STATISTICAL ANALYSIS PLAN
FOR PROTOCOL FENTANYL SUBLINGUAL SPRAY INS002-16-092

Sponsor:	
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Protocol Number:	INS002-16-092/ NCT02915978
Protocol Title:	A Phase 2 Multicenter, Randomized, Double-Blind, Multiple-Dose, Parallel-Group, Placebo-Controlled Study of Fentanyl Sublingual Spray for the Treatment of Moderate to Severe Post-Operative Pain
Protocol Date / Version:	Version 1.0 / 19-Sep-2016
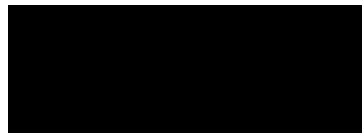
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Plan Version:	SAP - Final Version 1.0		
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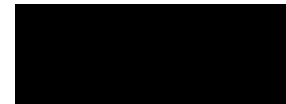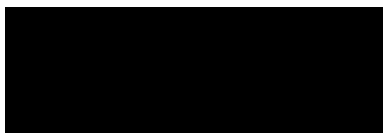|	
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SAP Version:	SAP - Final Version 1.0
SAP Date:	04 Jan 2017

I have read and approve the Statistical Analysis Plan specified above and agree with its content:

███████████████

Statis███   13 Jan 2017
                                                      Date

████████ 12 January 2016

████ opment Company, Inc. Representative   Date

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LIST OF ABBREVIATIONS

Abbreviation	Term
ACL	Access Control List
AE	Adverse Event
ANCOVA	Analysis of Covariance
ASA	American Statistical Association
BMI	body mass index
BP	Blood Pressure
°C	Celsius
CFR	Code of Federal Regulations
C.I.	Confidence Interval
cm	Centimeter
CM	Concomitant Medications
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
DMC	Data Monitoring Committee
EDC	Electronic Data Capture
EOS	End of Study
ET	Early Termination
°F	Fahrenheit
FDA	U.S. Food and Drug Administration
FUV	Follow-Up Visit
GCP	Good Clinical Practice
IA	Interim Analysis
ICF	Informed Consent Form

ICH	International Conference on Harmonization
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive Web Based System
MedRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
mm	Millimeter
NCS	Not Clinically Significant
NRS	Numeric Rating Scale
PI	Principal Investigator
PID	Pain Intensity difference
PP	Per Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SL	Sublingual
SOP	Standard Operating Procedure
SPID	Summed pain intensity difference
SPID-4	Summed Pain Intensity Scores over 1 to 4 hours
SPID-8	Summed Pain Intensity Scores over 1 to 8 hours
SPID-24	Summed Pain Intensity Scores over 1 to 24 hours
SPID-48	Summed Pain Intensity Scores over 1 to 48 hours
SSL	Secure Socket Layer

TEAE	Treatment Emergent Adverse Event
TOTPAR	Total Pain Relief
TOTPAR-4	Total Pain Relief over 0 to 4 Hours
TOTPAR-8	Total Pain Relief over 0 to 8 Hours
TOTPAR-24	Total Pain Relief over 0 to 24 Hours
TOTPAR-48	Total Pain Relief over 0 to 48 Hours
TV	Treatment Visit
ULN	upper limit of normal
WHO	World Health Organization

1.   INTRODUCTION

This Statistical Analysis Plan describes the planned analyses and reporting for the clinical trial protocol INS002-16-092, sponsored by Insys Development Company, Inc. The reader of this Statistical Analysis Plan (SAP) is encouraged to review the complete protocol as this plan contains only a limited overview of protocol information. The main objective of this plan is to provide details pertaining to statistical methodology, data conventions, and processes used for the analysis of data from this trial.

The format and content of this Statistical Analysis Plan are structured to provide sufficient detail to meet the requirements specified by the International Conference on Harmonization (ICH) E9: Guidance on Statistical Principles in Clinical Trials. All work planned and presented in this Statistical Analysis Plan will follow the ethical guidelines published by the American Statistical Association (ASA).

The following documents and references [1-6], were reviewed in preparation of this Statistical Analysis Plan:

- Version 1.0, protocol 19 September 2016

- US Federal Register, Department of Health and Human Services, FDA, Guidance on Statistical Principles for Clinical Trials (1998)

- ASA Ethical Guidelines for Statistical Practice (1999)

- The Royal Statistical Society: Code of Conduct (1993)

- ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3, 1996)

- ICH Guideline on General Considerations for Clinical Trials (ICH E8, 1997)

- ICH Guidance on the Statistical Principles for Clinical Trials (ICH E9, 1997)

2.   PROTOCOL DESIGN AND OBJECTIVES

2.1 Study Objectives

The primary objective of this study is to evaluate analgesic efficacy of Fentanyl Sublingual Spray compared with placebo in subjects with postoperative pain after a bunionectomy.

Secondary objectives are to evaluate the safety of Fentanyl Sublingual Spray compared with placebo in subjects with moderate to severe postoperative pain after a bunionectomy, evaluate the time to onset of analgesia for Fentanyl Sublingual Spray, and evaluate the time to rescue medication following administration of Fentanyl Sublingual Spray.

2.2 Design Overview

This is a Phase 2 multicenter, randomized, double blind, multiple dose, parallel group, and placebo controlled study to evaluate the safety and efficacy of up to 2 dosing regimens of Fentanyl Sublingual Spray (100 µg [q4h] or 200 µg [q4h]) and/or matching placebo in subjects with moderate to severe postoperative pain after a bunionectomy.

The study will comprise 4 periods: Screening Period (Days -28 to -1), Surgical Period (Day 0), Treatment Period (48 hours; Days 1 to 3), and Follow-up Period (Day 7 ± 2 days). The study design is represented schematically in Figure 1.

