaltrials.gov” and Sponsor will ensure that results are posted as required by local authorities.

Based on upcoming knowledge, Takeda might choose to terminate the study prematurely. In such case the Committee(s), study sites, IECs and authorities will be informed promptly.

7.2 Discussion of Study Design

This study is a non-interventional, international, prospective, multi-site cohort study in patients planned for laparoscopic surgery in the field of gynecology, urology or visceral surgery. A patient can be included in the study when the physician has decided to use pre-rolled TachoSil® according to the local SmPC.
There are no treatment groups or interventions to which the patients can be randomly assigned. Data will be collected in a routine setting. Participating physicians will not perform any medical procedures that are outside of their normal routine. All treatment decisions are at the sole discretion of the participating physicians and reflect their current standard of care. The decision to apply pre-rolled TachoSil® must be made independently from the decision to include a patient in this study.

Results from this study are prone to selection bias, e.g. by selecting sites experienced in using pre-rolled TachoSil® in laparoscopic surgery, or by including patients with known surgical outcome. Also confounding factors prevail in patients in a real-world setting, e.g. by indication, concurrent disease, concomitant drugs, or differing surgical procedures among sites.

It is acknowledged that such biases are present in any observational study. These limitations of the study design are inherent and result from the non-interventional character and the voluntary participation of physicians and patients.

7.3 Selection of Study Population

It is planned to include up to 105 Austrian and 360 German inpatients who have undergone laparoscopic surgery in the field of gynecology, urology and visceral surgery where pre-rolled TachoSil® was applied and who are 18 years or older.

Contraindications, such as hypersensitivity to the active pharmaceutical ingredient or to another ingredient of pre-rolled TachoSil®, are to be observed according to the current SmPC.

The observational period for individual patient will last from surgery (V0: Baseline) until date of discharge from hospital (V1: Final visit).

Data will be collected from patient files as well as study specific questions answered by the treating physician.

Written informed consent to use of collected data must always be obtained before collection of any study specific personal, sensitive data.

Subjects should be included in the study only once.

Data erroneously collected from subjects for which written consent is not available, will not be included in or will be deleted from the database.

7.4 Treatments

Non-interventional/observation – no experimental treatments/pharmacotherapy are applicable.

A patient can be included in the study when the physician has decided to use pre-rolled TachoSil® according to the local SmPC.

There are no treatment groups or interventions to which the patients can be randomly assigned. Data will be collected in a routine setting. Participating physicians will not perform any medical procedures that are outside of their normal routine. All treatment decisions are

at the sole discretion of the participating physicians and reflect their current standard of care. The decision to apply pre-rolled TachoSil® must be made independently from the decision to include a patient in this study.

8 Conduct

Data collection overview:

Type of data point	**Timing of data point**			
	Before diagnosis/ treatment	At time of surgery	Time interval 1 (After surgery until discharge from hospital)	End of data collection (day of discharge from hospital)
Investigator contract signed	x			
ICF signed			x	
Inclusion/Exclusion criteria			x	
Demographics		x		
Medical history	x	x		
Surgery parameters		x		
Adverse events after application of pre-rolled TachoSil®		x	x	x
Post-operative parameters			x	x
Assessment by the surgeon (5-Point-Likert-Scales)			x	x
Cost-effectiveness				x

Demographics:

- Age, gender (if gender is female, pregnancy/breast-feeding (yes/no) should be documented), height, weight

Inclusion criteria:

- Inpatient planned for laparoscopic surgery, in the field of gynecology, urology and visceral surgery where pre-rolled TachoSil® was applied and at least 18 years of age

Exclusion Criteria:

- Contraindications, such as hypersensitivity to the active pharmaceutical ingredient or to another ingredient of pre-rolled TachoSil®, according to the current SmPC.
- Patient participates in another clinical trial.

