Documentation of Statistical Methods

Statistical Analysis Plan, Amendment 3.0, dated 20-May-2020

Table, Listing, and Figure Shells, Amendment 3.0, dated 20-May-2020

Statistical Analysis Plan, Amendment 2.0, dated 18-May-2020

Table, Listing, and Figure Shells, Amendment 2.0, dated 18-May-2020

Statistical Analysis Plan, Amendment 1.0, dated 24-Feb-2020

Table, Listing, and Figure Shells, Amendment 1.0, dated 28-Feb-2020

Final Statistical Analysis Plan, Final Version 1.0, dated 07-Oct-2019

Sponsor	Reckitt Benckiser
Protocol Title:	A Randomized, Double-Blind, Double-Dummy, Parallel-Group, Multiple-Dose, Active and Placebo-Controlled Efficacy Study of Ibuprofen Prolonged-Release Tablets for the Treatment of Pain after Surgical Removal of Impacted Third Molars
Protocol Number:	5003601
Premier Research PCN:	RECK.177035
Document Version:	Amendment 3.0
Document Date:	20-May-2020

Approvals

Role	Signatures	Date (dd-Mmm-yyyy)
Biostatistician Premier Research	Print Name: Raghu Vishnubhotla Sign Name: DocuSigned by: Raghu Srinivas Vishnubhotla Signer Name: Raghu Srinivas Vishnubhotla Signing Reason: I am the author of this document Signing Time: 21-May-2020 | 15:35:53 EDT 46FE4E466250408E961764121635BB48	21-May-2020 | 15:35:57 EDT
Reckitt Benckiser Representative	Print Name: Darren Targett Sign Name: DTarget	21-MAY-2020

Document History

Reasons for Amendment 1

The statistical analysis plan was amended in the following ways:

1. The sensitivity analyses for the primary efficacy endpoint has been updated. A pattern-mixture model with control-based pattern imputation will now be used.
2. A comparison of individual NRS pain intensity difference scores has been added. P-values comparing the treatment arms (PR vs Placebo, IR vs Placebo) has been added.
3. Pain relief scores at each time point will be summarized and by p-values will be added for treatment comparison.

Reasons for Amendment 2

The statistical analysis plan was amended in the following ways:

1. Add clarification for how pain assessments recorded within 4-hours of rescue medication and missing pain assessments are handled in the repeated measures analysis of pain intensity difference and pain relief scores.

2. The sensitivity analyses for the primary efficacy endpoint have been further updated. A multiple imputation model under a Missing at Random (MAR) assumption has been added to account for missing data due to patient withdrawal, missing intermediate pain assessments and pain assessments impacted by rescue medication.

3. Sensitivity analyses have been added for the key secondary endpoint SPID24.

4. Updated methodology for handling pain assessments post non-permitted rescue medications. Added imputation windows for non-permitted rescue medications.

Reasons for Amendment 3

The statistical analysis plan was amended in the following ways:

1. Amend the analysis of pain relief at each time point to use a mixed model repeated measures analysis. It is considered that the assumptions underlying the proportional odds analysis at each and every time point is unlikely to be upheld. Since pain relief is measured on a 5-point ordinal scale, it is deemed acceptable to treat this as a continuous variable for purposes of analysis.

2. Corrected a typographical error in section 6.1.4, where section 8.2.12 should be referenced rather than 8.1.12.

3. In the event that imposing a specified range for imputed values leads to an error in the multiple imputation process, included the option to remove the restrictions on imputed values as part of the multiple imputation process, and then enforce them separately after the imputation is performed if necessary.

4. Added that if the proportional odds assumptions are violated, a non-proportional odds model will be explored. Also added clarification that in the proportional odds models, the lowest level of the categorization of the dependent variable will be the reference category, such that the probability of the higher response levels will be modelled.

5. Updated the version of MedDRA that is used.

Table of Contents

List of Tables

1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Reckitt Benckiser protocol number 5003601 (A Randomized, Double-Blind, Double-Dummy, Parallel-Group, Multiple-Dose, Active and Placebo-Controlled Efficacy Study of Ibuprofen Prolonged-Release Tablets for the Treatment of Pain after Surgical Removal of Impacted Third Molars), dated 19-Nov-2019, version 3.0. Reference materials for this statistical plan include the protocol and the accompanying sample data collection documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association[2] and the Royal Statistical Society[3], for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The statistical plan described hereafter is an *a priori* plan. It will be submitted to file prior to any unblinded inferential or descriptive analysis of data pertaining to Reckitt Benckiser's study 5003601.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective is:

- To evaluate the superiority of 2 x 300 mg ibuprofen PR tablets compared with placebo in subjects experiencing acute moderate to severe pain after third molar extraction over 12 hours post initial dose.

2.1.2. Secondary Objectives

The key secondary objectives are:

- To evaluate the analgesic performance of a total daily dose of 1200 mg of ibuprofen PR formulation compared to ibuprofen immediate release (IR) formulation over 24 hours post initial dose.
- To evaluate the safety and tolerability of 2 x 300 mg ibuprofen PR tablets.

Additional secondary objectives include:

- To evaluate the total analgesic effect, peak analgesic effect, onset and duration of action and the subject's overall assessment of the study medications.

2.2. Study Endpoints

2.2.1. Safety Endpoints

The safety endpoints of this study include the following:

- Incidence of treatment-emergent adverse events (TEAEs)
- Incidence of changes in vital sign measurements

2.2.2. Efficacy Endpoints

2.2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint of this study is the summed pain intensity difference (SPID) over 0 to 12 hours (SPID12).

2.2.2.2. Secondary Efficacy Endpoint(s)

The secondary efficacy endpoints of this study include the following:

- Summed pain intensity difference (SPID) over 0 to 24 hours (SPID24) after Time 0.
- SPID4, SPID8 and SPID12
- Sum of total pain relief (TOTPAR) over 0 to 4 hours (TOTPAR4), over 0 to 8 hours (TOTPAR8), over 0 to 12 hours (TOTPAR12) and over 0 to 24 hours (TOTPAR24) after Time 0.
- Summed pain relief and intensity difference (sum of TOTPAR and SPID [SPRID]) over 0 to 4 hours (SPRID4), over 0 to 8 hours (SPRID8), over 0 to 12 hours (SPRID12) and over 0 to 24 hours (SPRID24) after Time 0.
- Response to study drug
- Numeric rating scale (NRS) pain intensity difference (PID) at each scheduled timepoint after Time 0. NRS ranges from 0=no pain to 10=worst pain ever and pain relief is a 5 point categorical scale 0=none, 1=a little, 2=some, 3=a lot, 4=complete. PID is the difference in NRS pain intensity between each time point and Time 0.
- Pain intensity score at each scheduled time point after Time 0.
- Pain relief at each schedule time point after Time 0.
- Peak pain relief
- Time to onset of analgesia
- Time to first perceptible pain relief
- Time to meaningful pain relief

- Time to peak pain relief
- Proportion of subjects using rescue medication
- Time to first use of rescue medication

2.2.2.3. Exploratory Endpoint

- Patient's global evaluation of study drug. It is measured on a scale of 0=poor, 1=fair, 2=good, 3=very good, 4=excellent

3. Overall Study Design and Plan

3.1. Overall Design

3.2. Sample Size and Power

The sample size determination is based on the primary efficacy variable, SPID12. According to Farrar 2001, a clinically important improvement in pain is represented by a 2 point reduction on an 11-point NRS. Based on a baseline pain score of 7 this corresponds to an approximate 30% reduction in pain. An average 2 point difference in pain scores between ibuprofen PR and placebo across all 14 assessments up to 12 hours will correspond to a difference in SPID12 of 24 points. In a previous study, the pooled standard deviation (SD) for SPID12 was 31.65. Assuming the same variability in this study, a sample size of 40 subjects per group will have >90% power to detect a difference of 24 points in SPID12, between ibuprofen 2x300-mg PR tablets and placebo using a 2-sided test with an alpha level of 0.05. In order to provide a robust estimate of treatment effect differences between PR and IR, and to obtain a more precise estimate for this comparison, a 3:3:1 allocation ratio will be used, so that 120 subjects are randomized into each of the PR and IR groups. Thus 280 subjects will be enrolled in the study.

3.3. Study Population

Subjects with moderate to severe pain after extraction of 2 or more third molars will participate in this study.

3.4. Treatments Administered

Treatment A (test product): 2x300 mg ibuprofen PR tablets, BID (total daily dose 1200 mg)

Treatment B (reference product): 2x200 mg ibuprofen IR tablets, TID (total daily dose 1200 mg)

Treatment C: matching placebo tablets

3.5. Method of Assigning Subjects to Treatment Groups

Eligible subjects will be randomized in a 3:3:1 ratio to receive 2x300 mg ibuprofen PR tablets Q12h, 2x200 mg ibuprofen IR Q8h, or placebo using permuted blocks of fixed size. The randomization will be stratified by baseline pain category (moderate or severe) using a categorical scale that includes the categories of none (0), mild (1-4), moderate (5-7), and severe (8-10). The randomization schedule will be prepared by a statistician not otherwise involved in the study. Randomization will be performed using an interactive response system (IRT).

3.6. Blinding and Unblinding

This is a double-blind, double-dummy study. There will be two placebo tablets designed to be

comparable to each of the active products (PR and IR) in both shape, size, color and weight.

All subjects will receive 4 tablets at each dosing timepoint. All subject packs will be designed and labelled to ensure blinding is maintained.

Access to the unblinding codes will be restricted to personnel not otherwise involved in the study and will be available to the investigator only in the case of a subject requiring unblinding prior to database lock.

Unblinding will only occur after database lock or in the case of emergency unblinding.

3.7. Schedule of Events

A detailed schedule of events for the study is provided in Table 1.

Table 1: Schedule of Events

	Screening (Day -28 to Day -1)	Surgery (Day 1)						Day 2		Follow-up (Day 8 ±2 days) or ET[k]
			Post-op							
		Pre-Surgery	Pre-dose	0 h	15, 30, 45 min	1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 h	12 h	16 h	24h	
Written informed consent	X									
Assign a screening number	X									
Inclusion/exclusion criteria	X	X								
Demographics	X									
Medical history	X	X[b]								
Physical examination[c]	X									X
Vital signs[d]	X	X	X				X		X	X
Height, weight, and BMI	X									
Clinical laboratory tests (hematology, chemistry, urinalysis)	X									
Electrocardiogram	X									
Pregnancy test for female subjects of childbearing potential[e]	X	X								
Urine drug screen	X	X								
Alcohol breathalyzer test		X								
Oral radiography[f]	X									
Review study restrictions with subject	X									
Pain intensity (NRS)[g]			X		X	X	X	X	X	
Randomisation			X							
Dosing with study drug				0 h		8 h	12 h	16h		
Stopwatch assessment[h]				X						
Pain relief (5-point categorical scale)[g]					X	X	X		X	

	Screening (Day -28 to Day -1)	Surgery (Day 1)						Day 2		Follow-up (Day 8 ±2 days) or ET[k]
			Post-op							
		Pre-Surgery	Pre-dose	0 h	15, 30, 45 min	1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 h	12 h	16 h	24h	
Global evaluation of study drug[i]									X	
Concomitant medications		X[b]	X	X	X	X	X		X	X
Adverse events[j]		X	X	X	X	X	X		X	X
Dispense/prescribe pain medication for use at home, as needed									X	
Collect unused home pain medications, as needed										X
Discharge from study site									X	

Abbreviations: BMI=body mass index; ET=early termination; h=hour; min=minute; NRS=numeric rating scale; pre-op=pre-operative; post-op=post-operative.

a Times listed are relative to dosing with study drug.
b Medical history and concomitant medication use since Screening will be updated on Day 1 before surgery.
c A complete physical examination (excluding the genitourinary examination) will be performed at Screening. An abbreviated confirmatory physical assessment, including an examination of the subject's mouth and neck, will be performed at the Follow-up Visit (or Early Termination Visit).
d Vital signs will be recorded after the subject has been in a sitting position for 3 minutes at the following times: at Screening, before surgery, within 30 minutes before Time 0, 12 hours after Time 0, 24 hours after Time 0, and/or immediately before the first dose of rescue medication, and at the Follow-up Visit (or Early Termination Visit).
e Serum pregnancy test at Screening and urine pregnancy test before surgery on Day 1 (female subjects of childbearing potential only). Test results must be negative for the subject to continue in the study.
f Oral radiographs taken within 1 year before Screening will be acceptable and do not need to be repeated.
g Pain assessments will be conducted (pre-dose, if at one of the dosing timepoints of 0, 8, 12 or 16 hours) at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16 and 24 hours after Time 0 and immediately before each dose of rescue medication. Pain intensity will also be assessed pre-dose. At each assessment time point, the pain intensity assessment will be completed first and the pain relief assessment will be completed second. Subjects will not be able to compare their responses with their previous responses. Note for assessments less than 1 hour apart a window of +/-2 min is allowable whilst for assessments at least 1 hour apart a +/-5 min window is allowable.
h Two stopwatches will be started immediately after the subject has swallowed the first dose of study drug with 8 ounces of water (Time 0). Subjects will record the time to perceptible and meaningful pain relief, respectively, by stopping the stopwatches.