Figure 1: Study Design Schematic
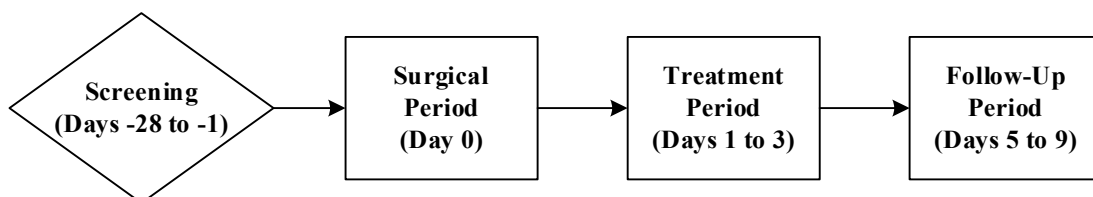
Subjects will be admitted to the study site on the morning of the scheduled surgery (Day 0), will remain at the study site until Postoperative Day 3 (a total of 3 nights at the study site), and will return for the Follow up Visit on Day 7 ± 2 days (5 to 9 days after surgery).

During the Screening Period, subjects who meet all inclusion and no exclusion criteria will be eligible for enrollment. After providing written Informed Consent, subjects will undergo study specific screening procedures. Eligible subjects will complete all screening procedures within 28 days before the surgery (Days -28 to 1).

On Day 0, regional anesthesia will be established using a Mayo block, using standardized techniques, after which subjects will undergo primary, unilateral, first metatarsal bunionectomy with osteotomy and internal fixation. When the regional anesthetic wears off and the subjects request pain medication, they will be asked to rate their pain intensity using an 11-point (0-10) Numeric Rating Scale (NRS). During the 9-hour period after discontinuation of the anesthetic block, subjects who experience a pain intensity rating of ≥4 on the NRS are eligible to be enrolled in the study. Pulse oximetry will be monitored continuously after the procedure as a safety measure.

An electrocardiogram (ECG) will be conducted after surgery but before the first dose of the study drug and serve as a baseline for comparison to subsequent tracings. The time of the NRS assessment before study drug administration is defined as Baseline; the time of administration of the first dose of study drug is defined as Time 0. Study drug will be provided by blinded study personnel in a predefined manner to ensure adequate blinding and appropriate dosing regimens for the active drug and placebo. Study drug will be administered by study subjects according to the directions provided by study staff. Subjects should not have anything orally except room-temperature water within 15 minutes of each dose. The Treatment Period will continue through 48 hours after Time 0. Pulse oximetry will be continuously monitored and SpO2 data will be recorded at select time points including baseline before first dose of study drug and 30, 60 and 90 minutes and 12, 24, and 48 hours after Time 0. Additional ECGs will be performed at 90 minutes, 12 hours, 24 hours, and 48 hours after Time 0.

Ibuprofen 400 mg will be allowed orally every 4 to 6 hours as needed for rescue medication after study drug treatment has begun. If subjects are unable to tolerate 400 mg ibuprofen or if there is insufficient pain relief, 30 mg of ketorolac tromethamine (i.e., Toradol®) may be administered intravenously or intramuscularly every 6 to 8 hours as needed for pain. The total daily (24 hour) dosage of ibuprofen medication should not exceed 2400 mg and ketorolac should not exceed 90 mg.

During the Treatment Period subjects will be allowed to use assigned study medication for primary rescue medication no more frequently than 4 hours from previous study medication dose and no more than 6 times in a 24-hour period. Subjects will be encouraged to wait for at least 1 hour after the first dose of study drug before receiving rescue medication to allow time for the study drug to exert its pharmacologic effect.

During the Treatment Period, subjects whose pain cannot be adequately managed (in the investigator's opinion) by a combination of study drug and rescue medication, or who develop unacceptable side effects during the study, will be discontinued from further study participation. Their pain will be managed according to usual standard of care at the investigator's discretion.

Pain will be assessed on an 11-point Numeric Rating Scale (NRS) at Baseline before Time 0. Thereafter, subjects will rate their pain intensity (NRS) and pain relief (on a 5-point categorical scale) and record their assessments in an inpatient subject diary at scheduled times during the 48-hour period after Time 0 (at 2.5, 5, 15, 30, and 45 minutes, and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24, 32, 40, and 48 hours) and immediately before each use of rescue analgesia during the Treatment Period. Time to perceptible pain relief and meaningful pain relief will be evaluated using the 2 stopwatch method (after the first dose only). Time to each rescue medication from the prior IP dose will be evaluated. Subjects will complete a subject's global evaluation of the study drug at the end of the Treatment Period (Day 3) before discharge from the study site.

If a subject discontinues the study prematurely, pain intensity, pain relief, and the subject's global satisfaction with study treatment should be assessed and recorded immediately before discontinuation.

Before discharge from the study site on Day 3, study personnel will dispense a prescription for outpatient pain medication (if not already dispensed) and subjects will be given an outpatient subject diary in which they will be instructed to record concomitant medications taken and adverse events (AEs) experienced after discharge. Subjects will also be instructed to return the outpatient subject diary to study personnel at the Follow-up Visit on Day 7 ± 2 days (5 to 9 days after surgery).

The Schedule of Assessments for the study is presented in the Appendix I of this SAP.

2.3 Study Duration

Subjects will be confined for approximately 72 hours at the study site for the Surgical and Treatment Periods. The maximum study duration for each subject is approximately 6 weeks. This duration includes up to 28 days of Screening Period, 1 day (Day 0) of Surgical Period, up to 9 hours post-surgery, 48 hours of treatment and inpatient assessments, and 5 to 9 days after surgery of follow up or early withdrawal.

2.4 Study Treatments and treatment assignments

2.4.1 Treatment Groups

The three treatment groups to be evaluated in this trial are described in Table 2-1 below

Table 2-1: Treatment Groups

Treatment group	Day 1						Day 2					
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6
100 µg	100 µg	100 µg	100 µg	100 µg	100 µg	100 µg	100 µg	100 µg	100 µg	100 µg	100 µg	100 µg
200 µg	200 µg	200 µg	200 µg	200 µg	200 µg	200 µg	200 µg	200 µg	200 µg	200 µg	200 µg	200 µg
Matching Placebo	P	P	P	P	P	P	P	P	P	P	P	P

2.4.2 Method of Treatment Assignment, Randomization Ratio, and Stratification

Subjects who have met all of the inclusion and none of the exclusion criteria, have provided written informed consent, and have experienced a pain intensity rating of ≥4 on the NRS during the 9-hour period after discontinuation of the anesthetic block are eligible to be enrolled in the study. They will be randomly assigned to 1 of 3 treatment groups: Fentanyl Sublingual Spray 100 µg q4h, 200 µg

q4h, or matching placebo. The randomization will be stratified by center and use mixed blocks with a 1:1:1 ratio to ensure even distribution of subjects across each treatment group in every site.