Medical history:

- Concomitant diseases
- Evaluation of haemorrhage risk
- Coagulation status

Intra-operative parameters:

- Coagulation status
- Diagnosis underlying surgery, including type of surgery (gynecology, urology or visceral surgery)
- Indication for use of pre-rolled TachoSil® (hemostasis, tissue sealing or suture support)
- Description of surgery (Type of minimal-invasive surgical technique, duration)
- Description of TachoSil application (diameter of trocar, dry/wet, localisation, number of pre-rolled TachoSil® applied during surgery, time of compression)
- Primary techniques used for tissue sealing/hemostasis
- Intra-operative adverse events after application of pre-rolled TachoSil®
- Assessment of pre-rolled TachoSil® by the surgeon:
- - ease of use (5-Point-Likert-Scale)
- - satisfaction with the application of pre-rolled TachoSil (5-Point-Likert-Scale)

Post-operative parameters:

- Post-operative adverse events, especially including bleeding and lymph leakage
- length of ICU and overall hospital stay

Overall assessment of pre-rolled TachoSil® by the surgeon:

- overall satisfaction with the application of pre-rolled TachoSil (5-Point-Likert-Scale
- cost-effectiveness, based on subjective assessment of the surgeon, shortening of surgery time and hospital stay.

Adverse events, exposure of a pregnant patient to pre-rolled TachoSil® or pregnancy/breast-feeding after application of pre-rolled TachoSil®, as well as medication error, suspected transmission of an infectious agent and lack of effect.

Informed Consent will be obtained before collection of the first data point.

9 Management and Reporting of Adverse Events

9.1 Definitions

Adverse Event

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product. All AEs (Serious adverse events (SAEs) and adverse events which do not meet the criteria of a SAE), will be recorded and reported in this study. SAEs are defined below in Section 9.2.

9.2 Classification

Serious Adverse Events

A Serious Adverse Event (SAE) is an AE that meets any of the following criteria:

- Is fatal or life threatening, i.e., in the view of the Investigator, places the patient at immediate risk of death from the reaction as it occurred. An event would not be classified as life threatening solely because, had it occurred in a more serious form, it might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening, even though drug-induced hepatitis can be fatal.
- Results in persistent or significant disability or incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Requires inpatient hospitalization or prolongation of an existing hospitalization.
- Is a congenital anomaly/birth defect.

- Any other important medical event that may not result in death, be life-threatening or require hospitalization, but based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Hospitalization for underlying disease progression will constitute an SAE. Hospitalization for an elective or planned procedure to treat a pre-existing condition is not considered an SAE, unless it results in one of the other outcomes listed above.

Severity

The Investigator will use the following definitions of severity in the evaluation of AEs:

- Mild: An AE that is easily tolerated and does not interfere with daily activities.
- Moderate: An AE that is sufficiently discomforting so as to interfere with daily activities.
- Severe: An AE that prevents normal everyday activity.

Note that “severe” is not synonymous with “serious”: an AE may be assessed as severe without meeting the criteria for an SAE (see above)

Assessment of Relationship to Study Drug

The following definitions of relationship should be used to characterize the suspected causality of each AE as either related or not related to pre-rolled TachoSil®. This assessment should be based on the Investigator's consideration of all available information about the event, including temporal relationship to drug administration, recognized association with drug product/class, pharmacological plausibility, and alternative etiology (e.g., underlying illness, concurrent conditions, concomitant treatments):

- Related: There is a reasonable possibility that the drug caused the event.
- Not related: There is not a reasonable possibility that the drug caused the event

Adverse Reactions

For the purposes of this study, an adverse reaction is an AE that is considered related to pre-rolled TachoSil® according to the definition above.

Outcome

- **Fatal:** The patient died due to the event. If the patient died due to other circumstances than the event the outcome should be stated as ‘Not recovered’ or ‘Recovering’.

- **Recovered/Resolved:** The patient has fully recovered from the event or the condition has returned to the level observed at baseline.
- **Recovering/Resolving:** The event is improving but the patient is still not fully recovered.
- **Not Recovered/Not Resolved:** The event is ongoing at the time of reporting and the patient has still not recovered.
- **Recovered with Sequelae/Resolved with Sequelae:** As a result of the event, the patient suffered persistent and significant disability/incapacity (e.g. became blind, deaf or paralysed).
- **Unknown:** If Outcome is not known or not reported.

9.3 Reporting of Adverse Events

Documentation of AEs will commence after a patient has provided informed consent and pre-rolled TachoSil® was applied in that patient. AEs and SAEs (which include all deaths) must be reported, whether or not considered causally related to pre-rolled TachoSil®.
In case of a SAE, the Investigator will notify the Sponsor through use of the SAE form, within 24 hours after the Investigator becomes aware of the event. The event must be documented in source documentation.

AEs which do not meet the criteria of SAEs are documented through use of the AE form within the study CRF.