4. Statistical Analysis and Reporting

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher). If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

Continuous (quantitative) variable summaries will include the number of subjects (n) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum.

Categorical (qualitative) variable summaries will include the frequency and percentage of subjects who are in the particular category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population in each of the treatment arms, unless otherwise specified.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and measures of spread (SD) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified.

Unless otherwise indicated, all statistical tests will be conducted at the 0.05 significance level using 2-tailed tests, and P values will be reported. Corresponding 95% confidence intervals (CIs) will be presented for statistical tests. In addition to what is detailed in the SAP, other additional analyses may be conducted on the data which will only serve as exploratory evidence and the unplanned nature of these analyses will be made clear in the Clinical Study Report.

4.2. Interim Analysis

No interim analyses are planned.

5. Analysis Populations

The following analysis populations are planned for this study:

- **Safety Population (SAF):** The Safety Population includes all subjects who receive any amount of planned study medication. Subjects will be assigned to treatment received.
- **Intent-To-Treat Population (ITT):** The ITT population includes all subjects who are treated with study drug and who have at least 1 pain assessment after Time 0. The ITT population is the primary population for the efficacy analysis. Subjects will be assigned to treatment randomized.
- **Per Protocol (PP)**: The PP Population will consist of all ITT subjects who do not incur a major protocol violation that would challenge the validity of their data. This population will be determined at a data review meeting prior to database lock and used to evaluate the sensitivity of the primary efficacy analysis. Subjects will be assigned to treatment received.

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

The last observation recorded prior to the first dose of study drug will be used as the baseline observation for all calculations of change from baseline.

6.1.2. Adjustments for Covariates

For the primary endpoint analysis, the baseline NRS pain score will be included as a covariate.

For the secondary endpoint analyses, baseline pain will be included as a covariate for SPID, SPRID, and TOTPAR variables.

For the proportion of subjects who are responders and the proportion of subjects using rescue medication, logistic regression models will adjust for baseline pain.

For time to event endpoints, baseline pain will be included as a stratification factor.

6.1.3. Multiple Comparisons

No adjustment for multiplicity is required for the primary efficacy analysis – a single comparison of SPID12 for placebo versus SPID12 for ibuprofen PR.

No adjustments will be made for multiple comparisons for other endpoints.

6.1.4. Handling of Dropouts or Missing Data

Missing pain assessments for all efficacy analyses will be handled as follows:

- Missing pain assessments scheduled before the first observed assessment will be imputed with the subject's worst observed pain assessment.
- Missing intermediate pain assessments will be replaced by linear interpolation.
- Missing pain assessments at the end of the observation period due to premature discontinuation of pain assessments will be imputed by carrying forward the last observation prior to that missing.

All data for assessments other than pain assessments will be analyzed as collected; missing data due to premature termination or any other reason will be left as missing. Since this is a short-term study and subjects remain at the study site throughout the 24-hour pain assessment period, the discontinuation rate and the amount of missing data is expected to be minimal.

A number of sensitivity analyses will be performed in order to evaluate the efficacy under various different assumptions regarding missing data and are described in Section 6.1.6

The exceptions to the above data handling rules are the descriptive summaries and repeated measures analyses by timepoint for pain intensity difference and pain relief, described in sections 8.2.11 and 8.2.12. In these repeated measures analyses, missing values are indirectly imputed

under an assumption of missing at random, and so missing pain assessments will not be explicitly imputed prior to analysis.

6.1.5. Adjustment of Pain Scores for Rescue Medication Use

Subjects are required to record their pain assessment (NRS and pain relief) immediately prior to each dose of rescue medication permitted in the protocol (1000mg paracetamol/acetaminophen or 5mg oxycodone). The primary analysis will use windowed worst observation carried forward (WOCF) methodology for subjects who use rescue medication. If a subject received rescue medication at time x, for any time point within x + 4 hours, the highest pain score from time 0 up until time x will be used. If the pain score for the windowed observation is higher than the worst observed score, it will not be replaced. The same approach will be used for pain relief scores. Subject who received other drug and non-drug therapies during the treatment period will be evaluated on a case-by-case basis at a data review meeting, prior to database lock. If these therapies are considered to modulate the pain response, the same approach described above will be used to replace pain intensity and pain relief scores within a 4-hour time window after medication was taken. The windowed WOCF method to adjust pain scores for subjects who use rescue medication is consistent with the hypothetical strategy estimand, where the intercurrent event is use of rescue medication, and will be the approach used for the primary efficacy analysis [5].

6.1.6. Sensitivity Analysis of SPID12 and SPID24

The following sensitivity analyses will also be performed for the primary endpoint SPID12 if any pain assessments are missing or if subjects take rescue medication. Each of these are consistent with the hypothetical strategy estimand, with the exception of analysis number 3, which uses the treatment policy strategy estimand.

1. Missing data and values after rescue medication handled as per the main analysis but based on the PP population.

2. Missing data imputed using WOCF (worst observed pain score at any timepoint, including baseline). Values after rescue medication handled as per the main analysis.

3. Missing data handled as per the main analysis. Pain assessments are used regardless of whether rescue medication has been taken, and no adjustment is made for use of rescue medication. In this analysis, the pain assessment recorded at the time of rescue medication is disregarded (unless it coincides with a planned pain assessment).

4. Missing data handled as per the main analysis. All pain assessments recorded after the first dose of rescue medication has been taken will be disregarded. WOCF, LOCF (Last Observation Carried Forward) and multiple imputation methods will then be used to impute the disregarded data.

    a. WOCF - The worst (highest) pain assessment (including baseline) until first dose of rescue medication will be used to impute all subsequent pain assessments. In

other words, this method would be treating the subject as if they got no worse than their worst observed value prior to rescue medication.

b. LOCF - In this LOCF analysis, the pain assessment taken immediately prior to/at the time of rescue medication will be taken as the last observed score, i.e., this method would be treating the subject as if they got no worse than their last observed value prior to rescue medication.

c. Multiple Imputation under a MAR assumption. Data will be imputed separately for each treatment group, using a Markov Chain Monte Carlo (MCMC) method for full imputation, with covariates for baseline and pain scores observed at each assessment. The methodology described in sensitivity analysis 6 below will be used. In this analysis, the pain assessment recorded at the time of rescue medication is disregarded (unless it coincides with a planned pain assessment).

5. Missing data imputed using multiple imputation (methodology described below). Values after rescue medication handled as per the main analysis.

For sensitivity analysis 5, a pattern-mixture model with control-based pattern imputation will be used. This model assumes that after withdrawal from the study, subjects from the experimental group (no longer receiving active treatment) will exhibit the same future evolution of pain scores as subjects in the placebo group (who are also not exposed to active treatment). Subjects that discontinue from the placebo group are assumed to evolve in the same way as placebo subjects that remain in the study. This imputation assumes that intermittent missing values are missing at random (MAR), and that values that are missing due to withdrawal are missing not at random (MNAR). When data are MAR, the missingness of the data does not depend on the missing value after conditioning on the observed data (i.e., prior assessments and baseline covariates). Note that when the missingness of the data depends on the values of the missing variables after conditioning on the observed data, the data are called "missing not at random" (MNAR). In order to assess the MAR assumption, a placebo-based pattern mixture model (PMM) will be utilized following the steps outlined in Ratitch B and O'Kelly, M.J. (2011) for SPID-12.

Briefly, the strategy for implementing this approach is as follows for subjects with missing data:

i. Impute all non-monotone (intermittent) missing data using the MCMC method of PROC MI. Note that this imputation will sample data within each treatment group. Note that PI_i is the NRS pain intensity at time T_i as mentioned in Section 6.1.7. SAS pseudo code is provided below. With MCMC option, SAS does 200 burn-in iterations (default) before each imputation.

```
PROC MI DATA=example seed = xxxx NIMPUTE = 20 OUT = outdata1 minimum=0 maximum=10;
        by <treatment>;
        MCMC chain=multiple impute=monotone;
        VAR  <PI0> <PI0.25> <PI0.5> <PI0.75><PI1> …..<PI12>;
RUN;
```

ii. Using the imputed datasets from Step #1 that are now monotone missing (no intermittent missing data), a single call to PROC MI (including the MNAR statement) will be utilized to impute the monotone missing data. Additional details are provided below.

a. Within the call to PROC MI, one timepoint is imputed at a time. The order in which pain scores are imputed will be PI_0, then $PI_{0.25}$...,PI_{12}

b. When imputing at timepoint t, the imputation step will include all placebo subjects, but only those from the active arms that have a value missing at timepoint t. Subjects with non-missing data that are on active arms will not contribute to the estimation for this step.

c. Repeat the above step for all timepoints *t*. Thus, the data for timepoint *t+1* uses the data imputed from previous timepoints.

SAS pseudo code is provided below. SAS accomplishes this iterative process in one step. Note that the treatment level 3 is the placebo treatment group. The MNAR statement imputes missing values for scenarios under the MNAR assumption. The MODEL option specifies that only observations in which treatment=3 are used to derive the imputation model for the pain score that time point. The minimum and maximum options are used to ensure that every pain score imputed ranges from 0-10. If forcing a specified range on the imputed values results in a SAS error of "imputed values to be out of range", the minimum and maximum options will be removed in a step-wise way, and the imputed values will be unrestricted. Once all values have been imputed, the desired range limits will be enforced separately after the imputation is performed if necessary, by replacing values >10 with 10 and values <0 with 0. The rationale is to ensure that all values are clinically possible (i.e. in the range of possible values present on the 0-10 numerical rating scale), and furthermore values outside the 0-10 range would likely have a larger impact on the resultant SPID values.

```
PROC MI DATA=OUTDATA1 seed = xxxx NIMPUTE = 1 OUT = outdata2 MINIMUM=. 0..0
MAXIMUM=. 10 10…10;
BY _IMPUTATION_;
CLASS <treatment>;
MONOTONE REG (/ details);
MNAR MODEL (PI0.25> <PI0.5> <PI0.75><PI1> …..<PI12>/ modelobs=(<treatment='3'>));
        VAR  <PI0> <PI0.25> <PI0.5> <PI0.75><PI1> …..<PI12>;
RUN;
```

iii. When all missing PI scores are imputed, SPID12 will be derived as described in 6.1.7 and analyzed using the ANCOVA models as described in Section 8.1. PROC MIANALYZE will be used to combine the parameters from the analyses for inference.

6. Missing data and values within the defined window after rescue medication are imputed using multiple imputation (methodology described below).

For sensitivity analysis 6, a multiple imputation model under a MAR assumption will be used. This assumes that the missingness of the data does not depend on the missing observations after

conditioning on the observed data (i.e., prior assessments and baseline as covariates). This is considered a reasonable assumption since patients are encouraged to use rescue medication only if needed (i.e. high pain scores), and thus it can be expected that the intercurrent event of rescue medication depends on the observed data (i.e. rescue medication likely to be taken when the preceding pain scores were high). It can then be inferred that the pain scores post-rescue can be predicted from the observed variables, and therefore the response can be estimated without bias using the observed data. In this analysis, the pain assessment recorded at the time of rescue medication is disregarded (unless it coincides with a planned pain assessment).

The strategy to be used is as follows:

i. Set pain scores recorded within the defined window after rescue medication to missing. Impute all missing data (due to subject withdrawal, missing intermittent values and that set to missing due to rescue medication) using the MCMC method of PROC MI. Note that this imputation will sample data within each treatment group. Note that PIi is the NRS pain intensity at time Ti as mentioned in Section 6.1.7. SAS pseudo code is provided below. With the MCMC option, SAS does 200 burn-in iterations (default) before each imputation. Twenty imputations will be performed.

```
PROC MI DATA=example seed = xxxx NIMPUTE = 20 OUT = outdata1 minimum=0 … 0
maximum=10 … 10;
        by <treatment>;
        MCMC chain=multiple;
        VAR  <PI0> <PI0.25> <PI0.5> <PI0.75><PI1> …..<PI12>;
RUN;
```

ii. When all missing PI scores are imputed, SPID12 will be derived as described in 6.1.7 and analyzed using the ANCOVA models as described in Section 8.1. PROC MIANALYZE will be used to combine the parameters from the analyses for inference

Sensitivity analyses 3 and 6 will also be performed for SPID24, with the necessary modifications to the SAS pseudo code in sensitivity analysis 6 to incorporate a covariate for PI_{24}.

6.1.7. Derived Variables

At each assessment time point, subjects will complete the pain intensity NRS assessment first and the pain relief assessment second.

Planned assessment time points are as follows: 0 (predose), 15, 30, and 45 minutes, and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hours after Time 0. Please see Table 2 below.

