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

NCT Number: NCT02685007

Certain information within this Statistical Analysis Plan 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.

Statistical Analysis Plan

Statistical Analysis Plan for the non-interventional study

TachoSil-4001 (RollOut)

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Document History

Date	Version	Author	Description
15-Sep-2017	1.0	PPD	New document

1 Introduction

This document describes the statistical analysis of the non-interventional study „TachoSil-4001" (RollOut).

1.1 Title

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

1.2 Protocol Number

Study Protocol Number: TachoSil-4001

1.3 Sponsor

Takeda Pharma Ges.m.b.H.
EURO PLAZA, Gebäude F
Technologiestraße 5
1120 Vienna
Austria

Medical Manager:

PPD

Drug Safety:

PPD

1.4 Investigational Medicinal Product (IMP)

TachoSil Sealant matrix

1.5 Indications

TachoSil is indicated in adults for supportive treatment in surgery for improvement of haemostasis, to promote tissue sealing, for suture support in vascular surgery where standard techniques are insufficient, and for supportive sealing of the dura mater to prevent postoperative cerebrospinal leakage following neurological surgery (Summary of Product Characteristics; TachoSil, 13.Sep.2017)

1.6 Patients

It is planned to document 120 patients in up to 12 Austrian centers.

1.7 Duration of Data Collection

February 2016 (FPFV) – September 2018 (LPLV)

1.8 Summary

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 (Study Protocol; 22. Feb. 2016).

1.9 Responsibilities

Company Confidential Information, is responsible for the analysis of this non-interventional study (NIS).

Contact:

Company Confidential Information

2 Analysis

2.1 Sample Size

Due to the character of this study (observational, non-interventional, no randomization or control group), only descriptive analysis will be conducted and no hypothesis will be tested. It is planned to include approximately 120 patients in this non-interventional study.

3 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.

(Study Protocol; 22. Feb. 2016)

4 Study Variables

Continuous variables will be analysed using minimim, maximum, arithmetic mean, median.
For discrete variables (ordinal, nominal), the frequency (absolute and relative) will be reported (arithmetic mean and median optionally).
If there are free text entries, these will be coded using dictionaries, if necessary.

4.1 Baseline

4.1.1 Informed Consent, Inclusion/Exclusion Criteria

- A valid Informed Consent, dated before start of documentation, must be present. All Inclusion Criteria must be fulfilled (and none of the Exclusion Criteria), otherwise the patient must be excluded from analysis.

4.1.2 Demographics

- Age (years)
  - minimum, maximum, median, arithmetic mean
  - Age groups and their frequencies

- Height (cm)
  - minimum, maximum, median, arithmetic mean
- Weight (kg)
  - minimum, maximum, median, arithmetic mean
- Gender
  - Frequencies
- Pregnancy
  - frequencies

4.1.3 Main Diagnosis

- Reason for Surgery
  - Code with MedDRA
  - Frequencies of coded terms

4.1.4 Concomitant Diseases

- Concomitant Diseases
  - Yes / No: Frequencies
  - Frequencies of disease groups
  - Other diseases: Code with MedDRA

4.1.5 Evaluation of Risk of Bleeding

- Patients with blood-thinning medication
  - Yes / No: Frequencies
  - Frequencies of medications
  - Other medication: grouping of terms, if possible
- Additional coagulation disorders
  - Yes / No: Frequencies
  - Frequencies of disorders
  - Other disorders: grouping of terms, if possible

4.1.6 Coagulation

- Thromboplastin value
  - Type (INR, Quick, no value): Frequencies
  - INR: minimum, maximum, median, arithmetic mean
  - Quick (%): minimum, maximum, median, arithmetic mean
- Partial thromboplastin time (seconds)
  - minimum, maximum, median, arithmetic mean
- Platelet count ($10^3/mm^3$)
  - minimum, maximum, median, arithmetic mean
- Platelet activity: Normal, reduced: Frequencies

4.1.7 Pre- & intraoperative Measures

- Pre- & intraoperative Measures:
  - Yes / No: Frequencies
  - Details: Frequencies, minimum, maximum, median, arithmetic mean

- Coagulation factor: Name, Dose, Unit
  - Frequencies, minimum, maximum, median, arithmetic mean
- Other: Coding of free text, if possible

