REC-17-023

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo- and Active-Controlled, Evaluation of the Efficacy and Safety of DEX-IN following Painful Outpatient Procedures

NCT03348423

Statistical Analysis Plan

19 January 2018

ARTICLE I.

Statistical Analysis plan

Protocol Number:	REC-17-023
Protocol Title:	A Phase 2, Multicenter, Randomized, Double-Blind, Placebo- and Active-Controlled, Evaluation of the Efficacy and Safety of DEX-IN following Painful Outpatient Procedure
Date of Protocol:	05 September 2017

REVISION HISTORY

Version No.	Version Date	Author	Description of Modification
0.1	10Nov2017	J. Nezzer	Initial Draft for Internal Review
0.2	28Nov2017	J. Nezzer	Updated per initial sponsor and internal review comments
0.3	05Jan2018	J. Nezzer	Updated per sponsor review
1.0	19Jan2018	J. Nezzer	Final version issued

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
abs	absolute value
AE	adverse event
BMI	body mass index
BPM	Beats per minute
CFB	Change from baseline
eCRF	Electronic case report form
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
HR	Heart Rate
ICH	International Conference on Harmonization
IN	Intranasal
ITT	Intent-to-treat
IV	Intravenous
mm Hg	millimeters of mercury
NPRS	Numeric Pain Rating Scale
NRS	Numeric Rating Scale
PCFB	Percent change from baseline
PCSC	Potentially Clinically Significant Change
PE	Physical Exam
PI	Pain Intensity
PID	Pain Intensity Difference
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard deviation
STAI-6	Six Item Spielberger State-Trait Anxiety Inventory
TEAE	treatment emergent adverse event

1. INTRODUCTION

The study (Protocol REC-17-023) is planned to evaluate the use of single doses of DEX-IN in an office based or outpatient surgery/procedure setting where patients may receive limited or no analgesic medications. Patients undergoing these procedures generally experience a range of pain and anxiety symptoms that may not be well managed under the current standard of care. This study will utilize a placebo control, as well as an active control arm (IV fentanyl) to evaluate the efficacy of DEX-IN dosing.

This Statistical Analysis Plan (SAP), prepared for Study REC-17-023, provides a more technical and detailed elaboration of the principal statistical features stated in the protocol. The objective of the SAP is to reasonably assure that the statistical methodologies to be used for analysis are complete and accurate.

In the development of this SAP, the following documents were used:

- Protocol REC-17-023, 05 September 2017
- REC-17-023 Cohort 1 Manual Face Peel – FINAL, 11SEP2017
- REC-17-023, eCRF, Final 1.0 31 October 2017

The principles in the following guidance documents are followed in preparation of this SAP:

- ICH E3 (1995): Structure and Content of Clinical Study Reports
- ICH E6 (1996): Guideline for Good Clinical Practice
- ICH E9 (1998): Statistical Principles for Clinical Trials

In the event that a discrepancy is found between the descriptions in the statistical section of the protocol and this document, the description in this document supersedes the descriptions in the statistical section of the protocol.

This SAP has been prepared based on the first cohort of the study. The data from each cohort will be unblinded and reviewed in interim analyses as appropriate to inform program development.

Data summary and analysis approaches identified for Cohort 1 in this SAP will be followed for other cohorts as appropriate. If new assessments are identified and included in the other cohorts, a SAP addendum will be prepared to document any cohort specific assessments and/or analysis. If the same assessment (ie, PI score, anxiety score) is applied with a different nominal time point in the new cohorts, the SAP will not need to be appended and summary tables will be produced based on the nominal time point and/or intervals for the specific cohort.

Exploratory or additional summaries not identified in this SAP (or subsequent addendum) that are performed post-hoc (ie. on data that has been unblinded) will be clearly identified as such in the CSR.

2. STUDY OVERVIEW

2.1. Study Design and Objectives

Protocol REC-17-023 is a Phase 2, randomized, multicenter, double-blind, placebo- and active-controlled evaluation of the efficacy and safety of DEX-IN in adult subjects undergoing painful outpatient and office based procedures. The study will enroll up to 250 subjects across up to 5 study cohorts, with approximately 50-75 subjects per cohort. Each study cohort will include subjects undergoing a specific painful procedure which may include, but is not limited to, cosmetic procedures (face peel, liposuction/liposculpture, sclerotherapy, etc.), dental procedures, biopsy procedures (prostate, colposcopy, etc.), or other procedures. The procedures to be evaluated in this study will be selected on an ongoing basis.

This study will enroll an adequate number of subjects to have approximately 50-75 subjects per cohort (25-37 subjects per treatment group) for the intent-to-treat (ITT) analysis set. For the current (Facial Peel) cohort approximately 45 subjects are expected to complete (15 per treatment group).