Table 2 Planned Assessment Times

i	T_i (hours)
0	0 (predose)

1	0.25
2	0.5
3	0.75
4	1
5	1.5
6	2
7	3
8	4
9	5
10	6
11	7
12	8
13	10
14	12
15	16
16	24

- SPID-12 = summed pain intensity difference (change from Time 0) under the numeric rating scale (NRS)-time curve from 15 min through 12 hours calculated using the linear trapezoidal rule and the actual time points, where Time 0 is the time of the first dose of study drug. Scheduled time points in Table 2 will be used when actual time is missing.

$$SPID_{12} = \sum_{i=1}^{14} (T_i - T_{i-1}) * PID_i$$

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

PID is defined as

$$PID_i = PI_i - PI_0$$

Where PI is the pain intensity as measured by the NRS scale.

- SPID-x = summed pain intensity difference (change from Time 0) under the numeric rating scale (NRS)-time curve from 15 min through x hours calculated using the linear trapezoidal rule and the actual time points, where Time 0 is the time of the first dose of study drug. Scheduled time points in Table 2 will be used when actual time is missing. X = 4, 8, and 24.

$$SPID_x = \sum_{i=1}^{y} (T_i - T_{i-1}) * PID_i$$

For x=4 y=8; x=8 y=12; x=24 y=16.

- TOTPAR-x = total pain relief under the Pain Relief Scale (0 – 4) from 15 min through x hours calculated using the linear trapezoidal rule and actual time points, where Time 0 is the time of the first dose of study drug. Scheduled time points in Table 2 will be used when actual time is missing. x = 4, 8, 12, and 24.

$$TOTPAR_x = \sum_{i=1}^{y} (T_i - T_{i-1}) * PAR_i$$

For x=4 y=8; x=8 y=12; x=12 y=14; x=24 y=16. PAR_i is the pain relief score on the Pain Relief Scale (0-4) at time T_i

- SPRID-x = summed pain relief (TOTPAR) and intensity difference (SPID) from 15 min through x hours calculated using the linear trapezoidal rule and actual time points, where Time 0 is the time of the first dose of study drug. Scheduled time points in Table 2 will be used when actual time is missing. X = 4, 8, 12, and 24.

$$SPRID_x = SPID_x + TOTPAR_x$$

- Responder: subject with ≥ 30% improvement in NRS pain intensity from T_0 (predose) without rescue medication during the first 8 hours. If a subject takes rescue medication prior to the 8-hour pain assessment or if the 8-hour assessment is not performed they will be considered a non-responder. i.e.,

$$\frac{(PI_0 - PI_8)}{PI_0} * 100 \geq 30$$

Where PI_0 and PI_8 are the predose and 8-hour NRS pain intensity measurements respectively.

- Time to onset of analgesia = If the subject has had meaningful pain relief (i.e., presses both stopwatches) then time to onset of analgesia is date/time of perceptible pain relief – date/time of the first dose of study drug. If subjects don't experience both perceptible pain relief and meaningful pain relief during the 8-hour interval after Time 0, time to onset to analgesia will be right censored at the time of their last pain assessment in the first 8 hours. For subjects who take rescue medication prior to onset of analgesia during the 8-hour interval after Time 0, time to onset of analgesia will be right censored at the time rescue medication was taken.

- Time to first perceptible pain relief = date/time of the first reported pain relief (any) as assessed by the subject (i.e. subject stops the first stopwatch (irrespective of the second stopwatch)) – date/time of the first dose of study drug. If subjects don't experience perceptible pain relief during the 8-hour interval after Time 0, time to first perceptible pain relief will be right censored at the time of their last pain assessment in the first 8 hours. If the first stopwatch is not stopped but the second stopwatch is stopped, time will be left censored at the time that the second stopwatch is stopped. In other words, it is assumed that the first stopwatch measurement has already occurred but was missed/not recorded. For subjects who take rescue medication prior to first perceptible pain relief during the 8-hour interval after Time 0, time to first perceptible pain relief will be right censored at the time rescue medication was taken.

- Time to meaningful pain relief = date/time of the first reported meaningful (subjective) pain relief as assessed by the subject (i.e. the subject stops the second stopwatch) – date/time of the first dose of study drug. If subjects don't experience meaningful pain relief during the 8-hour interval after Time 0, time to meaningful pain relief will be right censored at the time of their last pain assessment in the first 8 hours. If the subject stops the second stopwatch but doesn't stop the first stopwatch or the first stopwatch assessment is missing, then time to meaningful pain relief will be right censored at the time of their last pain assessment in the first 8 hours. For subjects who take rescue medication prior to achieving meaningful pain relief during the 8-hour interval after Time 0, time to meaningful pain relief will be right censored at the time rescue medication was taken.

- Peak pain relief- Pain relief is measured on a scale from 0 (None) to 4 (Complete). If PR_i is the pain relief measurement at time T_i , peak pain relief PPR is defined as

$$PPR = \max\{PR_1, PR_2, PR_3, \ldots, PR_{16}\}$$

- Time to first use of rescue medication = date/time to the first dose of rescue medication – date/time of the first dose of study drug. If subjects don't take rescue medication, subjects will be right censored at the time of their last pain assessment.

- Time to peak pain relief = date/time of peak pain relief– date/time of the first dose of study drug. Time of peak pain relief is the time T_i when peak pain relief (PPR) first occurs. If no pain relief is observed then the time to peak pain relief will be right censored at the time of their last pain assessment.

- Change from baseline = value at current time point – value at baseline.

- TEAE = TEAE is defined as any event that started or worsened in intensity or relationship to treatment on or after the first dose of study drug.

6.1.8. Data Adjustments/Handling/Conventions

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included only in the data listings.

All *P* values will be displayed in four decimals and rounded using standard scientific notation (e.g., 0.XXXX). If a *P* value less than 0.0001 occurs it will be shown in tables as <0.0001.

Adverse events will be coded using the MedDRA version 23.0 thesaurus.

A treatment related AE is any AE with a relationship to the study drug with possible, probable or certain causality to the study drug as determined by the Investigator.

If partial dates occur, the convention for replacing missing dates for the purpose of statistical analysis is as follows: if just day is missing then the day assigned is the first day of the month or the date of first dose (if in the same month), whichever is later; if just month is missing then the month assigned is the month of the first dose, unless that results in a date prior to the first dose in which case the month after the first dose is used; and if both month and day are missing then the month assigned is the month of the first dose and the day assigned is either the first day of the month or the first dose date, whichever is later.

If partial times occur, the convention is as follows: if the missing time occurs on the day of the first dose and both the hour and minute are missing then the time assigned is the time of the first dose, otherwise if both the hour and minute are missing and the date is not the date of first dose the time assigned is 12:00; if the date is the same as the date of the first dose and only hour is missing the hour assigned is 12 or the hour of first dose, whichever is later, and if the date is the same as the date of first dose and only the minute is missing the minute assigned is 30 or the minute of first dose, whichever is later. Otherwise the hour assigned is 12 if the hour is missing and the date is not the same as the date of first dose and the minute assigned is 30 is the the date is not the same as the date of first dose.

These conventions will be applied only to adverse event onset dates and times with the following precaution: if the missing date and time reflect the date and time of onset of an adverse event,

the modified date and time will be constructed to match the first documented date/time post drug administration while preserving the order in which the AE was reported in the CRF.

7. Study Patients/Subjects and Demographics

7.1. Disposition of Patients/Subjects and Withdrawals

Disposition will include tabulations of the number of subjects screened, number of subjects randomized into each treatment group, the number of subjects who received treatment, tabulated reasons for discontinuation from the study, and number of subjects in each analysis population.

7.2. Protocol Violations and Deviations

Protocol deviations will be summarized by deviation type (major/minor) and listed.

7.3. Demographics and Other Baseline Characteristics

Summary statistics for age, gender, race, ethnicity, height, weight, BMI, baseline pain category and baseline pain (continuous) will be presented by treatment groups and overall. For the continuous variables, the number of non-missing values and the mean, standard deviation, minimum, median and maximum will be tabulated.

For the categorical variables, the counts and proportions of each value will be tabulated.

These analyses will be conducted for the ITT, PP, and Safety populations.

The number and percent of subjects reporting various medical histories, grouped by MedDRA system organ class and preferred term (coded using MedDRA v23.0), will be tabulated by treatment group. This analysis will be conducted for the Safety Population. Physical examination findings will also be summarized by body system and examination result- Normal, Abnormal – Clinically Significant, Abnormal-Not Clinically Significant.

7.4. Exposure and Compliance

The number of doses taken and treatment duration will be summarized by descriptive statistics. All study drug will be administered in clinic. The total number of tablets taken, and the number of tablets with active ingredient taken at each time point will be summarized. The dosage (in mg) of active ingredient taken and duration of exposure, from first dose to last dose of the study treatment will be summarized using descriptive statistics. Any deviations from the planned dose should be reported.

8. Efficacy Analysis

8.1. Primary Efficacy Analysis

The primary efficacy endpoint is the summed pain intensity difference (SPID) over 0 to 12 hours (SPID12). The primary endpoint will be used to compare the test product (2x300 mg ibuprofen PR tablets) against placebo.

The primary efficacy hypothesis is that SPID12 for placebo is equal to SPID12 for ibuprofen 2x300 mg PR tablets. The primary analysis will be an ANCOVA model that includes the main effect of treatment and a covariate of the baseline NRS pain score and will use windowed worst observation carried forward (WOCF) imputation for subjects who use rescue medication. The primary analysis will be based on a 2-sided test at the significance level of 0.05. The treatment difference will be presented with a 95% confidence interval.

Normality assumptions will be tested. If the data is considered non-normal, the Wilcoxon rank sum test will be used for the comparison between treatments, and the point estimate and 95% confidence interval will be calculated using the Hodges-Lehmann estimator.

The primary efficacy analysis will be based on the ITT population. These analyses will be repeated for the PP population. SPID-12 scores will also be summarized by baseline pain category (moderate or severe).

8.2. Secondary Efficacy Analysis

8.2.1. SPID

Summed Pain Intensity Difference (SPID) will be calculated for secondary efficacy analysis as described in Section 6.1.7 at 4, 8, and 24 hours. Descriptive statistics by treatment regimen will be produced.

ANCOVA models for comparing placebo with other treatment regimens with SPID as the dependent variable and treatment group and baseline pain as covariates will be generated. These models will be computed for SPID4, SPID8 and SPID12. The least square (LS) mean and standard error (SE) for each treatment group will be estimated and the difference in LS means and 95% confidence interval (CI) for the comparison of placebo with the IR and PR treatment regimens will be estimated. P-values will be reported but no formal statistical inferences will be made on the basis of these tests. In addition, for the SPID24 endpoint, the difference in LS means and 95% CI for the IR versus PR groups will be presented. In the event that normality assumptions are violated for a parameter, non-parametric analysis methods will be used.

8.2.2. TOTPAR

Total pain relief (TOTPAR) will be calculated as described in Section 6.1.7 at 4, 8, 12 and 24 hours. Descriptive statistics by treatment regimen will be produced.

ANCOVA models for comparing placebo with other treatment regimens with TOTPAR as the dependent variable and treatment group and baseline pain as covariates will be generated. These models will be generated at TOTPAR4, TOTPAR8, TOTPAR12 and TOTPAR24. The LS mean and SE for each treatment group will be estimated and the difference in LS means and 95% CI for the comparison of placebo with the IR and PR treatment regimens will be estimated. P-values will be reported but no formal statistical inferences will be made on the basis of these tests. In the event that normality assumptions are violated for a parameter, non-parametric analysis methods will be used.

8.2.3. SPRID

Summed pain relief and intensity difference is the sum of TOTPAR and SPID and will be calculated at 4, 8, and 12 and 24 hours as described in Section 6.1.7.

Descriptive statistics by treatment regimen will be produced for SPRID at each planned assessment time point.

ANCOVA models for comparing placebo with other treatment regimens with SPRID as the dependent variable and treatment group and baseline pain as covariates will be generated. The LS mean and SE for each treatment group will be estimated and the difference in LS means and 95% CI for the comparison of placebo with the IR and PR treatment regimens will be estimated. P-values will be reported but no formal statistical inferences will be made on the basis of these tests. In the event that normality assumptions are violated for a parameter, non-parametric analysis methods will be used.

8.2.4. Peak Pain Relief

Peak pain relief will be calculated as described in Section 6.1.7 and will be summarized by counts (and percentages) for each pain relief score. It 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 a factor for treatment and baseline pain intensity as a continuous covariate. The lowest level of pain relief (0=none) will be used as the reference category, thus ensuring that the probability of the higher response levels will be modelled. For each of the PR and IR treatment regimens, the odds of being in a higher (better) pain relief category compared to placebo (odds ratio) will be presented with a 95% CI and associated p-value. If the proportional odds assumption does not hold, a non-proportional odds model will be considered.

8.2.5. 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 6.1.7. With baseline pain as a stratification factor, treatments will be compared to placebo using a stratified log-rank test or a stratified Wilcoxon test as appropriate. Summary tables will provide the number of subjects analyzed, the number of subjects censored, estimates for the 25^{th}, 75^{th} percentiles and median (including 95% CI), and associated p-value for comparisons versus placebo.