4.1.8 Documentation of Surgery

- Date of Surgery
- Type of Operation: Frequencies
- Minimal invasive technique: Frequencies
  - Other: Coding of free text, if possible
- Duration of surgery (minutes)
  - Minimum, maximum, median, arithmetic mean
- Conversion: yes / no: Frequencies
  - Reason(s): Frequencies
  - Other: Coding of free text, if possible
- Adverse Event: yes / no: Frequencies
- Main reason for prerolled TachoSil use: Frequencies
  - Other reason: Coding of free text, if possible
- Hemostatic actions before TachoSil: Frequencies
  - Details: Frequencies
  - Other: Coding of free text, if possible
- Application of TachoSil: Frequencies
  - Other: Coding of free text, if possible
- TachoSil replacing other therapy: Yes / No: Frequencies
  - Details: Frequencies
  - Other: Coding of free text, if possible
- Reason for Preference of TachoSil
  - Details: Frequencies
  - Other: Coding of free text, if possible
- Other advantages of TachoSil: Yes / No: Frequencies
  - Details: Frequencies
  - Other: Coding of free text, if possible
- Remodeling of TachoSil
  - Details: Frequencies
  - Other: Coding of free text, if possible
- Duration of TachoSil pressing: Frequencies
- Number of used TachoSil
  - Minimum, maximum, median, arithmetic mean
- Location of TachoSil application
  - Details: Frequencies
  - Other: Coding of free text, if possible

4.1.9 Assessment

- Assessment of manageability of TachoSil (1-5)
  - Frequencies
  - Median / Mean

- Assessment of satisfaction with TachoSil (1-5)
  - Frequencies
  - Median / Mean
-

4.2 Final Documentation

- Date of discharge

4.2.1 Complications

- Any complications after TachoSil application
  - Yes / No: Frequencies
- Number of Adverse Events
  - Minimum, maximum, median, arithmetic mean

4.2.2 Evaluation

- Previous TachoSil experience
  - Frequencies
- Surgery -specific TachoSil experience
  - Frequencies
- Assessment of satisfaction with TachoSil (1-5)
  - Frequencies
  - Median / Mean
- Reason for divergent satisfaction compared to Baseline evaluation
  - Free Text, grouping if possible
- Advantage of TachoSil
  - Reduction of surgery time (minutes)
    - Yes / No: Frequencies
    - Difference of duration of TachoSil, compared to alternative application: Maximum, median, arithmetic mean
  - Reduction of ICU time (days)
    - Yes / No: Frequencies
    - Difference of duration of TachoSil, compared to alternative application: Maximum, median, arithmetic mean
  - Reduction of total care time (days)
    - Yes / No: Frequencies
    - Difference of duration of TachoSil, compared to alternative application: Maximum, median, arithmetic mean
  - Other
    - Yes / No: Frequencies
    - Free text, grouping if possible

4.2.3 Discharge

- ICU stay: Yes / No: Frequencies
  - Discharge date (ICU)
- Discharge date (hospital)

4.3 Documentation of Adverse Events

Adverse Events will be reported immediately to the Sponsor's Pharmacovigilance department.

- Pregnancy: Yes - No: Frequencies
- Description of Adverse Event
  - Coding with MedDRA
    - Grouping by SOC, PT: Frequencies
- Causality: Yes / No: Frequencies
- Severity: Frequencies
- Actions taken
  - Frequencies
  - Other: coding if possible
- Outcome: Frequencies
  - If sequalae: coding of free text
  - If death: autopsy: yes – no: frequencies
- Serious: Yes / No: Frequencies
- SAE criteria: checked: Frequencies

5 Analysis Sets

5.1 Safety Analysis Set

Data of all patients that are eligible, have signed the Informed Consent and have documented all mandatory forms will be analysed.

The Safety Analysis Set contains all data including demographics, surgery data, evaluation of satisfaction of TachoSil, and Adverse Events.
There is no separate Per Protocol Analysis.

6 Data Entry

Each participating site documents data directly in the eCRFs.
Data is checked for completeness and correctness (e.g. mandatory fields, correct data type).
Users can unlock each CRF to correct wrongly entered data.

7 Analysis Details

Data analysis will be done using Statistics Software (Excel 2010, MedCalc 17.8.6).

Descriptive Statistics will be used (No testing of hypotheses):

- Number of observations
  - Absolute
  - Relative
- Arithmetic Mean
- Median
- Minimum
- Maximum

7.1 Presentation of Results

Data and results will be displayed in tables and graphs.

7.1.1 Tables

Tables include a table header, data rows, and a footer (containing the sums of each column).