In addition, an enrollment anticipated at each of the sites in the following:

- ███████████████████ (PI: Dr. ██████) = approximately 30 subjects
- ███████████████████ (PI: Dr. ██████) = approximately 15 subjects

The actual randomization assignment will be made through an Interactive Web Based System (IWRS) called ██). ██████████ is a Secure Socket Layer (SSL) web portal that allows 24/7 access to clinical trial information. Authorization is based on approved access control list (ACL) that determines a user's access to the site. The ██████████████████████, who is not otherwise involved with the study, is responsible for the implementation and maintenance of ████████. Each user will be trained in how to use the website. A ████████ user manual will be supplied to all study personnel with instructions on using the website.

The Randomization/Supply module of ████████ allows authorized users to request randomization (Site Personnel only) into the trial. The detailed description and instructions are included in the ████████ user manual. ██████████████████ has further documentation and validation of ████████ specifically with regards to preserving the blinding of this study.

2.5 Blinding

As this is a double-blind trial, all subjects and study personnel involved in the conduct of the study, including data management, will be blinded to treatment assignment.

2.5.1 Maintenance of Blinding

The randomization lists containing the assignment of subjects to treatment groups will be securely provided to the person involved in randomizing the subjects (i.e. the WebMaster), who has no role in screening, enrolling, qualifying, or evaluating study subjects. No other study personnel other than the WebMaster and the randomization code generator will have access to the randomization codes for the study.

2.5.2 Time to Un-blinding

Treatment un-blinding and release of the randomization codes of the investigational product (IP) assignments for the study will only occur 1) due to emergency un-blinding because of safety reasons or 2) at the time of database lock when all randomized subjects have completed the study or discontinued from the study and after all clinical data have been received and data inconsistencies have been resolved.

3. STUDY ASSESSMENTS/ ENDPOINTS

3.1 Efficacy Endpoints

3.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the NRS summed pain intensity difference (NRS SPID) (calculated as a time weighted average) over 0 to 48 hours (NRS SPID-48) after Time 0.

3.1.2 Secondary Efficacy Endpoints:

The secondary endpoints are the following:

- NRS SPID over 0 to 24 hours (NRS SPID-24), over 0 to 8 hours (NRS SPID-8), and over 0 to hours (NRS SPID-4) after Time 0

- Total pain relief (TOTPAR) over 0 to 48 hours (TOTPAR-48), over 0 to 24 hours (TOTPAR-24), over 0 to 8 hours (TOTPAR-8), and over 0 to 4 hours (TOTPAR-4) after Time 0

- Subject's global evaluation of study drug

- Time to onset of analgesia (measured as time to perceptible pain relief confirmed by meaningful pain relief using the 2-stopwatch method)

- Pain relief score on a 5-point categorical scale at each scheduled time point after Time 0

- Peak pain relief

- Time to peak pain relief

- Time to first perceptible pain relief

- Time to meaningful pain relief

- Proportion of subjects using rescue medication

- Time to first use of rescue medication (duration of analgesia) following each dose of IP

- Total use of rescue analgesia over 0 to 24 hours and over 0 to 48 hours

- NRS pain intensity difference (NRS PID) at each scheduled time point after Time 0

- NRS pain intensity score at each scheduled time point

3.2 Safety Assessments

Safety assessments will include the evaluation of AEs, physical and oral examinations, vital sign measurements, pulse oximetry, and 12-lead ECGs. Clinical laboratory tests will be performed at Screening only.

The safety endpoints are the incidence of treatment-emergent adverse events (TEAEs), physical and oral examination findings, and changes in vital signs, pulse oximetry, and ECG measurements.

4. SAMPLE SIZE DETERMINATION AND RATIONALE, STATISTICAL POWER, AND SIGNIFICANCE LEVEL

A total of 45 subjects are planned to be enrolled for the study. A sample size of 15 subjects per treatment group will provide ≥80% power to detect a minimal standardized effect size of 0.5 between the 100 µg q4h, 200 µg q4h active treatment arms, and placebo in NRS SPID-48 using a 3-group analysis of covariance (ANCOVA) with baseline NRS score as the covariate with a 0.05 two-sided significance level (EAST v6).

5. INTERIM ANALYSIS

No Interim Analysis is planned for this study.

6. ANALYSIS POPULATIONS

6.1 Intent-to-Treat (ITT) population

The intent to treat (ITT) population will consist of all subjects who are randomized. The ITT

population is the primary population for the efficacy analysis.

6.2 Per Protocol (PP) Population

The per protocol (PP) population will consist of all ITT subjects who receive at least 1 dose of study drug, who remain in the study for at least 48 hours of treatment, and who do not incur a major protocol violation that would challenge the validity of their data. This population will be used to evaluate the sensitivity of the primary efficacy analysis.

6.3 Safety Population

The safety population will include all subjects who are treated with at least one study drug. The safety population is the population for all safety assessments.

7. DATA CONVENTION AND RELATED DEFINITIONS

7.1 Baseline Definition

For all parameters, baseline will be defined as the last available value before the randomized treatment administration.

7.2 Duplicate Data

For unplanned duplicate data within a protocol-specified visit, the last measured value will be used for the analysis. If it is not possible to identify the "last measured value" the average of the duplicate values will be used.

No data will be excluded. All collected data will be listed.

7.3 Handling of Missing Data

7.3.1 Handling of Missing Data for Efficacy Assessments

Use of Rescue Medication: Any pain intensity or pain relief score occurring within 4 hours after a subject has taken rescue medication for pain will be replaced by the last pain intensity or pain relief score prior to that use of rescue medication. If a second rescue medication for pain is used within that 4 hour duration, the pain intensity or pain relief scores from the time of the first rescue medication will be replaced by the assessment prior to the second rescue medication for the next 4

hours. The same method will be employed for a third and subsequent rescue medication.

Missing due to Dropouts: Missing values for pain intensity after a subject drops out of the study will be imputed as follows in the primary analysis:

- For SPID endpoints, the last available SPID (truncated SPID) will be used for analysis (e.g., if a subject dropped out after 32 hours of initiation of treatment, the truncated SPID calculated using timepoints up to 32 hours will be used as the post 32 hour timepoints like 40 hours and 48 hours) .