A measure of the treatment effect comparing each of the active arms with placebo will be obtained by calculating a hazard ratio and 95% CI by fitting a Cox proportional hazards model with a factor for treatment group and baseline pain as a continuous covariate. The assumption of proportional hazards will first be evaluated.

8.2.6. Time to Meaningful Pain Relief

Time to first meaningful pain relief will be summarized using Kaplan-Meier methods. The definition and censoring rules are described in Section 6.1.7. With baseline pain as a stratification factor, treatments will be compared to placebo using a stratified log-rank test or a

stratified Wilcoxon test. Summary tables will provide the number of subjects analyzed, the number of subjects censored, estimates for the 25th, 75th percentiles and median (including 95% CI), and associated p-value for comparisons versus placebo.

A measure of the treatment effect comparing each of the active arms with placebo will be obtained by calculating a hazard ratio and 95% CI by fitting a Cox proportional hazards model with a factor for treatment group and baseline pain as a continuous covariate. The assumption of proportional hazards will first be evaluated.

8.2.7. Time to onset of Analgesia

Time to onset of analgesia will be summarized using Kaplan-Meier methods. The definition and censoring rules are described in Section 6.1.7. With baseline pain as a stratification factor, treatments will be compared to placebo and with each other (IR vs PR) using a stratified log-rank test or a stratified Wilcoxon test. The summary tables will provide the number of subjects analyzed, the number of subjects censored, estimates for the 25th, 75th percentiles and median (including 95% CI), and associated p-value for treatment comparisons.

A measure of the treatment effect comparing each of the active arms with placebo and with each other (IR vs PR) will be obtained by calculating a hazard ratio and 95% CI by fitting a Cox proportional hazards model with a factor for treatment group and baseline pain as a continuous covariate. The assumption of proportional hazards will first be evaluated.

8.2.8. 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 6.1.7. With baseline pain as a stratification factor, treatments will be compared to placebo using a stratified log-rank test or a stratified Wilcoxon test. The summary tables will provide the number of subjects analyzed, the number of subjects censored, estimates for the 25th, 75th percentiles and median (including 95% CI), and associated p-value for comparisons versus placebo.

A measure of the treatment effect comparing each of the active arms with placebo will be obtained by calculating a hazard ratio and 95% CI by fitting a Cox proportional hazards model with a factor for treatment group and baseline pain as a continuous covariate. The assumption of proportional hazards will first be evaluated.

8.2.9. Time to first use of Rescue Medication

Time to first use of rescue medication will be summarized using Kaplan-Meier methods. The definition of time to first use of rescue medication and censoring rules for subjects who don't take rescue medication are described in Section 6.1.7. With baseline pain as stratification factor, treatments will be compared to placebo using a stratified log-rank test or a stratified Wilcoxon test. The summary tables will provide the number of subjects analyzed, the number of subjects censored, estimates for the 25th, 75th percentiles and median (including 95% CI), and associated p-value for comparisons versus placebo.

A measure of the treatment effect comparing each of the active arms with placebo will be obtained by calculating a hazard ratio and 95% CI by fitting a Cox proportional hazards model

with a factor for treatment group and baseline pain as a continuous covariate. The assumption of proportional hazards will first be evaluated.

8.2.10. Proportion of Responders

For the proportion of subjects who are responders, a logistic regression model that adjusts for baseline pain (as a continuous covariate) and treatment arm will be used to evaluate the treatment effect. As a measure of treatment effect for each of the PR and IR groups versus placebo, odds ratios together with a 95% CI and p-values will be presented.

8.2.11. Numeric rating scale (NRS) pain intensity difference (PID)

PID at each time point will be calculated using the formula specified in Section 6.1.7, with pain scores recorded after rescue medication handled using the windowed WOCF method described in Section 6.1.5. Pain scores that are missing (assessment not performed or subject withdrew) will not be replaced. PID at each timepoint will be analyzed in a mixed model for repeated measures (MMRM) ANCOVA analysis. The model will include treatment, timepoint, treatment by timepoint, baseline and baseline by timepoint as fixed effects, and subject as a random effect. An unstructured covariance matrix will be used to model the within-subject correlations by timepoint. If the model fails to converge, alternative covariance structures, such as compound symmetry, will be tried instead. The model will be used to show estimated treatment effects at each timepoint. The LS mean and SE for each treatment group will be estimated and the difference in LS means and 95% CI for the comparison of placebo with the IR and PR treatment regimens will be estimated. P-values will be reported but no formal statistical inferences will be made on the basis of these tests. Descriptive summaries (including mean, SD, median, minimum and maximum) will be presented by treatment group.

Pain intensity is measured using NRS at planned assessment time points. Descriptive summaries (including mean, SD, median, minimum and maximum) will also be presented by treatment group. Pain scores recorded after rescue medication will be handled using the windowed WOCF method described in Section 6.1.5. Pain scores that are missing (assessment not performed or subject withdrew) will not be replaced.

8.2.12. Pain relief at each scheduled time point

Pain relief scores at each scheduled time point will be summarized using descriptive statistics (including mean, SD, median, minimum and maximum) as well as counts (and percentages) for each pain relief score by treatment group. Pain relief scores recorded after rescue medication will be handled using the windowed WOCF method described in Section 6.1.5. Pain relief scores that are missing (assessment not performed or subject withdrew) will not be replaced. Treatment comparison will be done in the following way:

- Pain relief at each timepoint will be analyzed in a mixed model for repeated measures (MMRM) ANCOVA analysis. The model will include treatment, timepoint, treatment by timepoint, baseline pain and baseline pain by timepoint as fixed effects, and subject as a random effect. An unstructured covariance matrix will be used to model the within-subject correlations by timepoint. If the model

fails to converge, alternative covariance structures, such as compound symmetry, will be tried instead. The model will be used to show estimated treatment effects at each timepoint. The LS mean and SE for each treatment group will be estimated and the difference in LS means and 95% CI for the comparison of placebo with the IR and PR treatment regimens will be estimated. P-values will be reported but no formal statistical inferences will be made on the basis of these tests.

8.2.13. Proportion of Subjects Rescue Medication

The definition of rescue medication use is presented in Section 6.1.5. The proportion of subjects using rescue medication for pain will be analyzed using logistic regression. The logistic regression model will include treatment arm and baseline pain (as a continuous covariate) as covariates. As a measure of treatment effect for each of the PR and IR groups versus placebo, odds ratios together with a 95% CI and p-values will be presented.

8.3. Exploratory Efficacy Analysis

8.3.1. 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 a factor for treatment group and baseline pain intensity as a continuous covariate. The lowest level of response (0=poor) will be used as the reference category, thus ensuring that the probability of the higher response levels will be modelled. For each of the PR and IR treatment regimens, the odds of being in a higher (better) evaluation category compared to placebo (odds ratio) will be presented with a 95% CI and associated p-value. If the proportional odds assumption does not hold, a non-proportional odds model will be considered.

9. Safety and Tolerability Analysis

Safety will be evaluated from reported AEs, and changes in vital signs.

All safety analyses will be performed on the Safety population.

9.1. Adverse Events

The number and percent of subjects reporting treatment emergent AEs, grouped by MedDRA system organ class and preferred term (coded using MedDRA v23.0), will be tabulated by severity and treatment group. In the case of multiple occurrences of the same TEAE within the same subject, each subject will only be counted once for each preferred term.

The frequency and percentage of subjects reporting TEAEs, grouped by MedDRA SOC and PT, will be tabulated by treatment group for the SAF. Such summaries will be displayed for the following:

- TEAEs by SOC and PT
- TEAEs by SOC, PT, and severity
- TEAEs by SOC, PT, and relationship to the study medication
- TEAEs leading to death by SOC, and PT
- Serious TEAEs other than deaths by SOC, and PT
- TEAEs leading to premature discontinuation by SOC, and PT
- Listing of non-TEAEs

In the case of multiple occurrences of the same AE within the same subject, each subject will only be counted once for each preferred term. In summaries of AE by SOC and PT, along with the number (%) of subjects with at least 1 AE in the category, the number of events will be displayed. In the summaries showing severity and relationship to study medication the event with the maximum severity or strongest relationship will be reported. If a particular event is missing the severity and/or relationship, then the strongest possible severity or relationship will be assumed for analysis (severity = severe, relationship = certain).

Missing and partially missing AE start and/or stop dates will be imputed for the purpose of statistical analysis, according to the specifications described in Section 6.1.7.

In the AE data listings, all AEs will be displayed. AEs that are not treatment-emergent will be flagged.

9.1.1. Adverse Events Leading to Withdrawal

A summary of incidence rates (frequencies and percentages) of TEAEs leading to withdrawal of study drug, by treatment group, SOC, and preferred term will be prepared for the Safety Population. No inferential statistical tests will be performed.

A data listing of AEs leading to withdrawal of study drug will also be provided, displaying details of the event(s) captured on the CRF.

9.1.2. Deaths and Serious Adverse Events

Any deaths that occur during the study will be listed.

Serious adverse events will be listed and also tabulated by system organ class and preferred term and presented by treatment.

9.2. Clinical Safety Laboratory Data

Descriptive statistics for clinical safety laboratory data (laboratory data) recorded at screening will be presented overall and by treatment regimen. Summary tables by treatment regimen will be presented for each category of data separately. Routine clinical laboratory data will include hematology, serum chemistry, and urinalysis. Quantitative laboratory test result summaries will include N (population count for each regimen), n (number of subjects with non-missing values), mean, SD, median, and range. Qualitative tests (e.g., some urinalysis assessments) will be categorized accordingly. The set of laboratory parameters included in each table will correspond

to those requested in the study protocol. Urine drug screen, alcohol breath analyzer and urine pregnancy test results will be presented in listings.

9.3. Vital Signs

Descriptive summaries of actual values and changes from baseline will be calculated for supine systolic blood pressure, supine diastolic blood pressure, heart rate, respiratory rate, and oral body temperature, and will be presented by treatment regimen. Summary statistics for 12-lead ECG parameters and counts for ECG interpretations at screening will be presented.

9.4. Concomitant Medication

Prior and concomitant medications will be summarized descriptively by treatment using counts and percentages.

Prior medications will be presented separately from concomitant medications. Medications that started prior to the first dose of study drug will be considered prior medications whether or not they were stopped prior to the first dose of study drug. Any medications continuing or starting post the first dose of study drug will be considered to be concomitant. If a medication starts prior to the first dose and continues after the first dose of study drug, it will be considered both prior and concomitant. Medications will be coded using March 2020 version of World Health Organization Drug Coding Dictionary (WHODD).

9.5. Rescue Medication use

The number of subjects taking rescue medication will be summarized by treatment group at the following post dose times -1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 10 hours, 12 hours, 16 hours and 24 hours. This will be done on the safety population.

10. Changes to analysis planned in the protocol

For the time to event endpoints an additional measure of the treatment effect comparing each of the active arms with placebo will be obtained by calculating a hazard ratio and 95% CI by fitting a Cox proportional hazards model with a factor for treatment group and baseline pain as a continuous covariate. The assumption of proportional hazards will first be evaluated.

There has been a clarification to the definition of the ITT population to that stated in the protocol. The ITT population is defined as all subjects who are treated with study drug and who have at least 1 pain assessment after Time 0. In the protocol the ITT population was defined as subjects who have at least 1 pain relief assessment.

11. References

1. ASA. (2016) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April 2016. http://www.amstat.org/about/ethicalguidelines.cfm
2. RSS. (2014) The Royal Statistical Society: Code of Conduct, 2014. http://www.rss.org.uk/Images/PDF/join-us/RSS-Code-of-Conduct-2014.pdf.

3. US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.
4. Ratitich, B. and O'Kelly, M.J. (2011). Implementation of Pattern-Mixture Models Using Standard SAS / STAT Procedures.
5. E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials

12. Tables, Listings, and Figures

All listings, tables, and graphs will have a header showing the sponsor company name and protocol and a footer showing the version of SAS, the file name and path, and the source of the data (CRF page or listing number).

12.1. Planned Table Descriptions

The following are planned summary tables for protocol number 5003601. The table numbers and page numbers are place holders only and will be determined when the tables are produced.