The primary objective of this study is to evaluate the analgesic efficacy of DEX-IN compared with placebo and active control (fentanyl), in subjects undergoing painful outpatient and office based procedures.

Secondary objectives of this study will include:

- To evaluate the anxiolytic effects of DEX-IN
- To determine the safety and tolerability of DEX-IN as evaluated with vital sign collection, and incidence of Adverse Events (AEs) and Serious AEs (SAEs).

Subjects planned to undergo a selected procedure, age 18 to 65, inclusive, will be qualified for enrollment at up to 5 sites in the United States. The study has a Screening Period, three Periods on the Day of the Procedure: 1) Pre-Procedure period, 2) Peri-Procedure period, and 3) Post-Procedure period, and a Follow-up period.

Efficacy assessments will include assessment of pain intensity, anxiety intensity, and subject satisfaction with pain experienced during the procedure. Safety assessments will include monitoring of AEs and SAEs, and vital sign measurements.

2.1.1. Cohort 1 Procedure Specific Overview

Subjects enrolled in the first cohort will undergo a chemical face peel after completing study dosing.

Chemical peel procedures will be performed in the office setting using trichloroacetic acid to be applied over approximately 50% or greater of the facial surface. The trichloroacetic acid should be used at a concentration between 15 and 30%.

The acid will be applied to areas as determined by the investigator and subject prior to the procedure, and will remain in place for approximately 20 minutes, before being neutralized/removed using water or another neutralizing solution.

The start of the procedure should be the time that the acid is applied to the facial skin. The end of the procedure (Hour 0) will be the time when the removal of the acid is completed.

Procedure specific details to be recorded in Cohort 1 will include:

- Start of acid application (Start time of the procedure)
- Completion of acid application
- Start of acid removal
- Completion of acid removal (End time of the procedure)
- Approximate surface area (%) treated
- Acid concentration
- Other significant notes

2.1.2. Cohort x Procedure Specific Overview

As Cohorts are selected for inclusion in the study protocol, a SAP addendum will be prepared if necessary to document any cohort specific assessments.

2.2. Study Assessments Schedule

Demographics information will be collected during screening visit including age, sex, ethnicity, race, weight, height, and BMI. The investigator or designee will document each subject's medical history during the screening visit. Medical history will be updated on Day 1 when the subject reports for the procedure, and the subject's eligibility will be reviewed to confirm that they continue to meet the required study criteria. The investigator or designee will perform a physical examination (HEENT, cardiovascular, respiratory, gastrointestinal, neurological, dermatologic, and musculoskeletal systems) during the screening visit and at check-in (Day 1) to the study site prior to randomization.

Efficacy assessments will include pain intensity, anxiety measurements (NRS - Numeric Rating Scale and STAI-6 - Six Item Spielberger State-Trait Anxiety Inventory), and Subject Satisfaction with Pain Experience. Safety assessments will include monitoring of AEs and vital sign measurements.

Clinical Labs and ECGs will be assessed at screening to determine eligibility, but will not be recorded in the eCRF. A Schedule of Events is presented in the Protocol REC-17-023 Appendix A and in the Cohort Manual.

2.3. Efficacy Assessments

Where assessments are performed at the same time point, the following sequence of events should be utilized whenever possible:

1. Pain Intensity
2. Anxiety – NRS
3. Worst Pain Intensity
4. Anxiety – STAI-6
5. Satisfaction with Pain Experience

2.3.1. Pain Intensity (PI)

PI will be assessed by the study subject for their current pain according to an 11-point numeric pain rating scale (NPRS; 0 - 10) at the following time points:

Pre-procedure: PI will be assessed 1 hour (within 5 minutes prior to IN dosing), 15 minutes (within 5 minutes prior to IV dosing), and 5 minutes before the start of the procedure.

Peri-procedure: PI will be assessed immediately after completing application of the acid (within 1 minute), and every 2±1 minutes during the procedure until immediately prior to removal of the acid.

Post-procedure: PI will also be assessed at Hour 0 (immediately following completion of acid removal), and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, and 4 hours following the end of procedure.

2.3.2. Worst Pain Intensity

Subjects will assess their worst pain intensity during the procedure and in the post-procedure period using the 11-point NPRS at the following time points.

- The worst pain during the procedure will be collected at Hour 0 (end of procedure); at that time subjects will be asked to rate their worst pain experienced during the procedure.
- At Hour 4, prior to discharge, subjects will be asked to rate their worst pain experienced in the time since the end of the procedure.