- For TOTPAR endpoints, the last available TOTPAR (truncated TOTPAR) will be used for analysis

- For PID endpoints, the last available pain intensity will be used to impute the missing pain intensity and to calculate the PID

In addition, a sensitivity analysis using 1) missing as missing (i.e., no imputation) for dropouts and 2) multiple imputation will be performed for the primary endpoint to explore the impact of missing data after a subject drops out. The details of the sensitivity analysis are described in Section 7.4.

7.3.2 *Handling of Missing Data For Safety Evaluations*
<u>**Adverse Event (AE) Summaries**</u>

With respect to summaries of AEs, only AEs that were treatment emergent will be tabulated. Treatment–emergent is defined as AEs with start date ≥ date of first treatment administration.

1) If AE start date is completely missing, the date of first treatment administration will be taken as the start date of the event.

2) If AE start date is partially missing:

   a. If the day part of the start date is missing, the start date will be estimated to be equal to the date of first treatment administration, provided the start month and year are the same as the date of first treatment administration and the stop date either after the

date of first treatment administration or completely missing. Otherwise, the AE will be assumed to have started on the first day of the month (01/MMM/YYYY)

b. If the month part of the start date is missing, the start month will be estimated to be equal to the month of the date of first treatment administration or the following month after the month of the date of first treatment administration depending on the day part of the start date provided that the start year is the same as the year of date of first treatment administration and the stop date is either after date of first treatment administration or completely missing. Otherwise, the AE will be assumed to have started on the first month of the year (DD/Jan/YYYY)

c. If both the day and month parts of the start date are missing, the start date will be estimated to be equal to the date of first treatment administration, provided the start year is the same as year of date of first treatment administration and the stop date is either after the date of first treatment administration or completely missing. Otherwise, the AE will be assumed to have started on first day and first month of the year (01/Jan/YYYY)

d. If all day, month and year parts of the start date are missing, the start date will be estimated to be equal to the date of first treatment administration (and thus treatment emergent) provided that the stop date is either after the date of first treatment administration or completely missing. Otherwise, the start date will be estimated to be the first day of the same year as the stop date.

3) If AE stop date is partially or completely missing:

a. If only the day portion of the stop date is unknown, the day will be assumed to be last date of the month (e.g., ??-Jan-2004 will be treated as 31-Jan-2004).

b. If both the day and month of stop date are unknown, the event will be assumed to have ceased on the last day of the year (e.g., ??-???-2004 will be treated as 31-Dec-2004).

c.   If the stop date is completely missing, the event will be assumed to be "Ongoing".

Concomitant medications (CM) Summaries

1) If CM start date is completely missing then the date of first treatment administration will be taken as the start date of the medication

2) If CM start date is partially missing:

   a.   If the Day part of the start date is missing, the CM will be assumed to have started on the first day of the month (01/MMM/ YYYY)

   b.   If the month part of the start date is missing, the CM will be assumed to have started on the first month of the year (dd/Jan/YYYY)

   c.   If both the day and month parts of the start date are missing, the CM will be assumed to have started on first day and first month of the year (01/Jan/YYYY)

7.4 Sensitivity Analyses

A sensitivity of the primary analysis using multiple imputation for missing data will be performed for the primary endpoint to assess the impact of missing data after subject's have dropped out. For the primary endpoint the following two sensitivity analyses will be conducted:

7.4.1 *Missing as Missing*

The primary endpoint analysis will be conducted without any imputation.

7.4.2 *Multiple Imputation*

All missing data for these subjects will be imputed using multiple imputation procedures. However, the multiple imputation is used for subjects that have some baseline and postbaseline data, i.e., if a subject is missing all pre and post baseline data, no data will be imputed.

The imputation will be carried out in SAS version 9.4 or later, using the full conditional specification method (FCS) with a regression model approach (Carpenter and Kenward, 2013). The variables included sequentially in the model are:

- Treatment as a main effect

- Site and baseline pain intensity as covariates

- SPID for each time point as the dependent variable

The analysis model will be an analysis of covariance (ANCOVA) with NRS-SP1D 48 as the dependent variable, treatment as a main effect and site and baseline pain intensity as the covariates.

The ANCOVA results from the multiply imputed datasets will be combined using the usual Rubin's rules for multiple imputation (Little and Rubin, 1987) and will be done in SAS using PROC MIANALYZE. A significance test of the treatment difference at the two-sided 0.05 level and corresponding 95% confidence intervals will be calculated.

7.5 Multiple Clinical Trials

This is a multi-center clinical trial with two sites.

7.6 Multiple Comparisons and Type I Error Rate Multiplicity adjustments

There will also be no Type I error adjustment on the hypotheses testing of this Phase 2 study.

7.7 Covariates and Prognostic Factors

Baseline pain intensity and site would be used as covariates for the analysis of the primary efficacy endpoint. Other prognostic factors may be included in the analysis model if they are found to be contributing factors.

7.8 Subgroups and Exploratory Analysis

There is no planned subgroup analysis; however subgroup and exploratory analysis may be conducted as postHoc analysis.

7.9 Standard Calculations

7.9.1 Age
Age will be calculated as the number of completed years between the date of informed consent and the subject's birth date.

Age (years) = integer of [(date of informed consent – date of birth)/ 365.25+ 0.5]

7.9.2 Height

For summary purposes height will be expressed in centimeters. Entries made in inches will be converted to centimeters using the formula noted below.

Height (cm) = Height (in)*2.54

7.9.3 Weight

For summary purposes weight will be expressed in kilograms. Entries made in pounds will be converted to kilograms using the formula noted below.

Weight (kg) = Weight (lb)/ 2.2046

7.9.4 Body Mass Index (BMI)

BMI will be calculated using height (in cm) and weight (in kg) according to the formula noted below.

$BMI (kg/m^2) = weight (kg) / [height (cm)/100]^2$

7.9.5 Pain Intensity (PI)

Subjects will assess their current pain intensity using an 11-point (0 to 10) Numerical Rating Scale (NRS). Each subject will be instructed to mark the number indicating his or her current pain intensity.