Table 3: Demographic Data Summary Tables

Table Number	Population	Table Title/Summary
14.1 Displays of Demographics and Disposition Data		
Table 14.1.1	All Subjects	Subject Disposition
Table 14.1.2	Safety Population	Demographics and Baseline Characteristics
Table 14.1.2.1	ITT Population	Demographics and Baseline Characteristics
Table 14.1.3	Safety Population	Medical History
Table 14.1.4	Safety Population	Prior Medications
Table 14.1.5	Safety Population	Concomitant Medications
Table 14.1.6	All Enrolled Subjects	Summary of Protocol Deviations
Table 14.1.7	Safety Population	Summary of Study Drug Exposure

12.2. Efficacy Data

Table 4: Efficacy Tables

Table Number	Population	Table Title/Summary
14.2.1	ITT Population	Analysis of SPID-12 Scores
14.2.1.1	PP Population	Analysis of SPID-12 Scores- Sensitivity Analysis 1
14.2.1.2	ITT Population	Analysis of SPID-12 Scores- Sensitivity Analysis 2-WOCF
14.2.1.3	ITT Population	Analysis of SPID-12 Scores- Sensitivity Analysis 3-No Rescue Adjustment
14.2.1.	ITT Population	Analysis of SPID-12 Scores- Sensitivity Analysis 4a-Rescue WOCF
14.2.1.5	ITT Population	Analysis of SPID-12 Scores- Sensitivity Analysis 4b-Rescue LOCF
14.2.1.6	ITT Population	Analysis of SPID-12 Scores- Sensitivity Analysis 4c-Multiple Imputation-Rescue Medication-MAR
14.2.1.7	ITT Population	Analysis of SPID-12 Scores- Sensitivity Analysis 5-Multiple Imputation-PMM
14.2.1.8	ITT Population	Analysis of SPID-12 Scores- Sensitivity Analysis 6-Multiple Imputation-MAR
14.2.1.9	ITT Population	Summary of SPID-12 Scores by Baseline Pain Category
14.2.2	ITT Population	Analysis of Summed Pain Intensity Difference Scores
14.2.2.1	ITT Population	Analysis of SPID-24 Scores- Sensitivity Analysis 7-No Rescue Adjustment
14.2.2.2	ITT Population	Analysis of SPID-24 Scores- Sensitivity Analysis 8-Multiple Imputation-MAR
14.2.3	ITT Population	Analysis of Total Pain Relief Scores
14.2.4	ITT Population	Analysis of Summed Pain Relief and Intensity Difference Scores
14.2.5	ITT Population	Comparison of SPID-24 in Ibuprofen PR and IR arms
14.2.5.1	ITT Population	Comparison of SPID-24 in Ibuprofen PR and IR arms-Sensitivity Analysis 7-No Rescue Adjustment
14.2.5.2	ITT Population	Comparison of SPID-24 in Ibuprofen PR and IR arms- Sensitivity Analysis 8-Multiple Imputation-MAR
14.2.6	ITT Population	Summary of Peak Pain Relief
14.2.7	ITT Population	Time to First Perceptible Pain Relief
14.2.8	ITT Population	Time to Meaningful Pain Relief
14.2.9	ITT Population	Time to Onset of Analgesia
14.2.10	ITT Population	Time to Peak Pain Relief
14.2.11	ITT Population	Time to First use of Rescue Medication
14.2.12	ITT Population	Proportion of Subjects Using Rescue Medication
14.2.13	ITT Population	Proportion of Responders

14.2.14	ITT Population	Summary of NRS Pain Intensity Difference Score
14.2.15	ITT Population	Summary of Pain Intensity Score at each Scheduled Time Point
14.2.16	ITT Population	Summary of Pain Relief at each Scheduled Time Point
14.2.17	ITT Population	Analysis of Patient Global Evaluation of Study Drug

12.3. Safety Data

Table 5: Safety Tables

Table Number	Population	Table Title/Summary
14.3.1 Summary of Treatment Emergent Adverse Events		
Table 14.3.1.1	Safety Population	Overall Summary of Treatment-Emergent Adverse Events
Table 14.3.1.2	Safety Population	Summary of Treatment-Emergent Adverse Events
Table 14.3.1.3	Safety Population	Summary of Treatment-Emergent Adverse Events by Maximum Severity
Table 14.3.1.4	Safety Population	Summary of Treatment-Emergent Adverse Events by Relationship to Study Drug
Table 14.3.1.5	Safety Population	Summary of Non-Serious Treatment-Emergent Adverse Events
14.3.2 Summary of Deaths, Other Serious and Significant Adverse Events		
Table 14.3.2.1	Safety Population	Summary of Serious Adverse Events
Table 14.3.2.2	Safety Population	Summary of Treatment Emergent Adverse Events Leading to Discontinuation
14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events		
Table 14.3.3.1	Safety Population	Listing of Serious Adverse Events
Table 14.3.3.2	Safety Population	Listing of Treatment Emergent Adverse Events Leading to Study Drug Discontinuation
14.3.4 Abnormal Laboratory Value		
Table 14.3.4.1	Safety Population	Listing of Potentially Clinically Significant Abnormal Laboratory Values
14.3.5 Laboratory Data Summary Tables		
Table 14.3.5.1	Safety Population	Summary of Serum Chemistry Laboratory Results
14.3.6 Other Safety Data Summary Tables		
Table 14.3.6.1	Safety Population	Summary of Vital Signs
Table 14.3.6.2	Safety Population	Summary of Electrocardiogram (ECG) Interpretations
Table 14.3.6.3	Safety Population	Summary of 12-Lead Electrocardiogram (ECG) Parameters
Table 14.3.6.4	Safety Population	Summary of Physical Examination Findings
Table 14.3.6.5	Safety Population	Rescue Medication use

12.4. Planned Listing Descriptions

The following are planned data and patient/subject data listings for protocol number 5003601.

In general, one listing will be produced per CRF domain. All listings will be sorted by treatment, site, and subject number. All calculated variables will be included in the listings.

In all listings a blank line will be placed between each subject. Within a data listing, if an item appears line after line (e.g., repetition of subject number), then only the first occurrence will be displayed.

In data listings, the information for one subject will be kept on one page if at all possible, rather than splitting a subject's information across pages.

Table 6: Planned Listings

Data Listing Number	Population	Data Listing Title / Summary
16.2.1 Subject Discontinuations/Completions		
Listing 16.2.1	All Subjects	Subject Disposition
16.2.2 Protocol Deviations		
Listing 16.2.2.1	All Subjects	Eligibility Criteria Not Met
Listing 16.2.2.2	All Subjects	Screen Failures
Listing 16.2.2.3	All Subjects	Protocol Deviations
16.2.3 Subjects in Analysis Populations		
Listing 16.2.3	All Subjects	Analysis Populations
16.2.4 Demographic Data and Other Baseline Characteristics		
Listing 16.2.4.1	Safety Population	Demographics and Baseline Characteristics
Listing 16.2.4.2	Safety Population	Medical History
Listing 16.2.4.3	All Randomized Subjects	Listing of Subject Randomization
Listing 16.2.4.4	Safety Population	Study Drug Administration
16.2.7 Adverse Event Listings (by Subject)		
Listing 16.2.7.1	Safety Population	Adverse Events
Listing 16.2.7.2	Safety Population	Serious Adverse Events
Listing 16.2.7.3	Safety Population	Treatment emergent Adverse Events Related to Study Drug
Listing 16.2.7.4	Safety Population	Deaths
16.2.8 Laboratory Values by Subject		
Listing 16.2.8.1	Safety Population	Clinical Laboratory Data: Serum Chemistry
Listing 16.2.8.2	Safety Population	Clinical Laboratory Data: Hematology
Listing 16.2.8.3	Safety Population	Clinical Laboratory Data: Urine
Listing 16.2.8.4	Safety Population	Clinical Laboratory Data: Coagulation
Listing 16.2.8.5	Safety Population	Serum and Urine Pregnancy Test
16.2.9 Other Clinical Observations and Measurements (by Subject)		
Listing 16.2.9.1	Safety Population	Prior and Concomitant Medications
Listing 16.2.9.1.1	Safety Population	Rescue Medications
Listing 16.2.9.2	Safety Population	Vital Signs Measurements
Listing 16.2.9.2.1	Safety Population	Physical Examination Findings
Listing 16.2.9.3	Safety Population	12-lead Electrocardiogram Measurements
Listing 16.2.9.3.1	Safety Population	Alcohol Breathalyzer Test
Listing 16.2.9.4	Safety Population	NRS Pain Intensity Assessment

Data Listing Number	Population	Data Listing Title / Summary
Listing 16.2.9.5	Safety Population	Pain Relief Scores
Listing 16.2.9.6	Safety Population	Time to Pain Relief (Stopwatches)
Listing 16.2.9.7	Safety Population	Subjects Global Evaluation of Study Drug

12.5. Planned Figure Descriptions

The following are planned summary figures for protocol number 5003601. The figure numbers and page numbers are place holders only and will be determined when the figures are produced.

Table 7: Planned Figures

Figure Number	Population	Figure Title / Summary
Figure 14.4.1.1	ITT Population	Kaplan-Meier Plot of Time to First Perceptible Pain Relief
Figure 14.4.1.2	ITT Population	Kaplan-Meier Plot of Time to Meaningful Pain Relief
Figure 14.4.1.3	ITT Population	Kaplan-Meier Plot of Time to Onset Of Analgesia
Figure 14.4.1.4	ITT Population	Kaplan-Meier Plot of Time to Peak Pain Relief
Figure 14.4.1.5	ITT Population	Kaplan-Meier Plot of Time to First Use Of Rescue Medication
Figure 14.4.1.6	ITT Population	Mean Pid Scores versus Time
Figure 14.4.1.7	ITT Population	Mean Pain Relief Scores versus Time

Appendix 1: Premier Research Library of Abbreviations

Abbreviation	Definition
aCRF	annotated case report form
AE	adverse event
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
BMI	body mass index
BSL	biostatistician lead
CCGs	CRF completion guidelines
CDISC	clinical data interchange standards consortium
CEC	central ethics committee
CFR	code of federal regulations
CI	confidence intervals
CM	clinical manager
CMP	clinical monitoring plan
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CS	clinically significant
CSR	clinical study report

Abbreviation	Definition
CTA	clinical trial administrator
CTM	clinical trial manager
CTMS	clinical trial management system
DB	database
DBL	database lock
DM	data management
DMB	data monitoring board
DMC	data monitoring committee
DMP	data management plan
DSMB	data safety monitoring board
DSP	data safety plan
DSUR	development safety update report
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
eTMF	electronic trial master file
EU	European Union
FDA	food and drug administration
FPI	first patient in
GCP	good clinical practice
HR	heart rate

Abbreviation	Definition
IB	investigator's brochure
IC or ICF	informed consent or informed consent form
ICH	international council for harmonization
IP	investigational product
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LPI	last patient in
LPLV	last patient last visit
LPO	last patient out
MedDRA	medical dictionary for regulatory activities
MHRA	medicines and healthcare products regulatory agency
MM	medical monitor
MMP	medical monitoring plan
MMRM	mixed effect model repeat measurement
N	number
NA	not applicable
NCS	non-clinically significant
NF	non-functional

Abbreviation	Definition
PD	protocol deviation
PDGP	protocol deviation guidance plan
PE	physical examination
PI	principal investigator
PK	pharmacokinetic
PKAP	pharmacokinetic analysis plan
PM	project manager
PMP	project management plan
PP	per-protocol
PS	project specialist
PV	pharmacovigilance
PVG	pharmacovigilance group
QA	quality assurance
QARC	quality assurance, risk and compliance
QC	quality control
QOL	quality of life
SAE	serious adverse event
SAF	Safety Population
SAP	statistical analysis plan
SAS®	a software system used for data analysis
SBP	systolic blood pressure

Abbreviation	Definition
SD	standard deviation
SDS	study design specifications
SDTM	study data tabulation model
SF	screen failure
SFT or SFTP	secure file transfer or secure file transfer plan
SIV	site initiation visit
SMP	safety management plan
SOC	system organ class
TEAE	treatment-emergent adverse event
TMF	trial master file
UAT	user acceptance testing
WHO	world health organization
WHO-DD	world health organization drug dictionary
WOCF	worst observation carried forward

Sponsor	Reckitt Benckiser
Protocol Title:	A Randomized, Double-Blind, Double-Dummy, Parallel-Group, Multiple-Dose, Active and Placebo-Controlled Efficacy Study of Ibuprofen Prolonged-Release Tablets for the Treatment of Pain after Surgical Removal of Impacted Third Molars
Protocol Number:	5003601
Premier Research PCN:	RECK.177035
Document Version:	Amendment 3.0
Document Date:	20-May-2020

Approvals

Role	Signatures	Date (dd-Mmm-yyyy)
Biostatistician Premier Research	Print Name: Raghu Vishnubhotla Sign Name: DocuSigned by: Signer Name: Raghu Srinivas Vishnubhotla Signing Reason: I am the author of this document Signing Time: 21-May-2020 | 15:53:25 EDT 46FE4E466250408E961764121635BB48	21-May-2020 | 15:53:27 EDT
Reckitt Benckiser Representative	Print Name: Darren Targett Sign Name: DTarget	21-MAY-2020

1.1. Planned Table Shells

Table 14.1.1
Subject Disposition
All Randomized Subjects

Disposition	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Study Populations [1]				
Screened				XXX
Safety Population	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
ITT Population	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Per-Protocol Population	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Completion Status [2]				
Completed Study	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Prematurely Discontinued Study Medication	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Prematurely Discontinued Study	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Reasons for discontinuation from Study				
Lost to Follow-up	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Protocol Violation	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Adverse Event	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Non-Compliance with Study Drug	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Death	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Lack of Efficacy	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Withdrawal by Subject	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Pregnancy	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Physician Decision	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Study Terminated by Sponsor	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Other	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Abbreviation: ITT= Intent-to-Treat
[1] Percentages are based on the number of randomized subjects.
[2] Percentages are based on the number of subjects in the Safety Population.
Source: Listing 16.2.1

Table 14.1.2
Demographics and Baseline Characteristics
Safety Population

Variable Statistic or Category	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Age (years)				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
Gender				
Male	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Female	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Ethnicity				
Hispanic or Latino	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Not Hispanic or Latino	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Missing/Not Answered	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Race				
American Indian/Alaska Native	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Asian	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Black or African-American	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Native Hawaiian or Other Pacific Islander	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
White	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Missing/Not Answered	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Baseline Pain [1]				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
Baseline Pain Category [2]				
Moderate	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Severe	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Height (cm)				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X

Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
Weight (kg)				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
BMI (kg/m2)				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
Surgery Duration (min)				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX

Abbreviation: BMI=Body Mass Index
Note: Percentage are based on the number of subjects in the Safety Population.
[1] Subjects rate their pain using a numeric rating scale (NRS) from 0 (no pain) to 10 (worst pain ever).
[2] NRS pain scores at baseline are categorized as moderate (5-7), and severe (8-10).