2.3.3. Anxiety

2.3.3.1. Numeric Rating Scale

Anxiety will be assessed by the study subject for their current anxiety according to an 11-point numeric rating scale (NRS; 0 - 10) at the following time points:

Pre-Procedure: Anxiety will be assessed using the NRS 1 hour (within 5 minutes prior to IN dosing), 15 minutes (within 5 minutes prior to IV dosing), 5 minutes before the start of the procedure, and immediately prior to the start of the procedure (within 1 minute).

Peri-procedure: Anxiety will be assessed using the NRS immediately after completing application of the acid (within 1 minute), and every 5±1 minutes during the procedure until immediately prior to removal of the acid.

Post-procedure: Anxiety will also be assessed using the 11-point NRS at Hour 0 (immediately following completion of the acid removal), and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, and 4 hours following the end of procedure.

2.3.3.2. Six Item Spielberger State-Trait Anxiety Inventory (STAI-6)

Anxiety will also be assessed by the subject using the 6-Item Spielberger State-Trait Anxiety Inventory (STAI-6) at the following time points:

Pre-Procedure: Anxiety will be assessed using the STAI-6 at screening, 1 hour (within 5 minutes prior to IN dosing), and 5 minutes before the start of the procedure.

Post-procedure: Anxiety will be assessed using the STAI-6 at Hour 0 (immediately following completion of the acid removal); no peri-procedural assessments will be completed.

2.3.4. Subject Satisfaction with Pain Experience

Subjects will report their satisfaction with the degree of pain experienced during the procedure and in the post-procedure period according to a 7-point Likert scale at the

- The subject assessment of satisfaction will be completed for pain experienced during the procedure at Hour 0,
- At Hour 4, prior to discharge, subject assessment of satisfaction will be completed for the pain experienced during the post-procedure period.

2.4. Study Endpoints

2.4.1. Efficacy Endpoints

The primary efficacy endpoint will be the mean PI score during the study procedure.

Secondary efficacy endpoints include:

1. Mean PI score at other intervals (Pre- and Post-procedure)
2. Worst pain intensity during and following the procedure
3. Mean anxiety score (NRS and STAI-6) at various intervals (Pre-procedure, during the procedure [from the start of the procedure to the end of the procedure], and post-procedure)
4. Subject satisfaction with pain during and following the procedure.

2.4.2. Safety Endpoints

The safety endpoints will include the following:

1. Incidence of AEs and SAEs
2. Change from baseline in vital signs; incidence of clinically significant changes in vital signs

2.5. Sample Size Consideration

The sample size for this study was selected empirically without a power calculation.

3. GENERAL CONSIDERATIONS

3.1. Analysis Population

The following analysis sets will be identified for this study.

Intent-to-Treat (ITT) Analysis Set: The ITT set will include randomized subjects. This dataset may also be referenced as the 'Randomized Set'. The ITT subjects may or may not receive randomized treatment.

Safety Set: The safety set will include all treated subjects and will be used for safety and tolerability summaries.

Efficacy Analysis Set: The Efficacy analysis set will include all subjects in the Safety analysis set who had at least one pain intensity assessment post dosing of study drug and will be used for all efficacy summaries.

3.2. Test Hypothesis and *P* Value Justification

The null hypothesis is that there is no difference between the treatment arms. The alternative hypothesis is that the treatment groups are different.

Differences between DEX-IN, fentanyl, and placebo groups will be evaluated via a 2-sided 2-sample t-test at the 0.05 level of significance. Nominal p-values for secondary endpoints will be reported without adjustment for multiplicity.

3.3. Procedures for Handling Missing Data

Unless indicated otherwise, no missing data imputation will be performed and all data will be shown as collected in listings. However, AEs with missing severity assessments will be tabulated as "severe," and AEs with missing relationship assessments will be tabulated as "related" for the purpose of analysis.

3.4. Baseline Definitions

Baseline: Baseline will be the last measurements taken before the subject receives the study medication

3.5. Derived Variables

3.5.1. Average PI Score

Average PI score at each interval (ie, pre-procedure, peri-procedure, and post-procedure) will be derived for each subject as a simple average of all non-missing PI scores within the interval from the subject.

3.5.2. Average Anxiety Scores

Average anxiety scores using the 11-point NRS scale at each interval (ie, pre-procedure, peri-procedure, and post-procedure) will be derived for each subject as simple average of all non-missing anxiety scores within the interval from the subject.

3.5.3. Potentially Clinically Significant Changes in Vital Signs

To identify potentially clinically significant changes (PCSC) in vital signs through the study, Change from baseline (CFB) and percent change from baseline (PCFB) in vital signs will be calculated for each post dosing vital signs as follows.

CFB = Post Baseline – Baseline

PCFB = 100*(CFB / Baseline)

4. STUDY POPULATION SUMMARIES

4.1. Disposition

A summary table (Table 14.1.1) will provide frequency counts for subject disposition (randomized (ITT), all treated subjects, subjects who completed the procedure day assessments, subjects who completed the follow up visit, subjects who discontinued from the study and reason for discontinuation) by treatment group and overall within the cohort based on safety set.