The subject is to record pain intensity (NRS) in the inpatient subject diary at Baseline before the first dose of study drug (Day 1), at Time 0. Thereafter, the subject is to record NRS pain intensity assessments at the following time points during the 48-hour period after Time 0:

- 2.5, 5, 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24, 32, 40 and 48 hours after Time 0, and immediately before each use of rescue analgesia.

i	Nominal Ti (hours)
0	0
1	0.0417

i	Nominal Ti (hours)
2	0.0833
3	0.25
4	0.5
5	0.75
6	1
7	1.5
8	2
9	3
10	4
11	5
12	6
13	7
14	8
15	12
16	16
17	20
18	24
19	32
20	40
21	48

7.9.6 Pain Intensity Difference (PID)

Pain intensity difference (PID) is to be calculated by subtracting the pain intensity at each time point from the pain intensity at time 0.

$$PID_i = PI_i - PI_0$$

7.9.7 Summed Pain Intensity Difference (SPID)

The summed pain intensity difference (SPID) is to be calculated by multiplying the PID score at each post dose time point by the duration (in hours) since the preceding time point and then summing the values over the relevant time period.

$$SPID\text{-}48 = \sum_{i=1}^{21}\left(T_i - T_{(i-1)}\right) * PID_i$$

$$SPID\text{-}24 = \sum_{i=1}^{18}\left(T_i - T_{(i-1)}\right) * PID_i$$

$$SPID\text{-}8 = \sum_{i=1}^{14}\left(T_i - T_{(i-1)}\right) * PID_i$$

$$SPID\text{-}4 = \sum_{i=1}^{10}\left(T_i - T_{(i-1)}\right) * PID_i$$

Where $T_0 = 0$, T_i is the actual time, and PID_i is the PID score at time T_i.

The durations between nominal time points will be calculated using the actual times of the pain score measurement. If the actual time is missing the nominal planned time will be used.

7.9.8 Pain Relief (PAR)

Subjects will assess their current pain relief using a 5-point categorical scale. Each subject will be instructed to mark the number indicating his or her current pain relief.

The subject is to record pain relief (5-point categorical rating scale) in the inpatient subject diary at the following time points during the 48-hour period after Time 0:

- 2.5, 5, 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24, 32, 40 and 48 hours after Time 0, and immediately before each use of rescue analgesia.

7.9.9 Total Pain Relief (TOTPAR)

Total pain relief (TOTPAR) is calculated by multiplying the pain relief score at each time point by the duration (in hours) since the preceding time point and then summing these over the relevant time period.

$$TOTPAR\text{-}T_k = \sum_{i=1}^{k}\left(T_i - T_{(i-1)}\right) * PAR_i$$

$$TOTPAR\text{-}48 = \sum_{i=1}^{21}\left(T_i - T_{(i-1)}\right) * PAR_i$$

$$TOTPAR\text{-}24 = \sum_{i=1}^{18}\left(T_i - T_{(i-1)}\right) * PAR_i$$

$$TOTPAR\text{-}8 = \sum_{i=1}^{14}\left(T_i - T_{(i-1)}\right) * PAR_i$$

$$TOTPAR\text{-}4 = \sum_{i=1}^{10}\left(T_i - T_{(i-1)}\right) * PAR_i$$

7.9.10 Two-Stopwatch Assessment of Pain Relief

Time to perceptible pain relief and meaningful pain relief will be evaluated using the 2 stopwatch method (after the first dose only). The study staff will start 2 stopwatches as soon as the first dose of study drug is administered. Each subject will be instructed to stop the first stopwatch when he or she experiences any perceptible pain relief and the second stopwatch when he or she experiences pain relief that is meaningful to them. Subjects will receive training for this procedure at their screening visit and prior to discontinuation of the regional anesthetic popliteal block.

7.9.11 Time to onset of analgesia

Time to onset of analgesia is the time that the first stopwatch is stopped (when the subject experiences first perceptible pain relief) given that the second stopwatch is stopped (when the subject experiences meaningful pain relief). If both stopwatches are not stopped or just one stopwatch is stopped, then the time to analgesia will be censored at the time of the second dose or the use of rescue medication, whichever comes first.

7.9.12 Peak Pain Relief

Peak pain relief is the highest value of pain relief experienced during the study. Values of pain relief after use of rescue medication for pain (up to four hours after use) will be replaced by the pain relief score collected prior to that use of rescue medication.

7.9.13 Time to Peak Pain Relief

Time to peak pain relief is the first time when the highest value of pain relief is observed. If no pain relief is observed then the time will be censored at the time of the last assessment.

7.9.14 Time to first Perceptible Relief

Time to first perceptible relief is the time when the subject experiences any perceptible pain relief after administration of study drug and stops the first stopwatch (irrespective of the second stopwatch). If it is not stopped, time will be censored at the time that the second stopwatch is stopped, the time of the second dose, or the first time that rescue medication was used, whichever comes first.

7.9.15 Time to meaningful relief

Time to meaningful relief is the time when the subject experiences relief that is meaningful after the administration of study drug and stops the second stopwatch, irrespective of the first stopwatch. If it is not stopped, time will be censored at the time of the second dose or the first use of rescue medication whichever comes first.

7.9.16 Rescue Medication Use

Total use of rescue medication is the number of times that a subject used rescue medication for pain during the specified time periods (0-24h and 0-48h). The proportion of subjects taking rescue medication for pain during each period will also be presented. A subject taking any amount of rescue medication during the specified period will be counted in this proportion.

7.9.17 Time to First Use of Rescue Medication

Time to first use of rescue medication for pain is defined as the time from Time 0 to the first use of rescue medication. Rescue medications for pain will be identified by the sites on the Concomitant Medications eCRF. If rescue medication for pain is not taken, the time will be censored at the time of the last pain assessment.

7.9.18 Subject's Global Evaluation of Study Drug

Subjects will complete a subject's global evaluation of study drug at the end of the treatment period (Day 3) before discharge from the study site or immediately before Early Withdrawal if a subject discontinues prematurely. The subject will be instructed to score his or her global evaluation of the study treatment on a 5-point categorical scale where 0 = poor, 1 = fair, 2 = good, 3 = very good, and 4 = excellent.