Source: Listing 16.2.4.1

Table 14.1.2.1
Demographics and Baseline Characteristics
ITT Population
Use Same Shell as Table 14.1.2
Programming Note- Update footnote Note: Percentage are based on the number of subjects in the ITT Population.

Table 14.1.3
Medical History
Safety Population

System Organ Class Preferred Term	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with at least One Recorded Medical History	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 1				
Preferred Term 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Notes: Percentages are based on number of subjects in the Safety Population.
Medical conditions were coded using MedDRA version 23.0 or later. Subjects were counted once for each system organ class (SOC) and once for each preferred term (PT). Medical history terms are displayed by descending frequency of SOC, then PT within SOC, and then alphabetically by PT.
SOURCE: Listing 16.2.4.2
Programming Note- Uncoded terms, if any, will be at the bottom of the table. They will have labels' Not Coded' for SOC and PT

Table 14.1.4
Prior Medications
Safety Population

ATC Class Level 4 Preferred Term (ATC Class Level 5)	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with at least one Prior Medication	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
ATC Class 1				
Preferred Term 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
ATC Class 2				
Preferred Term 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Notes: Percentages are on number of subjects in the Safety Population.
Medications are coded using WHO-DD B2E version March 2020.
Medications that started prior to the first dose of study drug will be considered prior medications whether or not they were stopped prior to the first dose of study drug.. Medications are displayed by descending frequency of Anatomic Therapeutic Chemical (ATC) Level 4 classification, by Preferred Term (PT) within ATC and then alphabetically.
Subjects were counted only once for each ATC and PT.
SOURCE: Listing 16.2.9.1

Table 14.1.5
Concomitant Medications
Safety Population
Use same shell as Table 14.1.4
Use this footnote for definition of concomitant medications- Any medications continuing or starting post the first dose of study drug will be considered as concomitant medications.

Table 14.1.6
Summary of Protocol Deviations
All Enrolled Subjects

Deviation Category Type of Deviation	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with any Protocol Deviation	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Subjects with Major Protocol Deviations	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Type of Protocol Deviation				
Deviation type 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Deviation type 2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
.....				
Subjects with Minor Protocol Deviations	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Type of Protocol Deviation				
Deviation type 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Deviation type 2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
....				

Notes: Subjects with one or more deviations within a deviation category (Major/Minor) or type of deviation were counted only once.
Percentages are based on number of all enrolled subjects.
SOURCE: Listing 16.2.2.3

Table 14.1.7
Summary of Study Drug Exposure
Safety Population

Category Statistic	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
Number of Tables Taken			
n	XX	XX	XX
Mean	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX
Number of Active Doses Taken [1]			
n	XX	XX	
Mean	XX.X	XX.X	
Std Dev	XX.XX	XX.XX	
Median	XX.X	XX.X	
Min, Max	XX, XX	XX, XX	
Quantity of Active Drug Taken (mg)			
n			
Mean	XX.X	XX.X	
Std Dev	XX.XX	XX.XX	
Median	XX.X	XX.X	
Min, Max	XX, XX	XX, XX	
Treatment Duration (Hours) [2]			
n	XX	XX	XX
Mean	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX

Note: Percentages are based on number of all enrolled subjects.
[1] Active dose is a dose where the tablet taken has an active ingredient
[2] Duration = date/time of last dose administered – date/time of first dose administered
SOURCE: Listing 16.2.4.4.1

Table 14.3.1.1
Overall Summary of Treatment Emergent Adverse Events
Safety Population

	Ibuprofen PR (N=XX)	Ibuprofen PR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with at least one TEAE	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
TEAE by Maximum Severity				
Mild	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Moderate	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Severe	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
TEAE by Strongest Relationship				
Unassessable/Unclassifiable	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Conditional/Unclassified	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unrelated	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unlikely	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Possible	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Probable	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Certain	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
AE leading to Discontinuation	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
SAE	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
AE leading to Death	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Abbreviations: TEAE = Treatment Emergent Adverse Event; SAE = Serious Adverse Event.
Notes: Percentages are based on number of subjects in the safety population..
TEAE is defined as any event that started or worsened in intensity or relationship to treatment on or after the first dose of study drug. Strongest possible severity or relationship will be assumed for TEAES with missing severity and/or relationship (severity=severe, relationship=certain)

SOURCE: Listing 16.2.7.1

Table 14.3.1.2
Summary of Treatment Emergent Adverse Events
Safety Population

System Organ Class Preferred Term	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with at least One TEAE	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]
System Organ Class 1				
Preferred Term 1	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]
Preferred Term 2	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]
Preferred Term 3	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]
System Organ Class 2				
Preferred Term 1	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]
Preferred Term 2	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]
Preferred Term 3	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]

Abbreviations: TEAE = Treatment Emergent Adverse Event.
Notes: The first number (n) corresponds to the count of unique subjects and percentage, while the second is the count of the number of events.

Percentages are based on number of subjects in the safety population. Subjects were counted only once for each System Organ Class (SOC) or Preferred Term.
TEAE is defined as any event that started or worsened in intensity or relationship to treatment on or after the first dose of study drug.
AEs were coded using MedDRA version 23.0.

SOURCE: Listing 16.2.7.1
Programmers Note- Ensure there is some space between the Number of subject (%) count and the number of events in the table

Table 14.3.1.3
Summary of Treatment Emergent Adverse Events by Maximum Severity
Safety Population

System Organ Class Preferred Term Maximum Severity [1]	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with at least One TEAE				
Mild	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Moderate	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Severe	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 1				
Mild	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Moderate	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Severe	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 1				
Mild	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Moderate	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Severe	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Abbreviations: TEAE = Treatment Emergent Adverse Event; SAE = Serious Adverse Event.
[1] The severity shown is the greatest severity reported for a particular subject (Severe > Moderate > Mild). AEs with missing severity have been classified as Severe.
Notes: Percentages are based on number of subjects in the safety population. Subjects were counted only once for each System Organ Class (SOC) or Preferred Term. TEAE is defined as any event that started or worsened in intensity or relationship to treatment on or after the first dose of study drug. AEs were coded using MedDRA version 23.0.
SOURCE: Listing 16.2.7.1

Table 14.3.1.4
Summary of Treatment Emergent Adverse Events by Relationship to Study Drug
Safety Population

System Organ Class Preferred Term Greatest Relationship [1]	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with at least One TEAE	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unassessable/Unclassifiable	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Conditional/Unclassified	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unrelated	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unlikely	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Possible	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Probable	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Certain	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unassessable/Unclassifiable	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Conditional/Unclassified	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unrelated	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unrelated	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unlikely	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Possible	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Probable	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Certain	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unassessable/Unclassifiable	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Conditional/Unclassified	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unrelated	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unrelated	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unlikely	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Possible	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Probable	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Certain	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

[1] AE relation is marked in the CRF. The relationship shown is the strongest relationship reported for a particular subject. AEs with missing relationship have been classified as Certain.
Abbreviations: TEAE = Treatment Emergent Adverse Event.
Notes: Percentages are based on number of subjects in the safety population.. Subjects were counted only once for each System Organ Class (SOC) or Preferred Term. TEAE is defined as any event that started or worsened in intensity or relationship to treatment on or after the first dose of study drug.. AEs were coded using MedDRA version 23.0.
SOURCE: Listing 16.2.7.1

Table 14.3.1.5
Summary of Non-Serious Treatment Emergent Adverse Events
Safety Population

System Organ Class Preferred Term	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with at least one non-serious TEAE	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
System Organ Class 1				
Preferred Term 1	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 2	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 3	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
System Organ Class 2				
Preferred Term 1	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 2	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 3	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X

Abbreviations: TEAE = Treatment Emergent Adverse Event.

Notes: The first number (n) corresponds to the count of unique subjects and percentage, while the second is the count of the number of events. Percentages are based on number of subjects in the safety population.. Subjects were counted only once for each System Organ Class (SOC) or Preferred Term.. TEAE is defined as any event that started or worsened in intensity or relationship to treatment on or after the first dose of study drug. AEs were coded using MedDRA version 23.0.

SOURCE: Listing 16.2.7.1
Programmers Note- Ensure there is some space between the Number of subject (%) count and the number of events in the table

Table 14.3.2.1
Summary of Serious Adverse Events
Safety Population

System Organ Class Preferred Term	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with at least one SAE	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
System Organ Class 1				
Preferred Term 1	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 2	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 3	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
System Organ Class 2				
Preferred Term 1	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 2	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 3	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X

Abbreviation: SAE = Serious Adverse Event.
Notes: The first number (n) corresponds to the count of unique subjects and percentage, while the second is the count of the number of events.
Percentages are based on number of subjects in the safety population. Subjects were counted only once for each System Organ Class (SOC) or Preferred Term.

AEs were coded using MedDRA version 23.0.
SOURCE: Listing 16.2.7.1

Programmers Note- Ensure there is some space between the Number of subject (%) count and the number of events in the table

Table 14.3.2.2
Summary of Treatment Emergent Adverse Events Leading to Study Drug Discontinuation
Safety Population

System Organ Class Preferred Term	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with at least one TEAE that led to study drug discontinuation	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
System Organ Class 1				
Preferred Term 1	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 2	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 3	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
System Organ Class 2				
Preferred Term 1	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 2	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 3	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X

Abbreviation: TEAE = Treatment Emergent Adverse Event.

Notes: The first number (n) corresponds to the count of unique subjects and percentage, while the second is the count of the number of events.
Percentages are based on number of subjects in the safety population. Subjects were counted only once for each System Organ Class (SOC) or Preferred Term.
TEAE is defined as any event that started or worsened in intensity or relationship to treatment on or after the first dose of study drug.
AEs were coded using MedDRA version 23.0.

SOURCE: Listing 16.2.7.1

Programmers Note- Ensure there is some space between the Number of subject (%) count and the number of events in the table

Table 14.3.3.1
Listing of Serious Adverse Events
Safety Population

Subject ID	Treatment Group	Gender	Age (years)	SAE	System Organ Class/ Preferred Term/ Verbatim Term	Start Date/Time (Study Day)/ End Date/Time (Study Day)	Severity/ Causality	Outcome/ Action Taken
XXXX		M	XX	XXXX	XXXX/XXX/XXX	DDMMMYYYY/THH:MM (XX)/ DDMMMYYYY/THH:MM (XX)	MILD/Related	XXX/XXX
				XXXX				

Abbreviation: SAE = Serious adverse event.
Note: AEs were coded using MedDRA version 23.0.
Study day is calculated relative to the date of first dose of study drug.
Source: Listing 16.2.7.2

Table 14.3.3.2
Listing of Treatment Emergent Adverse Events Leading to Study Drug Discontinuation
Safety Population

Subject ID	Treatment Group	Gender	Age (Years)	TEAE	System Organ Class/ Preferred Term/ Verbatim Term	Start Date/Time (Study Day)/ End Date/Time(Study Day)	Severity/ Causality	Outcome/ Action Taken
XXXX	XX	F	XX	XXXX	XXXX/XXX/XXX	DDMMMYYYYTHH:MM (XX)/ DDMMMYYYYTHH:MM (XX)	MILD/Related	XXX/XXX
XXXX	XX	M		XXXX	XXXX/XXX/XXX	DDMMMYYYYTHH:MM (XX)/ DDMMMYYYYTHH:MM (XX)	MILD/Related	XXX/XXX

Abbreviations: TEAE = Treatment Emergent Adverse Event.
Notes: AEs were coded using MedDRA version 23.0.
TEAE is defined as any event that started or worsened in intensity or relationship to treatment on or after the first dose of study drug. Study day is calculated relative to the date of first dose of study drug.