Disposition in terms of the number of subjects included from each analysis set will also be provided by treatment group and overall within the cohort in the disposition summary.

4.2. Demographics and Procedure Characteristics

The demographic summary will include descriptive statistics for age, sex, race, ethnicity, weight, height, and BMI for overall and by treatment group.

Procedure specific summaries for Cohort 1 will include:

- Duration of the procedure (start of acid application to completion of acid removal)
- Approximate surface area (%) treated
- Acid concentration

Any additional parameters that are collected for other cohorts will also be included in the demographics and procedure characteristics for the corresponding cohort(s).

Demographics and baseline characteristics will be tabulated for the safety set (Table 14.1.2) by treatment groups and overall within a cohort.

4.3. Protocol Deviations

All protocol deviations will be identified and categorized according to the following:

- Informed Consent Procedures
- Inclusion / Exclusion Criteria
- Prohibited Medications
- Study Procedures
- Study Drug Assignment / Treatment
- Visit or Assessment Time Window
- Missed Visit or Assessment
- Other

At the end of the study, and prior to database lock, the medical monitor will assign deviations as "deviation" or important deviation". Protocol deviations will be addressed in the study report without formal tabulation.

4.4. Treatment Compliance

Doses of study medication will be administered to the study subjects under the observation of study personnel while confined to the study site. The exact time of administration of study medication will be documented within each subject's source record and eCRF. No formal summary of treatment compliance will be produced.

4.5. Prior and Concomitant Medications

Prior and concomitant medications will be coded to the therapeutic drug classes and generic drug names using the World Health Organization (WHO) Drug classifications version March 1, 2017. No formal tabulations will be produced for concomitant medications.

5. EFFICACY ANALYSIS

All efficacy parameters will be tabulated within each cohort by treatment groups and nominal time points. All efficacy tables will be based on the efficacy set.

5.1. Pain Intensity

PI score at each nominal time point, the average PI score during each study interval (pre-, peri- and post-procedure) and the worst PI score at Hour 0 and 4-hours post procedure will be tabulated by treatment group (Table 14.2.1). Pairwise comparison between each group will be made via analysis of variance model that include the main effect of treatment.

5.2. Anxiety Assessment

Anxiety assessment scores using the 11-point NPRS scale at each nominal time point and the average anxiety score at each interval will be tabulated by treatment group (Table 14.2.2). Pair-wise comparisons between each group will be made via analysis of variance model that include the main effect of treatment.

Anxiety assessment scores using the STAI-6 scale at each nominal time point will be tabulated by treatment group (Table 14.2.3). Pair-wise comparisons between each group will be made via analysis of variance model that include the main effect of treatment.

5.3. Subject Satisfaction with Pain Experience

Subject satisfaction scores will be summarized (Table 14.2.4) by treatment at each nominal time point. The summary table will include distribution [subjects (%)] in each subject satisfaction category (1-Completely Dissatisfied, 2-Mostly Dissatisfied, 3-Somewhat Dissatisfied, 4-Neither Dissatisfied nor Satisfied, 5- Somewhat Satisfied, 6- Mostly Satisfied, or 7-Completely Satisfied) and the average score and standard deviation without any inferential test.

5.4. Subgroup Analyses for Efficacy

Subjects from each cohort will be analyzed separately. Data across cohorts may be pooled for analysis if data warrants. Additional subgroups may be identified if data warrants. No subgroup within a cohort is planned.

6. SAFETY AND TOLERABILITY EVALUATIONS

6.1. Extent of Exposure

This is a single dose study, therefore the maximum anticipated exposure in any subject will be 50 µg dexmedetomidine for subjects in the DEX-IN treatment group, and 50 µg fentanyl for subjects in the fentanyl treatment group. All subjects treated with a specific treatment will receive the same dose. No formal summary of treatment exposure will be produced.

6.2. Adverse Events

Adverse events reported post dosing throughout the final follow-up (7 days) will be considered as treatment emergent adverse events (TEAEs) and summarized. The Medical Dictionary for Regulatory Activities **(Version 20.1)** will be used to classify all AEs with respect to system organ class and preferred term.

Three types of summaries will be produced for the AE summary:

1. an overall summary of AEs: number of subjects with at least one event and number of events for all AEs, and SAEs (Table 14.3.1.1)
2. a summary table of AEs(Table 14.3.1.2) by system organ class and preferred term and severity
3. a summary table of AEs (Table 14.3.1.3) by preferred terms in descending order of total incidence

AEs will be tabulated by study cohort and treatment group. AEs that lead to premature discontinuation from the study and all SAEs will be presented in a data listing.