8.   STATISTICAL METHODS

All data collected during this study will be presented in subject data listings. All statistical analyses will be performed using SAS® for Windows, version 9.4 or later.

8.1 Summarizing and Tabulating the Collected Data

All data collected will be summarized according to the variable type:

o Continuous data summaries will include number of observations, mean, standard deviation, median, and minimum and maximum values.

o Categorical data summaries will include frequency counts and percentages.

8.1.1 Subject Disposition and Withdrawals

There will be a detailed accounting of all subjects that signed the informed consent to participate in this trial. The following will be summarized by treatment group:

- The number of subjects who signed the informed consent

- The number of subjects who are randomized

- The number of subjects who are randomized and not treated

- The number of randomized and treated

- The number of subjects who completed the treatment phase

- The number of subjects who completed the follow up phase

- The number of subjects who discontinued

Reasons for discontinuation will also be summarized.

In addition, there will also be a listing of all discontinued subjects, which will provide the clinical trial center, treatment group and the specific reason for discontinuation.

8.1.2 Protocol Deviations

Protocol deviations will be identified and classified as minor or major before un-blinding.

Protocol deviations occurring during the clinical trial will be summarized descriptively and also be presented as by-subject listings.

8.1.3 Demographics and Baseline Characteristics

Demographic and baseline characteristics (including age, gender, race, weight, height, BMI, surgery duration, and baseline pain intensity) will be summarized by treatment group and for the overall population by descriptive statistics. No formal statistical analyses will be performed. Medical history, clinical laboratory test results, and urine drug screen, alcohol breathalyzer test, X-ray and podiatric examination assessments will be listed.

The analyses of demographics and baseline characteristics will be conducted for the safety population.

8.1.4 Prior and Concomitant Medications

Prior and concomitant medications will be summarized by treatment group and by the number and percentage of subjects taking each medication. They will also be classified by using the World Health Organization Drug Dictionary Anatomical Therapeutic Chemical classes and preferred terms.

8.1.5 Exposure and Compliance

The exposure to study medication will be summarized by descriptive statistics. As the dose administration is under the control of the study sites, compliance is not excpected to be an issue.

8.2 Analysis of Efficacy Data

8.2.1 Primary Endpoint

The primary efficacy endpoint is the NRS summed pain intensity difference over 0 to 48 hours after Time 0 (NRS SPID-48). The formula for SPID-48 calculation is presented in Section 7.9.7. The primary variable will be analyzed using an analysis of covariance (ANCOVA) model, which will include treatment and site as main effects and baseline pain intensity as the covariate. The least square (LS) mean, standard error (SE) and 95% confidence interval (CI) for each treatment group will be estimated. In addition, the mean (LS mean) difference between each treatment and placebo, SE, p-value and the associated 95% CI will also be computed. Descriptive summaries (including mean, SD, median, minimum and maximum) will also be presented by treatment group. Missing values for pain intensity will NOT be imputed in the primary analysis.

8.2.2 Secondary Endpoints

Analysis of the secondary endpoints will be summarized according to the variable type. The details are presented in the following sections.

8.2.2.1 *NRS SPID over 0 to 24 hours (NRS SPID-24), over 0 to 8 hours (NRS SPID-8), and over 0 to hours (NRS SPID-4) after Time 0*

NRS SPID-24, SPID-8 and SPID-4 would be calculated using the formula specified in Section 7.9.7. Similar methods used for analysis of the primary endpoint will be assessed differences between the treatment groups in these metrics.

8.2.2.2 *Total pain relief (TOTPAR) over 0 to 48 hours (TOTPAR-48), over 0 to 24 hours (TOTPAR-24), over 0 to 8 hours(TOTPAR-8), over 0 to 4 hours (TOTPAR-4)*

TOTPAR over 0-48, 0-24, 0-8 and 0-4 hours will be calculated using the formula specified in Section 7.9.9. The differences in TOTPAR between the treatment groups and placebo will compared using an analysis of covariance (ANCOVA) model, which will include treatment and site as main effects and baseline pain intensity as the covariate. The last square (LS) mean, standard error (SE) and 95% confidence interval (CI) for each treatment group will be estimated. In addition, the mean (LS mean) difference between each treatment and placebo, SE, p-value and the associated 95% CI will also be computed. Descriptive summaries (including mean, SD, median, minimum and maximum) will also be presented by treatment group.

8.2.2.3 *Subject's global evaluation of study drug*

Subject's global evaluation of study drug will be analyzed using a proportional odds model (an extension of the logistic regression). This method allows for an ordinal response variable with more than two categories. This model will include factors site, treatment and baseline pain intensity.

8.2.2.4 *Time to onset of analgesia (measured as time to perceptible pain relief confirmed by meaningful pain relief using the 2-stopwatch method)*

Time to onset of analgesia will be summarized using Kaplan-Meier methods. The definition and censoring rules are described in Section 7.9.11. Treatments will be compared to placebo using a log-rank test which will compare the survival distributions of the treatments.

8.2.2.5 Pain relief score on a 5-point categorical scale at each scheduled time point after Time 0

The differences in pain relief between the treatment groups and placebo will be compared using a proportional odds model (an extension of logistic regression model) which allows for an ordinal response variable with more than two categories. This model will include factors site, treatment and baseline pain intensity.

In addition, the pain relief scores at each time point will also be summarized descriptive in tables and also presented as by-subject listings.

8.2.2.6 Peak pain relief

The peak pain relief score for each subject will be identified using the description in Section 7.9.12. The data for this endpoint will be analyzed using a proportional odds model (an extension of logistic regression model) which allows for an ordinal response variable with more than two categories. This model will include factors site, treatment and baseline pain intensity.

8.2.2.7 Time to peak pain relief

Time to peak pain relief will be summarized using Kaplan-Meier methods. The definition and censoring rules are described in Section 7.9.13. Treatments will be compared to placebo using a log-rank test which will compare the survival distributions of the treatments.

8.2.2.8 Time to first perceptible pain relief

Time to first perceptible pain relief will be summarized using Kaplan-Meier methods. The definition and censoring rules are described in Section 7.9.14. Treatments will be compared to placebo using a log-rank test which will compare the survival distributions of the treatments.

