STATISTICAL ANALYIS PLAN (SAP)

Study Details:

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SAP Version Control:

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1. List of Abbreviations

Abbreviation	Definition
ADL	Activities of Daily Living (KOOS)
IKDC	International Knee Documentation Committee
KOOS	Knee Disability and Osteoarthritic Outcome Score
QOL	Quality of Life (KOOS)
S&N	Smith & Nephew Inc.
SAP	Statistical Analysis Plan
TFL	Tables, Figures, and Listings

2. Introduction

The following Statistical Analysis Plan (SAP) details the statistical considerations, including the data analysis methods, for the Study Protocol CTX-CP001 (14th-Dec-2014). Related documents to this SAP are the Study Protocol, Case Report Form (CRF), and Tables, Figures and Listings (TFL) Templates Shells. The statistical analyses specifications presented herein will thus form the basis of the 2-year final study report.

3. Study Design

The study is an interventional trial designed as a non-randomized, single-arm, open-label study of horizontal repairs of the meniscus tears using commercially available products. The study was designed to enroll 30 subjects at up to 10 investigational sites in the United States.

Table 3.1 shows the planned visit schedule.

Table 3.1. Study Visit Schedule

STUDY ACTIVITY SCHEDULE

Activity	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Screen < 4 weeks	Procedure	7-15 Days	90 Day ±7 days	185 Day ±14 days	365 Day ±30 days	730 Day ±30 days
Informed consent	X						
Screening Inclusion / Exclusion	X						
Demographics / Medical History	X						
Radiographs	X[1,5]						X[1]
MRI	X[5]					X[2]	
Images		X[3]					
Arthroscopy Inclusion / Exclusion		X					
Study Procedure		**X**					
Details of Procedure		X					
Details of Pathology		X					
Safety Follow-Up			X	X	X	X	X
KOOS	X			X	X	X	X
IKDC Subjective	X			X	X	X	X
Lyshlom	X			X	X	X	X
Tenger	X			X	X	X	X
In-office Arthroscopy					**X[4]**		

[1]Standing AP X-ray
[2]MRI 1.5 T or greater, no contrast to be reviewed by independent radiologist appointed by sponsor.
[3]Video, still photographs and diagrams of procedure.
[4]If available.
[5] Within 6 months of Procedure

4. Study Objectives

The primary objectives of this study are to assess reoperation rate, improvements in knee pain and function, and meniscus repair rate following all-suture-based repair of the horizontal meniscal tear.

5. Study Endpoints

5.1 Primary Endpoint(s)

The primary endpoints include:

- Freedom from reoperation of the index meniscus repair site at 6 months, 1 year, and 2 years;
- Improvements in knee pain and function as measured by KOOS
- IKDC Knee evaluation,
- Lysholm Knee scale, and
- Tegner Activity Scale

5.2 Safety Endpoint(s)

Safety follow-up includes reporting of a:

Complication

A complication is any untoward medical occurrence, unfavorable and unintended sign (including clinically significant abnormal laboratory finding), symptom, or condition experienced by the subject and temporally associated with the procedure whether or not considered related to the procedure.

Major Complication

Any complication attributable to the meniscal repair procedure that, in the view of either the Investigator or Sponsor, results in any of the following outcomes:

- Death;
- Life-threatening illness or injury;
- Inpatient hospitalization or prolongation of existing hospitalization;

- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Important medical events that, based upon appropriate medical judgment, require medical or surgical intervention to prevent one of the above outcomes.

6. Statistical Considerations

6.1 Determination of Sample Size

There was no formal sample size calculation carried out for this clinical observational study because the study was not planned to test any formal hypothesis. Prior to the study commencement, it was planned to enroll 30 subjects into the study, and the sample size was accrued. However, a total of 3subjects were excluded from all analyses for having met protocol deviations.

6.2Randomization

No randomization was planned for this study as it was a non-comparative study.

6.3Interim Analysis

No interim analyses were planned for this study.

7. Statistical Analysis

7.1 General

Smith & Nephew's Global Biostatistics group will conduct the statistical analysis for this study. Unless otherwise stated, all significance tests and hypothesis testing will be two-sided, performed at the 5% significance level. Resulting p-values will be quoted and 95% two-sided confidence intervals will be generated where appropriate. All p-values will be rounded to three decimal places, p-values less than 0.001 will be presented as '<0.001' in all tables.

Where data summaries are specified, categorical and ordinal variables will be summarized with frequencies and percentages. Continuous variables will be summarized with the following summary

statistics: number of observations, mean, median, standard deviation, minimum and maximum values. All analyses will be performed in SAS 9.4 or later.