6.3. Clinical Laboratory Tests

Laboratory values, will be collected at screening to assess subject eligibility, but will not be collected in the eCRF. No formal summary of laboratory results will be produced.

6.4. Vital Sign Measurements

Resting vital sign values and postural vital sign values at each time point collected will be summarized by treatment and time point without formal statistical testing (Table 14.3.2.1).

PCSC in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) measurements will be defined as follows:

- Hypotension: SBP < 90 mm Hg with a decrease ≥ 20 mm Hg from predose, or a DBP ≤ 50 mm Hg and decrease ≥ 15 mm Hg from predose.

- Hypertension: SBP ≥ 180 mm Hg with an increase of ≥ 20 mm Hg from predose, or a DBP ≥105 and an increase ≥ 15 mm Hg from predose
- Bradycardia: HR ≤ 50 BPM with a decrease ≥15 BPM from predose
- Tachycardia: HR ≥ 120 BPM with an increase ≥15 BPM from predose.

A summary table will be produced to examine number (%) subjects meeting the PCSC criteria (SBP abs(CFB) ≥ 20 mm Hg or DBP abs(CFB) ≥ 15 mm Hg) at various time points where abs=absolute value (Table 14.3.2.2).

6.5. Electrocardiograms

12-Lead ECG will be performed at screening to assess subject eligibility, but will not be collected in the eCRF. No formal summary of ECG results will be produced.

6.6. Subgroup Analyses for Safety Endpoints

No subgroup analysis is planned for this study.

7. REFERENCES

None

APPENDIX 1 - TABLE OF CONTENTS OF PLANNED ANALYSIS

	Number	Title	Analysis Set
Tables	14.1.1	Disposition Summary	ITT Set
Tables	14.1.2	Demographic and Baseline Characteristics	Safety Set
		Efficacy Endpoints Summary	
Tables	14.2.1	Summary of Pain Intensity Score by Time Point, Average Pain Intensity Score by Interval, and Worst Pain Intensity by Time Point Treatment	Efficacy Set
Tables	14.2.2	Summary of Anxiety Intensity (NRS) Score by Time Point and Average Anxiety Score by Interval	Efficacy Set
Tables	14.2.3	Summary of Anxiety Intensity (STAI-6) by Time Point	Efficacy Set
Tables	14.2.4	Summary of Subject Satisfaction with Pain Experience by Time Point	Efficacy Set
		Safety Endpoint Overall Summary	
Tables	14.3.1.1	Topline Summary of Treatment Emergent Adverse Events	Safety Set
Tables	14.3.1.2	All TEAE by SOC, Preferred Term and Severity	Safety Set
Tables	14.3.1.3	All TEAE by Preferred Term – Displayed in Descending Order of Total Events	Safety Set
Table	14.3.2.1	Values and Changes from Baseline in Vital Signs by Time Point	Safety Set
Table	14.3.2.2	Incidence of PCSC in Blood Pressure by Time Point	Safety Set

APPENDIX 2 - TABLE OF CONTENTS OF DATA LISTINGS

Number	Listings Title	Analysis Set
16.2.1	All Adverse Events from Subjects Who Had ≥1 SAE, an AE resulting in Death or Subjects Who Discontinued Due to AE	Safety Set

Table of Contents

Table 14.1.1
Disposition Summary
Intent-to-Treat Analysis Set

	Placebo n (%)	Fentanyl IV n (%)	DEX-IN n (%)	Total n (%)
Subjects randomized (ITT)	XXX	XXX	XXX	XXX
Subjects treated with study drug (Safety)	XX (X.X)	XX (X.X)	XX (X.X)	XX (X.X)
Subjects completed Procedure Day Assessments	XX (X.X)	XX (X.X)	XX (X.X)	XX (X.X)
Subjects completed 7 day Follow Up	XX (X.X)	XX (X.X)	XX (X.X)	XX (X.X)
Efficacy Analysis Set	XX (X.X)	XX (X.X)	XX (X.X)	XX (X.X)
Subjects discontinued from study				
Reason for discontinuation from study				
Adverse Event	XX (X.X)	XX (X.X)	XX (X.X)	XX (X.X)
Death	XX (X.X)	XX (X.X)	XX (X.X)	XX (X.X)
Withdrawal of Consent by Subject	XX (X.X)	XX (X.X)	XX (X.X)	XX (X.X)
Investigator Decision	XX (X.X)	XX (X.X)	XX (X.X)	XX (X.X)
Protocol Deviation	XX (X.X)	XX (X.X)	XX (X.X)	XX (X.X)
Lost to follow up	XX (X.X)	XX (X.X)	XX (X.X)	XX (X.X)
Other	XX (X.X)	XX (X.X)	XX (X.X)	XX (X.X)

[1] Percentages are based on the number of randomized subjects in each group.
All subjects were grouped based on their randomized treatment group.