Example table:

Gender	n	%
male	213	54.90%
female	175	45.10%
TOTAL	**388**	**100.00%**

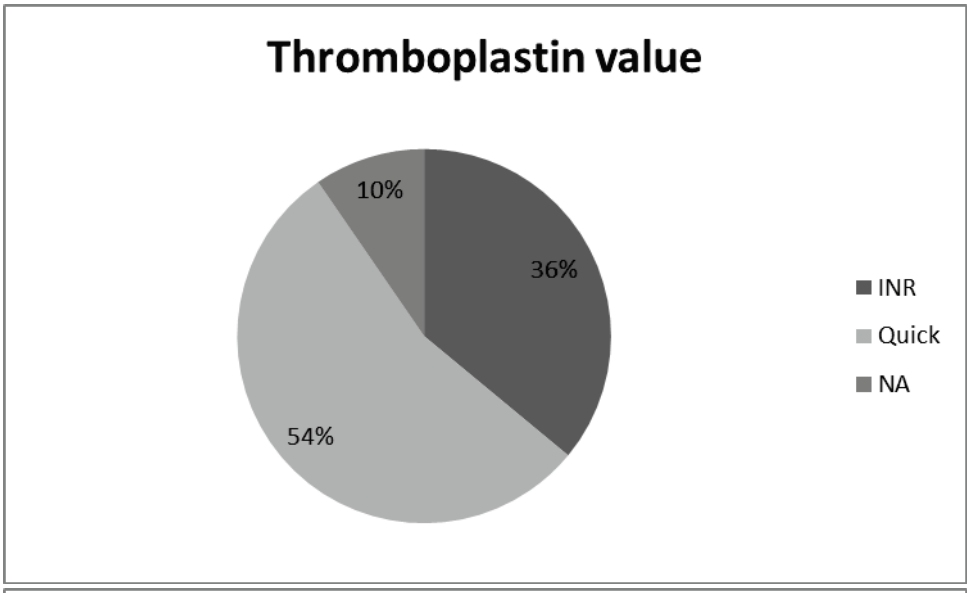
7.1.2 Graphs

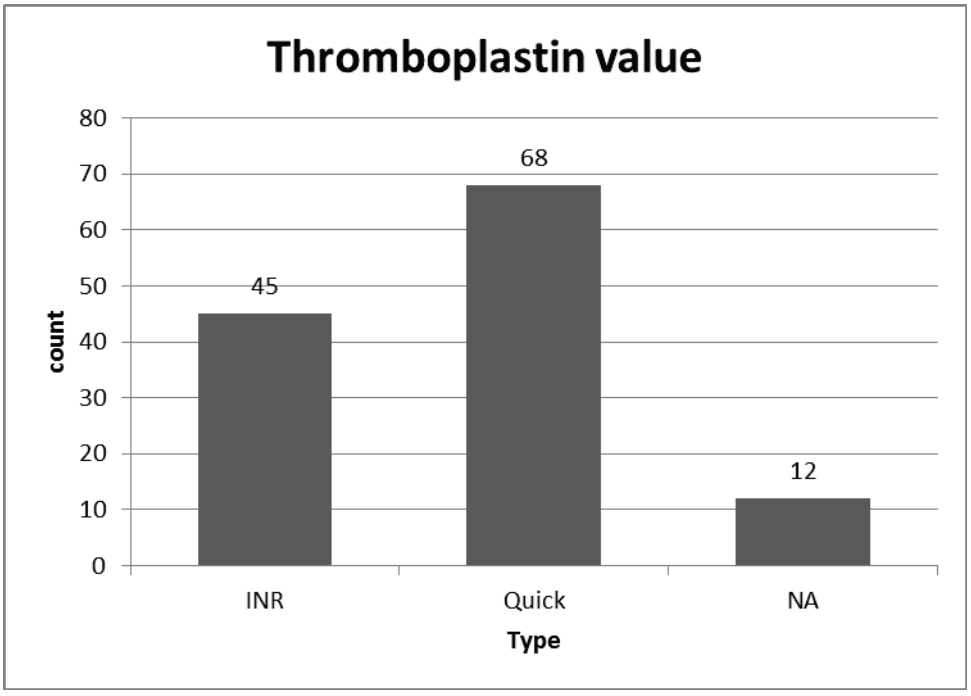
The appropriate graph type will be selected and displayed:

- Pie Chart
- Column Chart
- Line Chart

X and y axis will be labelled accordingly.

Example graphs:





8 Coding and Data Handling

8.1 Coding

Medical Coding will be used for the following categories:

- Adverse Events (MedDRA)
- …

8.2 Data Handling

Missing data will not be replaced (e.g. Last Observation Carried Forward (LOCF)), thus are not part of the analysis.

9 Documents

Reports will be generated as PDFs in print quality.
Raw Data will be available as Excel File(s).

10 References

1 Summary of Product Characteristics TachoSil®; 13.Sep.2017 (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000505/WC500032413.pdf)

2 Study Protocol TachoSil 4001 (RollOut), 22. Feb. 2016

3 Data Management Plan TachoSil-4001 (DMP TachoSil-4001), 18.Feb.2016

11 Abbreviations

(e)CRF	(electronic) Case Report Form
FPFV	First Patient First Visit
ICU	Intensive Care Unit
LOCF	Last Observation Carried Forward
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-interventional Study
SAP	Statistical Analysis Plan

SMPC	Summary of Product Characteristics