7.2 Analysis Populations

Safety Population (SAF): all subjects who receive study treatment. This population include all enrolled subjects who receive the protocol-defined treatment of suture-based meniscal repair. This will be used for summaries of disposition of the subjects, protocol deviations/violations, and safety.

Analysis Population (AS): all SAF subjects with no significant protocol deviations, meet the inclusion/exclusion criteria, and did not withdraw early (except for closure at any time). This population will be used for supportive evidence of the primary variable.

7.3 Handling of Missing, Incomplete and Repeat Data

All data will be analyzed as observed cases unless otherwise indicated

7.4 Derived Data

The study visits for this study are:

Stud Visit 1 = Screening visit

Study Visit 2 = Procedure visit

Study Visit 3 = Day 7-15

Study Visit 4 =Day 90

Study Visit 5 = Day 185

Study Visit 6 = Day 365

Study Visit 7 = Day 730

Analysis Populations

- Indicator for inclusion in the safety population.
- Indicator for inclusion in the analysis population.

Study Duration (will be calculated for each subject):

Study duration [days] = Date of study discontinuation – date of initial surgery

Freedom from reoperation of the index meniscus repair site (will be calculated at each visit):

$$\text{Proportion of sujects with freedom from reoperation of the index meniscus repair site} = \frac{\text{Number of subjects whose known status were without repair}}{\text{Total number of participants with known repair status}} * 100\%$$

Change from pre-operative to post-operative visits in patient reported outcomes:

Change from pre- to post-operative visit will be calculated as:

Post – operative value $_{\text{Study Visit } n}$ – Pre – operative value $_{\text{(Study Visit 1)}}$, $where\ n$ = 4,5,6,

Time since injury:

Time since injury will be calculated as:

Time since injury (in wk) = (Date of surgery – Date of injury)/7

Time to re-operation:

Time to reoperation will be calculated as:

Time to re-operation (in wk) = (Date of re-operation surgery – Date of original surgery)/7

Minimal clinically important differences (MCIDs):

- MCID-IKDC (Day185) Indicator = 1 if IKDC difference from baseline to Day 185>6.3,
  = 0 otherwise;
- MCID-IKDC (Day 365) Indicator = 1 if IKDC difference from baseline to Day 365 >16.7,
  = 0 otherwise;
- MCID-Lysholm (Day365) Indicator = 1 if Lysholm difference from baseline to Day 365 >10.1,
  = 0 otherwise;

Adverse Events

- Individual flags for whether each adverse event was a new complication, a major complication (if answer was yes to at least one of the following: related to a fall or other injury, related to surgical procedure, related to meniscal repair, related to device(s) used, resolved, not resolved/ongoing, and/or death.
- The duration of adverse events defined as:
  - Duration of resolved AE (in day) = End date – start date
  - Duration of unresolved AE (in day) = Date of study completion – start date

7.5 Baseline Data

Demographic and baseline variables whose information is available either at the preoperative or at the operative visit will be summarized using descriptive characteristics for continuous or categorical data:

- Demographics:
  - Age (in yr)
  - Gender

  - Ethnicity
  - Weight (in lb)
  - Height (in inch)
  - BMI (in kg/m^2)
- Medical history:
  - Duration of symptoms before surgery (in wk)
  - Time since injury (weeks)
  - Primary diagnosis
- Pathology:
  - Side of tear (left knee, right knee)
  - Study meniscus compartment (medial, lateral)
  - Tear depth type (partial/complete and whether red/red-white/complete)
  - Rim width, deepest zone (Zone 1, Zone 2, Zone 3)
  - Posterior-Mid body-Anterior Location
  - Central to popliteal hiatus (Yes/No)
  - Quality of tissue (non-degenerative, generative, undetermined)
  - Length of tear (in mm)
  - Primary orientation (Horizontal/Oblique)
- Surgery details:
  - Surgery time (in min)
  - Anesthesiology Time (minutes)
  - Meniscal repair time (in min)
  - Completion of partial meniscectomy of the White Zone (Yes/No)
  - Medial/Lateral/Over-all percentages of the meniscus excised (in %)
  - Number of sutures used
  - Knot location (tibial, femoral, extra-capsular, others)
  - Surgical technique
  - Devices used
  - Suture configurations used

7.6 Disposition Data

The number of subjects that are screened, that entered the study, and that attended the study visits will be presented as numbers and percentages.

The reasons for study completion and withdrawals will be summarized. A listing of these reasons will be presented. The number of subjects that were prematurely terminated at the time of the 2-year analysis will be presented as number and percentage.