Table 14.1.2
Demographic and Baseline Characteristics
Safety Analysis Set

	Category or Statistics	Placebo (N=XX)	Fentanyl IV (N=XX)	DEX-IN (N=XX)	Total (N=XX)
Age (years)	n	XX	XX	XX	XX
	Mean	XX.X	XX.X	XX.X	XX.X
	SD	X.X	X.X	X.X	X.X
	Minimum	XX	XX	XX	XX
	Median	XX	XX	XX	XX
	Maximum	XX	XX	XX	XX
Sex: n (%)	Male	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Female	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Race: n (%)	White	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Black or African American	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Asian	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	American Indian or Alaskan Native	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Native Hawaiian/Other Pacific Islander	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Other	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Ethnicity: n (%)	Hispanic	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Non-Hispanic	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)

Table 14.1.2(continued)

	Category Or Statistics	Placebo (N=XX)	Fentanyl IV (N=XX)	DEX-IN (N=XX)	Total (N=XX)
Baseline Height (cm)	n	XX	XX	XX	XX
	Mean	X.X	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX
	Median	XX	XX	XX	XX
	Maximum	XX	XX	XX	XX
Baseline Weight (kg)	n	XX	XX	XX	XX
	Mean	X.X	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX
	Median	XX	XX	XX	XX
	Maximum	XX	XX	XX	XX
Baseline BMI (kg/m^2)	n	XX	XX	XX	XX
	Mean	X.X	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX
	Median	XX	XX	XX	XX
	Maximum	XX	XX	XX	XX

Table 14.1.2 (continued)

	Category Or Statistics	Placebo (N=XX)	Fentanyl IV (N=XX)	DEX-IN (N=XX)	Total (N=XX)
Procedure Duration (hr)	n	XX	XX	XX	XX
	Mean	X.X	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX
	Median	XX	XX	XX	XX
	Maximum	XX	XX	XX	XX
Approximate Surface Area (%) treated	n	XX	XX	XX	XX
	Mean	X.X	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX
	Median	XX	XX	XX	XX
	Maximum	XX	XX	XX	XX
Acid Concentration	n	XX	XX	XX	XX
	Mean	X.X	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX
	Median	XX	XX	XX	XX
	Maximum	XX	XX	XX	XX

Note to programmer:

1) Create a Missing category only if there are missing data; percentages are calculated per non-missing data in each group.

Table 14.2.1
Summary of Pain Intensity Score by Time Point, Average Pain Intensity Score by Interval, and Worst Pain Intensity by Time Point
Efficacy Analysis Set

Parameter	Time Point	Statistics	Placebo (N=XX)	Fentanyl IV (N=XX)	DEX-IN (N=XX)
Pain Intensity	60 min Pre	n	XX	XX	XX
		Mean	XX.X	XX.X	XX.X
		SD	X.XX	X.XX	X.XX
		Minimum	XX.X	XX.X	XX.X
		Median	XX.X	XX.X	XX.X
		Maximum	XX.X	XX.X	XX.X
		P Value Active vs Placebo		0.xxxx	0.xxxx
		P Value DEX-IN vs Fentanyl			0.xxxx
	15 min Pre	n	XX	XX	XX
		Mean	XX.X	XX.X	XX.X
		SD	X.XX	X.XX	X.XX
		Minimum	XX.X	XX.X	XX.X
		Median	XX.X	XX.X	XX.X
		Maximum	XX.X	XX.X	XX.X
		P Value Active vs Placebo		0.xxxx	0.xxxx
		P Value DEX-IN vs Fentanyl			0.xxxx
	2 min Post Etc for all time points				
Average Pain Intensity	Pre-Procedure	n	XX	XX	XX
		Mean	XX.X	XX.X	XX.X
		SD	X.XX	X.XX	X.XX
		Minimum	XX.X	XX.X	XX.X
		Median	XX.X	XX.X	XX.X

		Maximum	XX.X	XX.X	XX.X
		P Value Active vs Placebo		0.xxxx	0.xxxx
		P Value DEX-IN vs Fentanyl			0.xxxx
	Etc				
Worst Pain	Hour 0	Etc.			

[1] Difference = DEX-IN – Placebo or DEX-IN - Fentanyl; ANCOVA analysis with Treatment as a main effect.