8.2.2.9 Time to meaningful pain relief

Time to meaningful pain relief will be summarized using Kaplan-Meier methods. The definition and censoring rules are described in Section 7.9.15. Treatments will be compared to placebo using a

log-rank test which will compare the survival distributions of the treatments.

8.2.2.10 Proportion of subjects using rescue medication

The definition of rescue medication use is presented in Section 7.9.16. The proportion of subjects using rescue medication for pain will be analyzed using logistic regression. The logistic regression model will include factors site, treatment and baseline pain intensity.

8.2.2.11 Time to first use of rescue medication (duration of analgesia) following each dose of IP

Time to time to first use of rescue medication will be summarized using Kaplan-Meier methods. Censoring will be applied as described in Section 7.9.17. Treatments will be compared to placebo using a log-rank test which will compare the survival distributions of the treatments.

8.2.2.12 Total use of rescue analgesia over 0 to 24 hours and over 0 to 48 hours

The frequency of use of rescue analgesia will be calculated for each subject over 0 to 24 and 0-48 hours. The differences in total use of rescue analgesia between the treatment groups and placebo will compared using an analysis of covariance (ANCOVA) model, which will include treatment and site as main effects and baseline pain intensity as the covariate. The last square (LS) mean, standard error (SE) and 95% confidence interval (CI) for each treatment group will be estimated for each time interval 0-24 hours and 0-48 hours. In addition, the mean (LS mean) difference between each treatment and placebo, SE, p-value and the associated 95% CI will also be computed. Descriptive summaries (including mean, SD, median, minimum and maximum) will also be presented by treatment group.

8.2.2.13 NRS pain intensity difference (NRS PID) at each scheduled time point after Time 0

The PID at each scheduled time point will be calculated using the formula specified in Section7.9.6. The differences in NRS PID between the treatment groups and placebo will compared using an analysis of covariance (ANCOVA) model, which will include treatment and site as main effects and baseline pain intensity as the covariate. The last square (LS) mean, standard error (SE) and 95%

confidence interval (CI) for each treatment group will be estimated. In addition, the mean (LS mean) difference between each treatment and placebo, SE, p-value and the associated 95% CI will also be computed. Descriptive summaries (including mean, SD, median, minimum and maximum) will also be presented by treatment group.

8.2.2.14 NRS pain intensity score at each scheduled time point

The differences in NRS pain intensity between the treatment groups and placebo will compared using an analysis of covariance (ANCOVA) model, which will include treatment and site as main effects and baseline pain intensity as the covariate. The last square (LS) mean, standard error (SE) and 95% confidence interval (CI) for each treatment group will be estimated. In addition, the mean (LS mean) difference between each treatment and placebo, SE, p-value and the associated 95% CI will also be computed. Descriptive summaries (including mean, SD, median, minimum and maximum) will also be presented by treatment group.

In addition, the pain intensity scores at each time point will also be summarized descriptively in tables and figures.

8.2.3 Analysis of Safety Data

The safety population is the population for all safety assessments. No imputation will be used in the safety assessments. No inferential statistics are planned. No formal inferential analyses will be conducted for safety variables.

For continuous variables data will be summarized by treatment using n, mean, SD, minimum and maximum values. For categorical variables data will be summarized by treatment using frequency and percentage.

8.2.4 Adverse Events

Adverse events will be classified by system organ class (SOC) and preferred term (PT) according to the most recent MedDRA dictionary (Version 19.1 or higher).

All adverse events that occur on or after the date of first administration of clinical trial treatment until the end of study procedures are completed will be listed and summarized, using frequency

counts and percentages, by treatment group.

- Overall (*i.e.,* regardless of severity or relationship to treatment)

- By severity grade (mild, moderate, severe,)

- By relationship to clinical trial treatment (definitely related, probably related, possibly related, unlikely related, not related)

Unless otherwise specified, at each level of subject summarization, a subject will be counted only once. If there is more than one occurrence of an event, the event of the worst severity or the worst-case relationship category will be summarized.

AEs leading to premature discontinuation of clinical trial treatment, AEs of special interest, AEs that lead to study discontinuation, AEs that lead to death and Serious Adverse Events (SAEs) will also be summarized by treatment group and relationship. Adverse Events leading to premature discontinuation of clinical trial treatment will be defined as any adverse event with an Action Taken equal to "study drug discontinued" or "drug withdrawn".

8.2.5 Clinical Laboratory Evaluations

Laboratory data is only collected for the screening visit. All available results of the clinical laboratory evaluations (e.g., Hematology, Chemistry, and Urinalysis) will be listed and descriptive summaries (mean, SD, median, minimum and maximum) of actual (absolute) values will be presented for clinical laboratory values for each treatment group.

8.2.6 Serum Pregnancy Test

All the results for serum pregnancy test will be presented as a by-subject listing.

8.2.7 Physical Examination / Oral Examination

The number and percentage of subjects with normal and abnormal findings in the physical and oral examinations at the Follow-up or Early Termination Visit will be displayed for each treatment group. All physical/oral examination findings will also be presented as a by-subject listing.

8.2.8 ECG

The number and percentage of subjects with clinically relevant abnormal ECG findings will be summarized for each treatment group at each time point.

All available ECG data will also be presented as by-subject listing.

8.2.9 Vital Signs

Tabulations of raw data and change from baseline values will be presented by time point for each vital sign parameter [*i.e.,* heart rate (beats/min), respiratory rate, oral body temperature (^{0}C / ^{0}F), systolic BP (mmHg), diastolic BP (mmHg), pulse oximetry (%)].

Summary will include the number of observations, mean, standard deviation, median, and minimum and maximum values. For change from baseline summaries, subjects with an undefined change from baseline, because of missing data, will be excluded.