The study duration of all subjects will be summarized using descriptive characteristics for continuous variables (i.e. mean, median, SD, minimum, and maximum values).

Dates of first subject first visit and of last subject last visit will be reported.

7.7 Protocol Deviations

The frequency and type of protocol deviations will be summarized along with the number of subjects experiencing each.

7.8 Multiplicity

No adjustments for multiplicity are planned for this study.

7.9 Analysis of Primary Endpoint(s)

Freedom from re-operation of the index meniscus repair site:

The number and proportion of subjects experiencing freedom from reoperation of the index meniscus repair site at 6 months, 1 year, and 2 years will be presented together with a 95% confidence interval (calculated using the Clopper-Pearson Exact method [1].

Logistic regression will be fitted to determine baseline predictors of freedom from re-operation success status. As a minimum the model will contain subject age and BMI. The following terms will be added to the model using a stepwise selection procedure with an F-value to attain a significance level of 0.1: tear compartment, circumferential length of tear, primarily horizontal vs. oblique, subject gender, study site, partial meniscectomy vs. no meniscectomy, and meniscal surgical technique.

Reoperations:

The number and proportion of patients requiring reoperations will be summarized and will be presented together with a 95% confidence interval (calculated using the Clopper-Pearson Exact method [1].

Of those requiring re-operations, their time to re-operation will be summarized (using descriptive characteristics for continuous variables, i.e. mean, median, SD, minimum, and maximum values), along with the following:

- Surgery time (in min)
- Anesthesiology Time (minutes)
- Meniscal repair time (in min)
- Type of meniscal repair (Unicompartmental/Bicompartmental)
- Surgical technique (Inside-Out/Outside-In/All inside/Others)
- Device(s) used
- Completion of partial meniscectomy of the White Zone (Yes/No)
- Number of sutures used
- Suture configuration used (
- Knot location (tibial, femoral, extra-capsular, others)

Patient Reported Outcomes:

The patient reported outcomes (IKDC, KOOS Pain, KOOS Symptom, KOOS ADL, KOOS Sport, KOOS QOL, Lysholm, Tegner) will be summarized at each visit using descriptive characteristics for continuous variables (i.e. mean, median, SD, minimum, and maximum values). In addition, changes from baseline (Study Visit 1) to the subsequent follow-up visits will be similarly summarized. Results will be presented in narrative and graphically.

These measures will also be analyzed using inferential statistics. As appropriate, a repeated measure ANOVA or Wilcoxon signed rank test will be completed for each outcome measure. If a significant trend is identified, significance among time points, especially preoperative measures, may be further explored using the appropriate pair-wise comparisons. In all cases a p value equal to or less than 0.05 will be considered significant. Ninety-five percent (95%) CIs will be presented as well as corresponding p-values from the pair-wise comparisons of means from baseline to planned visits of interest (i.e. from Study Visit 1 to Day 90, Day 185, Day 365, and Day 730).

In addition, for Lysholm and/or IKDC, the numbers and proportions of subjects (out of total number of subjects providing data), together with a 95% confidence interval (calculated using the Clopper-

Pearson Exact method [1], meeting the minimal clinically important differences (MCIDs) from baseline to Days 185 and 365 ($MCID185_{IKDC}$=6.3, $MCID365_{Lysholm}$ =10.1, $MCID365_{IKDC}$=16.7) will be presented. There was no MCID for Lysholm at Day 185.

7.10 Analysis of Safety Endpoints:

All safety analyses and summaries will be done using the Safety Population.

The safety analyses will summarize the number (n) and percentages (%) of:

- the incidence according to subjects with at least one new complication,
- the incidence according to subjects with at least one new major complication,
- the incidence according to subjects whose complication was related to fall or injury,
- the incidence according to subjects who had at least one complication possibly, probably, or definitely related to surgical procedure,
- the incidence according to subjects who had at least one complication possibly, probably, or definitely related to meniscal repair, and
- the incidence according to subjects who had at least one complication possibly, probably, or definitely related to device(s) used.

A summary table will be presented that summarizes the complications by code according to subjects who had at least one new complication of a particular code.

In addition, for each complication, the following will be summarized: the relationship to the surgical procedure, the relationship to meniscal repair, the relationship to device(s) used, outcome and duration of he resolved complications and the duration of the complications at study discontinuation.

A listing of all new complications per subject will also be presented, along with duration, major complication status (yes/no), resolution status (resolved or ongoing), and relatedness to surgical procedure, meniscal repair, and device(s) used.

7.11 Changes in Analysis Methods Specified in the Protocol

Not applicable.

8. References

1. Clopper, CJ & Pearson ES. (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika, 26, 404–413.

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