Table 14.2.2
Summary of Anxiety Intensity (NRS) Score by Time Point and Average Anxiety Score by Interval
Efficacy Analysis Set

See Mock Table 14.2.1 – include Anxiety NRS at each time point and Average Anxiety at study interval parameters

Table 14.2.3
Summary of Anxiety Intensity Endpoints (STAI-6) by Time Point
Efficacy Analysis Set

See Mock Table 14.2.1 – include Anxiety NRS at each time point and Average Anxiety (STAI-6) at study time points

Table 14.2.4
Summary of Subject Satisfaction with Pain Experience by Time Point
Efficacy Analysis Set

Time Point	Category/Statistics [1]	Placebo (N=XX)	Fentanyl IV (N=XX)	DEX-IN (N=XX)
Hour 0	1-Completely dissatisfied	XX (X.X%)	XX (X.X%)	XX (X.X%)
	2-Mostly Dissatisfied	XX (X.X%)	XX (X.X%)	XX (X.X%)
	3-Somewhat Dissatisfied	XX (X.X%)	XX (X.X%)	XX (X.X%)
	4-Neither Dissatisfied nor Satisfied	XX (X.X%)	XX (X.X%)	XX (X.X%)
	5- Somewhat Satisfied	XX (X.X%)	XX (X.X%)	XX (X.X%)
	6- Mostly Satisfied	XX (X.X%)	XX (X.X%)	XX (X.X%)
	7-Completely Satisfied	XX (X.X%)	XX (X.X%)	XX (X.X%)
	Average (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Hour 4	1-Completely dissatisfied	XX (X.X%)	XX (X.X%)	XX (X.X%)
	2-Mostly Dissatisfied	XX (X.X%)	XX (X.X%)	XX (X.X%)
	3-Somewhat Dissatisfied	XX (X.X%)	XX (X.X%)	XX (X.X%)
	4-Neither Dissatisfied nor Satisfied	XX (X.X%)	XX (X.X%)	XX (X.X%)
	5- Somewhat Satisfied	XX (X.X%)	XX (X.X%)	XX (X.X%)
	6- Mostly Satisfied	XX (X.X%)	XX (X.X%)	XX (X.X%)
	7-Completely Satisfied	XX (X.X%)	XX (X.X%)	XX (X.X%)
	Average (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)

Table 14.3.1.1
Topline Summary of Treatment Emergent Adverse Events
Safety Analysis Set

Category [1, 2]	Category /Statistics	Placebo (N=XX)		Fentanyl IV (N=XX)		DEX-IN (N=XX)		Total (N=XX)	
		n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Reported >=1 TEAE		XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
TEAE by Severity	Mild	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
	Moderate	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
	Severe	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
TEAE by Seriousness	Serious	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
	Not Serious	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
TEAE by Relationship	Not Related	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
	Possibly Related	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
	Probably Related	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
	Definitely Related	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
TEAE by Outcome	Resolved	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
	Resolved with Sequelae	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
	Not Resolved	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
	Unknown	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
	Death	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX

'n' = subjects in a category; percentage was calculated from total subjects in a group. 'Events' = Total number of events in a category.

[1] A subject could be counted in more than one category but only once per category for summary of 'Subjects', Hence, sum of subjects across all categories could be greater than the total number of subjects in the study.

[2] All events in each category were included in the 'Total Events'.

(Table 14.3.1.1 continued)

Category [1, 2]	Category /Statistics	Placebo (N=XX)		Fentanyl IV (N=XX)		DEX-IN (N=XX)		Total (N=XX)	
		n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Total Number of TEAEs by subject	n		XX		XX		XX		XX
	Mean		XX.X		XX.X		XX.X		XX.X
	SD		X.XX		X.XX		X.XX		X.XX
	Minimum		X		X		X		X
	Median		X		X		X		X
	Maximum		X		X		X		X

[1] A subject could be counted more than one category but only once per category for summary of 'Subjects', Hence, sum of subjects across all categories could be greater than the total number of subjects in the study.

[2] All events in each category were included in the 'Events'.

Table 14.3.1.2
All TEAE by SOC, Preferred Term and Severity
Safety Analysis Set

SOC Preferred Term (MedDRA 19.1)	Intensity [1]	Placebo (N=XX) n (%)	 Events	Fentanyl IV (N=XX) n (%)	 Events	DEX-IN (N=XX) n (%)	 Events	Total (N=XX) n (%)	 Events
Subjects with >=1 Event	All	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
	Mild	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
	Moderate	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
	Severe	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
SOC 1	All	XX (X.X)		XX (X.X)		XX (X.X)		XX (X.X)	
	Mild	XX (X.X)		XX (X.X)		XX (X.X)		XX (X.X)	
	Moderate	XX (X.X)		XX (X.X)		XX (X.X)		XX (X.X)	
	Severe	XX (X.X)		XX (X.X)		XX (X.X)		XX (X.X)	
Preferred Term 1	All	XX (X.X)		XX (X.X)		XX (X.X)		XX (X.X)	
	Mild	XX (X.X)		XX (X.X)		XX (X.X)		XX (X.X)	
	Moderate	XX (X.X)		XX (X.X)		XX (X.X)		XX (X.X)	
	Severe	XX (X.X)		XX (X.X)		XX (X.X)		XX (X.X)	
Preferred Term 2	(repeat above)								
Preferred Term 3	(repeat above)								
SOC 2	All								
	Mild								