After receipt of the initial report, the information will be reviewed, and the Investigator might be contacted to request additional information or for data clarification. If required, a follow-up report, including all new information obtained on the event, must be prepared and sent to the designated contact of the Sponsor.

The Sponsor assumes responsibility for reporting of AEs/SAEs occurring in patients exposed to pre-rolled TachoSil® to regulatory authorities according to legal requirements.

9.3.1 Reporting of Pregnancy and Breast-feeding

Any case in which a pregnant patient or a patient that is breast-feeding is exposed to pre-rolled TachoSil® this information needs to be forwarded to the Sponsor using the SAE form regardless whether an AE results or not.

9.3.2 Reporting of Medication Error

All information of medicinal product medication error, suspected transmission of an infectious agent or lack of effect relating to pre-rolled TachoSil® regardless of whether an SAE results or not, need to be forwared to the Sponsor using the SAE form.

10 Data Quality Control and Assurance

10.1 Quality Control

The quality of data and adherence to the NIS protocol, to legal and ethical requirements will be overseen by the CRO applying a combination of centralized and on-site monitoring.
All CRFs will be reviewed for pre-defined criteria (e.g. ICF, AEs and study treatment), and queries will be raised in case of deviations.
On-site visits will be scheduled in approx. 5% of sites (1 Austrian and 3 German sites), including source data verification of pre-defined items (e.g. ICF, AE data and Patient Identification List).
The extent and nature of quality assurance will be described in detail in the monitoring plan.
If applicable, for further information see sponsor SOPs: G-SOP-MA-005, C-GUID-DO-354 and C-GUID-DO-333.

10.2 Audit from Quality Assurance Unit

The Quality Assurance (QA) unit may audit the study to ensure that study procedures comply with the protocol and standard operating procedures, and that collected data is correct and complete.

10.3 Inspection by IEC or Competent Authority

Representatives from EC or Competent Authority may in rare cases wish to inspect the study on site. Upon receiving notification of such inspection, the Study Site Responsible must immediately contact the Sponsor and must make the records available as requested.

10.4 Data Management

The CRO is responsible for Data Management carried out according to a Data Management Plan. A data management plan, which will include the description of plausibility checks, will be prepared before the start of data entry.
If the written informed consent of a patient is known not to be available in spite of it being required, data for this patient is not entered into or is deleted from the database.

If a patient is erroneously included in the study more than once only the data relating to the first inclusion will be kept in the database and be available for analysis.

If a patient is included in the study in spite of being treated off-label (not according to the SmPC), data is kept in the database and analysed as described in the Statistical Analysis Plan.

The current Standard Coding Instructions for coding of medical history, concomitant illness (MedDRA), concomitant medication (WHO-Drug) and adverse events (MedDRA) must be followed.

The patients will be identified in the database only by Study ID, Site ID, patient number, year of birth, and gender.

10.4.1 Data Collection Tools and Flow

The Study Site will receive data collection tools (Case Report Forms (CRFs)) from CCI CCI. Whenever possible, complete data sets should be entered. Text field entries and any data collected on paper should be legible and follow the requested language standard.

The Study Site Responsible must sign off the complete data set for each patient, confirming the collected data. SAE data collected and reported according to section 9.3 should be signed off separately by a physician who may or may not be involved in the study.

The Study Site will provide completed CRFs directly to the responsible CRO syneed medidata.

10.4.2 Query management

In case of incomplete or inconsistent entries regarding predefined CRF-items (e.g. informed consent, study treatment) the CRO will contact the respective physician in writing for clarification or completion of missing data.
In case of incomplete or inconsistent entries regarding AEs or SAEs, the Sponsor will contact the respective physician for clarification. Prior to database lock, a reconciliation of study-related safety information with the sponsor's safety database will be performed.

11 Statistical Methods and Determination of Sample Size

In general, summary statistics (mean, median, standard deviation, minimum, and maximum) will be provided for continuous variables, and the number and percentage of each category will be provided for categorical data. Any changes in the original statistical methodology will be documented in the statistical analysis plan (SAP), a separate document provided by the CRO CCI [redacted]

11.1 Statistical Analysis Plan

This study is observational and epidemiological methods will be employed for data analyses. All statistical details including calculated variables and proposed format and content of tables will be detailed in the SAP, a separate document provided by the CRO CCI [redacted]

The SAP will be finalized before study database lock. The analysis will be performed in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology [R5].

Statistical analyses will be performed using validated statistical software (e.g. SAS®, SAS Institute Inc.).