9. APPENDIX 1: SCHEDULE OF ASSESSMENTS

	Screening (Days -28 to -1 before surgery)	Surgery Day 0	Treatment Period			Follow-up Day 7 ± 2 days (5 to 9 days after surgery) or Early Withdrawal
			Day 1 (Baseline; before dosing)	Day 1 First dose (Time 0)	Days 2 and 3 Subsequent doses	
Written informed consent	X					
Inclusion/exclusion criteria	X	X				
Demographics	X					
Medical history	X	X[a]				
Physical examination[b]	X					X
Oral examination[c]	X			X		X
Vital signs[d]	X	X	X	X	X	X
Height, weight, and body mass index	X					
Pulse oximetry[e]			X	X	X	
12-lead electrocardiogram[f]	X		X	X	X	
Clinical laboratory tests (hematology, chemistry, urinalysis)	X					
Pregnancy test for female subjects[g]	X	X				
Urine drug screen[h]	X	X				
Alcohol breathalyzer test		X				
X-ray and podiatric examination[i]	X					
First metatarsal bunionectomy procedure		X				

	Screening (Days -28 to -1 before surgery)	Surgery Day 0	Treatment Period			Follow-up Day 7 ± 2 days (5 to 9 days after surgery) or Early Withdrawal
			Day 1 (Baseline; before dosing)	Day 1 First dose (Time 0)	Days 2 and 3 Subsequent doses	
Discontinue anesthetic block at approximately 3:00 AM[j]			X			
Assign randomization number			X			
Pain assessments[k]			X	X	X	
Administer study drug[l]				X	X	
Start stopwatches for perceptible and meaningful pain relief[m]				X		
Subject's global evaluation of study drug[n]					X	
Concomitant medications	X	X	X	X	X	X
Adverse events		X	X	X	X	X
Dispense outpatient pain medication and outpatient subject diary[o]					X	
Discharge subject from the study site[p]					X	
Collect and review diary for completion						X

Abbreviations: ET=early termination; NRS=numeric rating scale

a Medical history should be reviewed for any changes since Screening.

b A complete physical examination (excluding the genitourinary examination) will be performed at Screening. An abbreviated physical examination, including an examination of the subject's surgical site, will be performed at the Follow-up Visit.

c The postdose oral examination should be conducted 1 hour (±10 minutes) after dosing.

d Vital signs, including blood pressure, heart rate, respiratory rate, and oral body temperature, will be measured after the subject has been in a resting position for 5 minutes. Vital signs will be measured at Screening and before surgery on Day 0 immediately before and 1 hour (±10 minutes) after the first dose of study drug on Day 0, immediately before and 1 hour (±10 minutes) after the 24-hour and 40-hour doses, and at 48 hours (±10 minutes). Vital signs will also be measured before ET if a subject discontinues.

e Pulse oximetry will be measured continuously for safety; pulse oximetry will be recorded at selected times (±10 minutes), including baseline before Time 0 and at 90 minutes and 12, 24, and 48 hours after Time 0 (T_{max}).

f An ECG will be performed before the first dose of study drug, and then at 90 minutes (±10 minutes), and at 12, 24, and 48 hours (±10 minutes) after Time 0.

g A serum pregnancy test will be performed at Screening and a urine pregnancy test will be performed before surgery on Day 0. The test results must be negative for the subject to continue in the study.

h A urine drug screen will be collected at Screening and before surgery on Day 0. The test results must be negative for the subject to continue in the study, except in cases where a valid physician's prescription can be verified.

i Radiographs taken within 6 months before Screening will be acceptable.

j Immediately after the anesthetic block is discontinued, subjects will be instructed to request pain medication when they experience pain.

k The subject will record pain intensity (numerical rating scale) in the inpatient subject diary at Baseline before the first dose of study drug (Day 1). Thereafter, pain intensity and pain relief (5-point categorical scale) assessments will be recorded at the following time points (± 5 minutes):
- At 2.5, 5, 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24, 32, 40 and 48 hours after Time 0, and immediately before each use of rescue analgesia.

- At Early Withdrawal if a subject discontinues prematurely.

l The first dose of study drug will be administered within 9 hours (±10 minutes) after the anesthetic block has been discontinued when a subject's pain intensity is ≥4 on the 11-point (0-10) NRS. Study drug will be administered from Time 0 through 48 hours within 10-minute windows.

m Start stopwatches as soon as the first dose of study drug is administered. Stopwatches should be discontinued if the subject has not stopped them by the time of the second IP dose or first use of rescue medication (whichever occurs first).

n Subjects will complete a subject's global evaluation of study drug at the end of the Treatment Period (Day 3) before discharge from the study site or immediately before ET if a subject discontinues prematurely.

o Outpatient pain medication and an outpatient subject diary will be dispensed before discharge from the study site on Day 3.

p Subjects will be discharged from the study site on Day 3 (approximately 72 hours after completion of surgery)

10. APPENDIX 2 – PLANNED TLG

10.1 Planned by-subject listings

DISPOSITION/WITHDRAWALS (LISTINGS 16.2.1.X)

ELIGIBILTY AND PROTOCOL DEVIATIONS (LISTINGS 16.2.2.X)

EXCLUDED SUBJECTS (LISTINGS 16.2.3.X)

DEMOGRAPHICS, POPULATION, AND BASELINE CHARACTERISTICS (LISTINGS 16.2.4.X)

DRUG COMPLIANCE AND DRUG CONCENTRATION LISTINGS (LISTINGS 16.2.5.X)

EFFICACY RESPONSE DATA (LISTINGS 16.2.6.X)

ADVERSE EVENT DATA (LISTINGS 16.2.7.X)

SAFETY DATA (LISTINGS 16.2.8.1.X)

10.2 Planned Summary Tables

POPULATION DISPOSITION AND PROTOCOL DEVIATIONS

POPULATION DEMOGRAPHICS AND BASELINE CHARACTERISTICS

CONCOMITANT MEDICATION USAGE

EFFICACY SUMMARIES

SAFETY SUMMARIES

     ADVERSE EVENT SUMMARIES

     SERIOUS ADVERSE EVENTS

     LABORATORY

     VITAL SIGNS AND PE

     OTHER SAFETY

10.3 Planned Summary Figure

KM Curves for time to endpoints

Figures for Pain intensity and Pain relief

11. VERSION HISTORY

This is the first Version of the document.

12. REFERENCES

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2. The Royal Statistical Society: Code of Conduct (1993).

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5. Guideline for the Format and Content of the Clinical and Statistical Section of an Application, 1988.

6. Guideline for Industry: Structure and Content of Clinical Study Reports (ICH E3), July 1996.

7. Guideline on Missing Data in Confirmatory Clinical Trials: EMA/CPMP/EWP/1776/99 Rev. 1

8. The Prevention and Treatment of Missing Data in Clinical Trials: National Research Council of the national academies