SOC Preferred Term (MedDRA 19.1)	Intensity [1]	Placebo (N=XX)	Fentanyl IV (N=XX)	DEX-IN (N=XX)	Total (N=XX)
	Moderate				
	Severe				
Preferred Term 1	(repeat above)				
	(repeat above)				

[1] 'n' = Number of subjects reported >=1 event of the preferred term; A subject was counted only once, in the most severe category, if the subject had the multiple events in different intensity category; the subject was counted once in the 'All' summary.

Table 14.3.1.3
All TEAE by Preferred Term – Displayed in Descending Order of Total Events
Safety Analysis Set

Preferred Term (MedDRA 19.1)	Total Events [1]	Placebo (N=XX)		Fentanyl IV (N=XX)		DEX-IN (N=XX)		Total (N=XX)	
		n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Subjects with >=1 Event	XXXX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
Preferred Term 1	120	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
Preferred Term 2	109	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
Preferred Term 3	95	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
Preferred Term 4	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
Preferred Term 5	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
Preferred Term 6	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
Preferred Term 7	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
Preferred Term 8	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
Preferred Term 9	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
Preferred Term 10	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX
Preferred Term 11	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX	XX (X.X)	XX

[1] 'n' = Number of subjects reported >=1 event of the preferred term; 'Total Events' = total number of events across all treatment groups. A subject was counted only once per preferred term but all events were included in the 'Events'.

Table 14.3.2.1
Values and Change from Baseline in Vital Signs by Time Point
Safety Analysis Set

Time Point	Statistics	Placebo (N=XX)			Fentanyl IV (N=XX)			DEX-IN (N=XX)			Total (N=XX)		
		Value	CFB	CFB (%)	Value	CFB	CFB (%)	Value	CFB	CFB (%)	Value	CFB	CFB (%)
Pre-Dose	n	XX			XX			XX			XX		
1 Hour	Mean	XX.X			XX.X			XX.X			XX.X		
	SD	X.XX			X.XX			X.XX			X.XX		
	Minimum	XX.X			XX.X			XX.X			XX.X		
	Median	XX.X			XX.X			XX.X			XX.X		
	Maximum	XX.X			XX.X			XX.X			XX.X		
Pre-Dose	n	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX
15 Min	Mean	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
	Minimum	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	Maximum	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Repeat for All remaining Time points													

[1]CFB = Change from Baseline: Post Baseline – Baseline Result. CFB (%) = Post Baseline – Baseline / Baseline *100.

Table 14.3.2.2
Incidence of PCSC in Blood Pressure by Time Point
Safety Analysis Set

Time Point	Category/Statistics [1]	Placebo (N=XX)	Fentanyl IV (N=XX)	DEX-IN (N=XX)	Total (N=XX)
Pre-Dose	Hypotension	XX (X.X%)	XX (X.X%)	XX (X.X%)	XX (X.X%)
1 Hour	Hypertension	XX (X.X%)	XX (X.X%)	XX (X.X%)	XX (X.X%)
	Bradycardia	XX (X.X%)	XX (X.X%)	XX (X.X%)	XX (X.X%)
	Tachycardia	XX (X.X%)	XX (X.X%)	XX (X.X%)	XX (X.X%)
	Hypertension	XX (X.X%)	XX (X.X%)	XX (X.X%)	XX (X.X%)
Pre-Dose	Bradycardia	XX (X.X%)	XX (X.X%)	XX (X.X%)	XX (X.X%)
15 Min	Tachycardia	XX (X.X%)	XX (X.X%)	XX (X.X%)	XX (X.X%)
	Hypotension	XX (X.X%)	XX (X.X%)	XX (X.X%)	XX (X.X%)
Repeat for All remaining Time points					

Note: Hypotension: SBP < 90 mm Hg with a decrease ≥ 20 mm Hg from predose, or a DBP ≤ 50 mm Hg and decrease ≥ 15 mm Hg from predose. Hypertension: SBP ≥ 180 mm Hg with an increase of ≥ 20 mm Hg from predose, or a DBP ≥105 and an increase ≥ 15 mm Hg from predose, Bradycardia: HR ≤ 50 BPM with a decrease ≥15 BPM from predose, Tachycardia: HR ≥ 120 BPM with an increase ≥15 BPM from predose.