Descriptive analysis will be performed of all collected data except data collected only for the purpose of data cleaning. All AEs will be listed as described in the SAP in section 5.

The main outcomes of the study are:

<u>Primary</u>

Assessment by the surgeon with respect to ease of use and overall satisfaction in the operation, using 5-Point-Likert-Scales[12] (1 = easy/satisfied, 5 = difficult/ not satisfied)

[Time Frame: intra- and post-surgery until hospital discharge]

Secondary

- Length of hospital stay (ICU and normal hospital station)
  [Time Frame: Date of surgery until hospital discharge]

- Pharmaco-economic evaluation as assessed by the surgeon
  [Time Frame: intra- and post-surgery until hospital discharge]

- Safety intra- and post-operative adverse events
  [Time Frame: from study start to study end]

Health economics

Cost analysis (length of hospital/ICU stay, avoidance of complications, cost savings) based on information given by physicians and pecuniary considerations (cost per minute of surgery/day in ICU/day in normal ward)

AEs/SAEs reported in the study as well as AEs/SAEs reported directly to authorities and to Takeda Drug Safety according to section 9.3 and not captured in the study database will be extracted from the overall safety database and the study database and listed or tabulated in the final report in the standard way of presenting such data in a Periodic Safety Update Report (PSUR).

11.2 Interim Analyses

No interim analyses are planned for this study.

11.3 Determination of Sample Size

It is planned to collect data from up to 50 german hospitals and 10 ustrian hospitals performing laparoscopic surgery, from departments of gynecology, urology and visceral surgery. Each study centre should document only up to 20 patients.

As primary outcome measures the peri- and post-surgery assessment by the surgeon with respect to ease of use and overall satisfaction in the operation, using 5-point-Likert-Scales (1 = easy/satisfied, 5 = difficult/ not satisfied) are fixed in the study protocol. It is expected that

the use of pre-rolled TachoSil® is easier than the application of planar TachoSil® prepared/rolled by the surgeons themselves.
No published paper could be found with an identical outcome measure 'ease of use', which could have served as base for sample size calculation. Therefore the results of an older study with a specific MIS -applicator as a surrogate approach (Nycomed Arzneimittel GmbH 1998) were used.

Amongst others a parameter called 'Handhabungs-Score' (handling- score) was considered as outcome parameter according to the study protocol. This parameter comes very close to the parameter 'ease of use' intended to be used in the present RollOut-study. This score was calculated as the sum of the answers from a questionnaire with 5 AMISA-specific items. In the best case, this score takes a value of 5, in the worst case a value of 17. The results for the handling score showed that in 82% of cases the score was less or equal 9 points and about 18% greater than 9 points.

To show in a 1-group design (NIS) that this rate can be reduced with the use of pre-rolled TachoSil® significantly to 9%- points (α= 0.05, power = 80%, two-tailed one group Chi^2- test) it takes a minimum of 122 patients without any drop-out (see Table 2 below). To investigate this hypothesis in 3 fields of surgery (gynecology, urology and visceral surgery) independently, a total of 366 patients is needed. Since it is expected to improve the power from 80% up to 90% a minimum of 155 patients in each field and a total up to 465 should be included into the Study.

Test significance level, α	0.050	0,050
1 or 2 sided test?	2	2
Null hypothesis proportion, π_0	0.180	0,180
Alternative proportion, π_A	0.090	0,090
Power (%)	80	90
N	122	155

Table 2: Comparison of a portion π_A against a fixed portion π_0 (asymptotic Chi^2-test); determined with the program N-Query 7.0 according to Dixon et al. (1983)

12 Reports

A Non-Interventional Study Report based on the results obtained will be prepared and submitted to Global Medical Affairs for distribution. The Final Study Report should be available within one year from database lock.

13 Publications

Takeda aims to have the results of this study published.

Takeda has the right to use the data and results for regulatory purposes and for internal presentation within the company and to partners.

14 Archiving of Study Documentation

During the course of the study the Site Responsible must as a minimum file the essential documents (Section 5.4), the protocol, any amendments, the list of participating patients, the written informed consents, the CRFs and the progress reports in the Study Site File. After final database lock the Site Responsible must as a minimum store the list of participating patients and the signed Informed Consent Forms on site for 10 years. The Site Responsible should store additional study documentation for a longer period of time as required by any local regulations and/or hospital requirement.

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