Source: Listing 16.2.7.1

Table 14.3.4.1
Listing of Potentially Clinically Significant Abnormal Laboratory Values
Safety Population

Subject Number	Treatment Group	Gender	Age (Years)	Lab Category	Lab Parameter (Units)	Parameter Value	Reference Range	Test Result Assessment	Date/Time of Collection (Study Day)
XXXX	XX	M	XX	Hematology	Hemoglobin	XXXXX	XX-XX	High/Low	XXXXX(XX)
					Haematocrit	XXXX			

Abbreviation: NA=Not ApplicableNotes: Study day is calculated relative to the date of first dose of study drug.
Source: Listings 16.2.8.1, 16.2.8.2, 16.2.8.3, 16.2.8.4
Programming note- Category will be Hematology/Chemistry/Urinalysis/Coagulation. Sort by subject id, treatment group, and paramn.

Table 14.3.5.1
Summary of Clinical Laboratory Results
Safety Population

Lab Category: Chemistry/Hematology/Urinalysis

Parameter:XXXX Visit/ Statistic	Iburprofen PR (N=XX)	Iburprofen PR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Lab Parameter: XXXXX				
Screening				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX

Notes- Clinical laboratory tests (hematology, chemistry, urinalysis) tests are only done at Screening.

SOURCE: Listing 16.2.8.1, 16.2.8.2, 16.2.8.3, 16.2.8.4
Programming Note- Lab Category is Hematology or Chemistry or Urinalysis or Coagulation

Table 14.3.6.1
Summary of Vital Signs
Safety Population

Parameter:XXXXX

Visit/ Statistic	Iburprofen PR (N=XX)	Iburprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Baseline				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
12 hours				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
Change from Baseline to 12 hours				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
…….				

Notes- Baseline is defined as the last observation recorded prior to the first dose.
Programming Note- Calculate summary stats and change from baseline for 12 hours, 24 hours and Day 8/ET visit.
Source:Listing 16.2.9.2

Table 14.3.6.2
Summary of Electrocardiogram (ECG) Interpretations
Safety Population

Visit Category	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Screening				
Normal	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Abnormal - CS	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Abnormal - NCS	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Abbreviations: CS = clinically significant; NCS = not clinically significant

SOURCE: Listing 16.2.9.3

Table 14.3.6.3
Summary of 12-Lead Electrocardiogram (ECG) Parameters
Safety Population

Parameter: XXXXXX

Visit/ Statistic	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Screening				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX

SOURCE: Listing 16.2.9.3.

Table 14.3.6.4
Summary of Physical Examination Findings
Safety Population

Body System=XXXXXX

Visit Category	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Visit				
Normal	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Abnormal - CS	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Abnormal - NCS	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
.....				

Abbreviations: CS = clinically significant; NCS = not clinically significant ET: end of treatment

SOURCE: Listing 16.2.9.3

Table 14.3.6.5
Rescue Medication Use
Safety Population

Any rescue medication	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Total
At Any time	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
In the first 1 hour after dosing	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
In the first 2 hours after dosing	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
.....				

Note: At each level of summarization subjects taking multiple rescue medication are counted only once. Percentage is based on number of subjects in the safety population.
Programming note- Please complete table for the following time points 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 10 hours, 12 hours, 16 hours and 24 hours.

Table 14.2.1
Analysis of SPID-12 Scores
ITT Population

Statistics	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
n	XX	XX	XX
Mean	XX.XX	XX.XX	XX.XX
Std Dev	XX.XXX	XX.XXX	XX.XXX
Median	XX.XX	XX.XX	XX.XX
Min, Max	XX.X,XX.X	XX.X,XX.X	XX.X,XX.X
ANCOVA Statistics[1]			
LS Mean (SE)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)
LS Mean Difference from Placebo (95% CI)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	
p-value	0.XXXX	0.XXXX	
.....			

Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error.
[1] Estimates are from an analysis of covariance model with SPID-12 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.
Notes: SPID-12 is summed pain intensity difference (SPID) over 0 to 12 hours. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Baseline pain is also recorded using the NRS scale. For subjects who use rescue medication, windowed worst observation carried forward (WOCF) is used. Missing intermediate pain assessments imputed by linear interpolation. Missing pain assessments due to premature discontinuation imputed by LOCF.

Source: Listing 16.x.xx

Table 14.2.1.1
Analysis of SPID-12 Scores – Sensitivity Analysis 1
PP Population

(Same Shell as Table 14.2.1)

Table 14.2.1.2
Analysis of SPID-12 Scores- Sensitivity Analysis 2-WOCF
ITT Population
(Same Shell as Table 14.2.1)

Please add these footnotes: Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error.

[1] Estimates are from an analysis of covariance model with SPID-12 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.

Note: SPID-12 is summed pain intensity difference (SPID) over 0 to 12 hours. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Baseline pain is also recorded using the NRS scale. For subjects who use rescue medication, windowed worst observation carried forward (WOCF) is used. Missing pain assessments imputed by WOCF

(Programming Note-This is sensitivity analysis # 2 in section 6.1.6 of the SAP.)

Table 14.2.1.3
Analysis of SPID-12 Scores- Sensitivity Analysis 3-No Rescue Adjustment
ITT Population
(Same Shell as Table 14.2.1)

Please add these footnotes: Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error.

[1] Estimates are from an analysis of covariance model with SPID-12 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.

Note: SPID-12 is summed pain intensity difference (SPID) over 0 to 12 hours. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Baseline pain is also recorded using the NRS scale. No adjustment made to pain scores after use of rescue medication. Missing intermediate pain assessments imputed by linear interpolation. Missing pain assessments due to premature discontinuation imputed by LOCF.

(Programming Note-This is sensitivity analysis # 3 in section 6.1.6 of the SAP.)

Table 14.2.1.4
Analysis of SPID-12 Scores- Sensitivity Analysis 4a-Rescue WOCF
ITT Population
(Same Shell as Table 14.2.1)

Please add these footnotes: Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error.

[1] Estimates are from an analysis of covariance model with SPID-12 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.

Note: SPID-12 is summed pain intensity difference (SPID) over 0 to 12 hours. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Baseline pain is also recorded using the NRS scale. Worst observation carried forward (WOCF) is used to impute all subsequent pain scores after first use of rescue medication. Missing intermediate pain assessments imputed by linear interpolation. Missing pain assessments due to premature discontinuation imputed by LOCF.

(Programming Note-This is sensitivity analysis # 4a in section 6.1.6 of the SAP.)

Table 14.2.1.5
Analysis of SPID-12 Scores- Sensitivity Analysis 4b-Rescue LOCF
ITT Population
(Same Shell as Table 14.2.1)

Please add these footnotes: Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error.
[1] Estimates are from an analysis of covariance model with SPID-12 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.
Note: SPID-12 is summed pain intensity difference (SPID) over 0 to 12 hours. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Baseline pain is also recorded using the NRS scale. Last observation carried forward (LOCF) is used to impute all subsequent pain scores after first use of rescue medication. Missing intermediate pain assessments imputed by linear interpolation. Missing pain assessments due to premature discontinuation imputed by LOCF.

(Programming Note-This is sensitivity analysis # 4b in section 6.1.6 of the SAP.)

Table 14.2.1.6
Analysis of SPID-12 Scores- Sensitivity Analysis 4c-Multiple Imputation-Rescue Medication-MAR
ITT Population
(Same Shell as Table 14.2.1)

Footnotes: Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error.
[1] Estimates are from an analysis of covariance model with SPID-12 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.
Note: SPID-12 is summed pain intensity difference (SPID) over 0 to 12 hours. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Baseline pain is also recorded using the NRS scale. All pain scores after rescue medication are imputed using an MCMC method under missing at random assumption. Intermediate pain assessments imputed by linear interpolation. Missing pain assessments due to premature discontinuation imputed by LOCF.

(Programming Note-This is sensitivity analysis # 4c in section 6.1.6 of the SAP.)

Table 14.2.1.7
Analysis of SPID-12 Scores- Sensitivity Analysis 5-Multiple Imputation-PMM
ITT Population
(Same Shell as Table 14.2.1)

Footnotes: Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error.
[1] Estimates are from an analysis of covariance model with SPID-12 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.
Note: SPID-12 is summed pain intensity difference (SPID) over 0 to 12 hours. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Baseline pain is also recorded using the NRS scale. For subjects who use rescue medication, windowed worst observation carried forward (WOCF) is used. Intermittent missing values are replaced by an MCMC method under a missing at random assumption. Missing pain assessments due to premature discontinuation are replaced using a pattern-mixture model with control-based imputation.

(Programming Note-This is sensitivity analysis # 5 in section 6.1.6 of the SAP.)

Table 14.2.1.8
Analysis of SPID-12 Scores- Sensitivity Analysis 6-Multiple Imputation-MAR
ITT Population
(Same Shell as Table 14.2.1)

Footnotes: Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error.
[1] Estimates are from an analysis of covariance model with SPID-12 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.
Note: SPID-12 is summed pain intensity difference (SPID) over 0 to 12 hours. Subjects rate their pain intensity using a numeric rating (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Baseline pain is also recorded using the NRS scale. Missing pain scores and values within the defined window after rescue medication are imputed using multiple imputation under the MAR assumption.

(Programming Note-This is sensitivity analysis # 5 in section 6.1.6 of the SAP.)

Table 14.2.1.9
Summary of SPID-12 Scores by Baseline Pain Category
ITT Population

Category/Statistic	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
Baseline Pain Category-Moderate			
n	XX	XX	XX
Mean	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX
Median	XX	XX	XX
Min, Max	XX,XX	XX,XX	XX,XX
.....			

Notes- SPID-12 is summed pain intensity difference (SPID) over 0 to 12 hours. Subjects will rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Baseline pain using a categorical scale that includes moderate (5-7), and severe (8-10). For subjects who use rescue medication, windowed worst observation carried forward (WOCF) is used. Missing intermediate pain assessments imputed by linear interpolation. Missing pain assessments due to premature discontinuation imputed by LOCF.

Programming Note- Please complete table for all baseline pain categories.

Table 14.2.2
Analysis of Summed Pain Intensity Difference Scores
ITT Population

Category/Statistics	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
SPID-4			
n	XX	XX	XX
Mean	XX.XX	XX.XX	XX.XX
Std Dev	XX.XXX	XX.XXX	XX.XXX
Median	XX.XX	XX.XX	XX.XX
Min, Max	XX.X,XX.X	XX.X,XX.X	XX.X,XX.X
ANCOVA Statistics[1]			
LS Mean (SE)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)
LS Mean Difference from Placebo (95% CI)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	
p-value	0.XXXX	0.XXXX	
.....			

Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error.
[1] Estimates are from an analysis of covariance model with SPID score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.
Notes: SPID-4/8/12 is summed pain intensity difference (SPID) over 0 to 4/8/12 hours. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Baseline pain is also recorded using the NRS scale. For subjects who use rescue medication, windowed worst observation carried forward (WOCF) is used. Missing intermediate pain assessments imputed by linear interpolation. Missing pain assessments due to premature discontinuation imputed by LOCF.

Programming Note- Please program for SPID-4 SPID-8 and SPID-24.

Source: Listing 16.x.xx

Table 14.2.2.1
Analysis of SPID-24 Scores- Sensitivity Analysis 7-No Rescue Adjustment
ITT Population
(Same Shell as Table 14.2.1)

Please add these footnotes: Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error.
[1] Estimates are from an analysis of covariance model with SPID-12 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.
Note: SPID-12 is summed pain intensity difference (SPID) over 0 to 12 hours. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Baseline pain is also recorded using the NRS scale. No adjustment made to pain scores after use of rescue medication. Missing intermediate pain assessments imputed by linear interpolation. Missing pain assessments due to premature discontinuation imputed by LOCF.

Table 14.2.2.2
Analysis of SPID-24 Scores- Sensitivity Analysis 8-Multiple Imputation-MAR
ITT Population
(Same Shell as Table 14.2.1)

Footnotes: Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error.
[1] Estimates are from an analysis of covariance model with SPID-12 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.
Note: SPID-24 is summed pain intensity difference (SPID) over 0 to 24 hours. Subjects rate their pain intensity using a numeric rating (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Baseline pain is also recorded using the NRS scale. Missing pain scores and values within the defined window after rescue medication are imputed using multiple imputation under the MAR assumption

Table 14.2.3
Analysis of Total Pain Relief Scores
ITT Population

(Programming Note- Use same shell as Table 14.2.2. Please add the following footnote defining sum of total pain relief (TOTPAR) Note- Total pain relief (TOTPAR) is summed total pain relief under the Pain Relief Scale (0 – 4) from 15 min through 4/8/12/24 hours)

Table 14.2.4
Analysis of Summed Pain Relief and Intensity Difference Scores
ITT Population
(Use same shell as Table 14.2.2)

Table 14.2.5
Comparison of SPID-24 in Ibuprofen PR and IR arms
ITT Population

Category/Statistics	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)
SPID-24		
ANCOVA Statistics[1]		
LS Mean (SE)	XX.XX (XX.XX)	XX.XX (XX.XX)
LS Mean Difference (95% CI)	XX.XX (XX.XX, XX.XX)	
p-value	0.XXXX	
.....		

Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error, SPID=summed pain intensity difference.
[1] Estimates are from an analysis of covariance model with SPID-24/TOTPAR-24/SPRID-24 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.
Notes-SPID-24 is summed pain intensity difference (SPID) over 0 to 24 hours. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. For subjects who use rescue medication, windowed worst observation carried forward (WOCF) is used. Missing intermediate pain assessments imputed by linear interpolation. Missing pain assessments due to premature discontinuation imputed by LOCF.

Table 14.2.5.1
Comparison of SPID-24 in Ibuprofen PR and IR arms-Sensitivity Analysis 7-No Rescue Adjustment
ITT Population

Use same shell as Table 14.2.5
Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error, SPID=summed pain intensity difference.
[1] Estimates are from an analysis of covariance model with SPID-24 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.
Notes-SPID-24 is summed pain intensity difference (SPID) over 0 to 24 hours. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. No adjustment made to pain scores after use of rescue medication. Missing intermediate pain assessments imputed by linear interpolation. Missing pain assessments due to premature discontinuation imputed by LOCF.

Table 14.2.5.2
Comparison of SPID-24 in Ibuprofen PR and IR arms-Sensitivity Analysis 8- Multiple Imputation
ITT Population

Use same shell as Table 14.2.5
Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error, SPID=summed pain intensity difference.
[1] Estimates are from an analysis of covariance model with SPID-24 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.
Notes-SPID-24 is summed pain intensity difference (SPID) over 0 to 24 hours. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10

= worst pain ever. No adjustment made to pain scores after use of rescue medication. Missing pain scores and values within the defined window after rescue medication are imputed using multiple imputation under the MAR assumption

Table 14.2.6
Summary of Peak Pain Relief
ITT Population

Category/Statistics	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
None	X (XX.X%)	X (XX.X%)	X (XX.X%)
A Little Relief	X (XX.X%)	X (XX.X%)	X (XX.X%)
Some Relief	X (XX.X%)	X (XX.X%)	X (XX.X%)
A lot of Relief	X (XX.X%)	X (XX.X%)	X (XX.X%)
Complete Relief	X (XX.X%)	X (XX.X%)	X (XX.X%)
Odds Ratio (vs placebo) [1]	XX.XX	XX.XX	
95% CI	(XX.XX,XX.XX)	XX.XX,XX.XX)	
p-value	0.XXXX	0.XXXX	

Abbreviations: CI=Confidence Interval
[1] From a proportional odds model treatment group and baseline pain as covariates. An odds ratio > 1 means that patients experienced higher peak pain relief than the placebo.
Notes- Subjects rate their pain relief relative to Time 0 using a 5-point categorical scale, none = 0, a little = 1, some = 2, a lot = 3, and complete = 4.

SOURCE: Listing 16.x.xx

Table 14.2.7
Time to First Perceptible Pain Relief
ITT Population

Category/Statistic	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
Number of Subjects with First Perceptible Pain Relief	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of Subjects Censored	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Time to first perceptible pain relief (hours) [1]			
Median (95% CI)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)
Q1	XX.XX	XX.XX	XX.XX
Q3	XX.XX	XX.XX	XX.XX
Range (Min-Max)	XX.X-XX.X	XX.X-XX.X	XX-XX
p-value (vs placebo) [2]	0.XXXX	0.XXXX	
Hazard Ratio (vs placebo) [3]	XX.XX	XX.XX	
95% CI	(XX.XX,XX.XX)	(XX.XX,XX.XX)	

Abbreviation- Q1- 25th Percentile, Q3- 75th Percentile
[1] From Kaplan-Meier Estimates
[2] From Log-rank/Wilcoxon test stratified by baseline pain
[3] Hazard Ratio calculated from Cox proportional hazards model with treatment group as a categorical factor and baseline pain as a continuous covariate. A hazard ratio of <1 means that patients in the Ibuprofen groups achieved pain relief faster than the placebo.
Notes- Time of first perceptible pain relief is the time of first reported pain relief as assessed by the subject (i.e. subject stops the first stopwatch (irrespective of the second stopwatch)). Pain scores at baseline are categorized as moderate (5-7), and severe (8-10).

Table 14.2.8
Time to Meaningful Pain Relief
ITT Population

Use same shell as Table 14.2.7
(Programmers Note- Please add the following footnote- Abbreviation- Q1- 25th Percentile, Q3- 75th Percentile
[1] From Kaplan-Meier Estimates.
[2] From Log-rank/Wilcoxon test stratified by baseline pain.
[3] Hazard Ratio calculated from Cox proportional hazards model with treatment group as a categorical factor and baseline pain as a continuous covariate. A hazard ratio of <1 means that patients in the Ibuprofen groups achieved pain relief faster than the placebo.
Notes- Time of meaningful pain relief is the time of the first reported meaningful (subjective) pain relief assessed by stopping the second stopwatch. Pain scores at baseline pain) are categorized as moderate (5-7), and severe (8-10

Table 14.2.9
Time to Onset of Analgesia
ITT Population

Category/Statistic	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
Number of Subjects with First Perceptible Pain Relief and Meaningful Pain Relief	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of Subjects Censored	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Time to onset of analgesia (hours) [1]			
Median (95% CI)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)
Q1	XX.XX	XX.XX	XX.XX
Q3	XX.XX	XX.XX	XX.XX
p-value (vs placebo) [2]	0.XXXX	0.XXXX	
p-value (PR vs IR) [2]	0.XXXX		
Range (Min-Max)	XX.X-XX.X	XX.X-XX.X	XX.X-XX.X
Hazard Ratio (95% CI) (vs placebo) [3]	XX.XX (XX.XX,XX.XX)	XX.XX (XX.XX,XX.XX)	
Hazard Ratio (95% CI) (PR vs IR) [4]	XX.XX (XX.XX,XX.XX)		

(Programmers Note- Please add the following footnote- Abbreviation- Q1- 25th Percentile, Q3- 75th Percentile
[1] From Kaplan-Meier Estimates
[2] From Log-rank/Wilcoxon test stratified by baseline pain.
[3] Hazard Ratio calculated from Cox proportional hazards model with treatment group as a categorical factor and baseline pain as a continuous covariate. If hazard ratio <1 means that patients in the Ibuprofen groups achieved pain relief faster than the placebo
[4] Hazard Ratio calculated from Cox proportional hazards model with treatment group as a categorical factor and baseline pain as a continuous covariate. If hazard ratio <1 means that patients in the PR group achieved pain relief faster than the IR.
Notes- If the subject has had meaningful pain relief (i.e., presses both stopwatches) then time to onset of analgesia is date/time when the first stopwatch is stopped. Pain scores at baseline are categorized as moderate (5-7), and severe (8-10).

Table 14.2.10
Time to Peak Pain Relief
ITT Population
Use same shell as Table 14.2.7

(Programmers Note- Please add the following footnote- Abbreviation- Q1- 25th Percentile, Q3- 75th Percentile
[1] From Kaplan-Meier Estimates
[2] From Log-rank/Wilcoxon test stratified by baseline pain.
[3] Hazard Ratio calculated from Cox proportional hazards model with treatment group as a categorical factor and baseline pain as a continuous covariate. A hazard ratio of <1 means

that patients in the Ibuprofen groups achieved pain relief faster than the placebo.
Note- Time of peak pain relief is the time when pain relief, which is measured on a scale from 0 (none)-4 (complete), is maximum. Subjects who do not experience any pain relief are censored at the time of their last pain assessment.

Table 14.2.11
Time to First use of Rescue Medication
ITT Population

Use same shell as Table 14.2.7

(Programmers Note- Please add the following footnote- Abbreviation- Q1- 25th Percentile, Q3- 75th Percentile
[1] From Kaplan-Meier Estimates
[2] From Log-rank/Wilcoxon test stratified by baseline pain.
[3] Hazard Ratio calculated from Cox proportional hazards model with treatment group as a categorical factor and baseline pain as a continuous covariate. A hazard ratio of >1 means that patients in the Ibuprofen groups refrained from taking rescue medication for longer than the placebo.

Notes- Subjects who do not take rescue medication are censored at the time of their last pain assessment.

Table 14.2.12
Proportion of Subjects Using Rescue Medication
ITT Population

Category/Statistic	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
Number of subjects using Rescue Medication	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Odds Ratio for Rescue Medication (Active/Placebo) [1]	XX.XX	XX.XX	
(95% CI)	(XX.XX,XX.XX)	(XX.XX,XX.XX)	
p-value	0.XXXX	0.XXXX	

Abbreviation: CI= Confidence Interval
[1] Odds ratio, CI, and p-value are from a logistic regression model estimating the probability of using rescue medication with baseline pain and treatment arm as covariates in the model. An odds ratio < 1 means patients in the Ibuprofen groups are less likely to have used rescue medication compared to those in placebo.

Table 14.2.13
Proportion of Responders
ITT Population

(Use same shell as 14.2.12. Please use footnote below.)

Abbreviation: CI=Confidence Interval
Notes- A subject with ≥ 30% improvement in NRS pain intensity from T0 (predose) without rescue medication during the first 8 hours is considered a responder.
[1] Odds ratio, CI, and p-value are from a logistic regression model estimating the probability of being a responder with baseline pain and treatment arm as covariates in the model. An odds ratio > 1 means patients in the Ibuprofen groups are more likely to be responders compared to those in placebo.

Table 14.2.14
Summary of NRS Pain Intensity Difference Score
ITT Population

	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
PID 15 mins after Time 0			
n	XX	XX	XX
Mean	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX
Median	XX	XX	XX
Min, Max	XX,XX	XX,XX	XX,XX
MMRM Statistics [1]			
LS Mean (SE)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
LS Mean Difference from Placebo (95% CI)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)	
p-value (vs Placebo)	0.XXXX	0.XXXX	

Abbreviations: MMRM = Mixed Model Repeated Measures, CI = confidence interval, LS=least-squares, SE = standard error, PID= Pain Intensity Difference NRS- Numeric Rating Scale.
[1] Estimates are from a repeated measures mixed model with PID score as the dependent variable. Terms for treatment, timepoint, treatment by timepoint, baseline and baseline by timepoint as fixed effects, and subject as a random effect.
Notes- Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Pain intensity difference score at a time point is the difference in NRS pain intensity from baseline to that time point. For subjects who use rescue medication, windowed worst observation carried forward (WOCF) is used. Missing data due to missing intermediate assessments or premature discontinuation is not imputed.

Programming Note- Please complete table for all scheduled time assessments. Only impute using wWOCF for assessments after rescue medication. Do not impute for missing data.

Table 14.2.15
Summary of Pain Intensity Score at each Scheduled Time Point
ITT Population
Use same shell as Table 14.2.14

(Programmers please add the following footnote-
Note- Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. For subjects who use rescue medication, windowed worst observation carried forward (WOCF) is used. Missing data due to missing intermediate assessments or premature discontinuation is not imputed.
Programming Note- Please complete table for all scheduled time assessments. No need for LS mean difference 95%CI and p value from 14.2.14 shell). Only impute using wWOCF for assessments after rescue medication. Do not impute for missing data.

Table 14.2.16
Summary of Pain Relief at each Scheduled Time Point
ITT Population

	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
Pain Relief 5 mins after Time 0			
None	X (XX.X%)	X (XX.X%)	X (XX.X%)
A Little Relief	X (XX.X%)	X (XX.X%)	X (XX.X%)
Some Relief	X (XX.X%)	X (XX.X%)	X (XX.X%)
A lot of Relief	X (XX.X%)	X (XX.X%)	X (XX.X%)
Complete Relief	X (XX.X%)	X (XX.X%)	X (XX.X%)
n	XX	XX	XX
Mean	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX
Median	XX	XX	XX
Min, Max	XX,XX	XX,XX	XX,XX
MMRM Statistics[1]			
LS Mean (SE)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
LS Mean Difference from Placebo (95% CI)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)	
p-value (vs Placebo)	0.XXXX	0.XXXX	

Abbreviations: MMRM = Mixed Model Repeated Measures, CI = confidence interval, LS=least-squares, SE = standard error.
[1] Estimates are from a repeated measures mixed model with pain relief as the dependent variable. Terms for treatment, timepoint, treatment by timepoint, baseline pain and baseline pain by timepoint as fixed effects, and subject as a random effect.
Notes- Subjects rate their pain relief relative to Time 0 using a 5-point categorical scale, none = 0, a little = 1, some = 2, a lot = 3, and complete = 4. For subjects who use rescue medication, windowed worst observation carried forward (WOCF) is used. Missing data due to missing intermediate assessments or premature discontinuation is not imputed.

Programming Note- Please complete table for all scheduled time assessments. Only impute using wWOCF for assessments after rescue medication. Do not impute for missing data.

Table 14.2.17
Analysis of Patient Global Evaluation of Study Drug
ITT Population

Category/Statistics	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
Poor	X (XX.X%)	X (XX.X%)	X (XX.X%)
Fair	X (XX.X%)	X (XX.X%)	X (XX.X%)
Good	X (XX.X%)	X (XX.X%)	X (XX.X%)
Very Good	X (XX.X%)	X (XX.X%)	X (XX.X%)
Excellent	X (XX.X%)	X (XX.X%)	X (XX.X%)
Odds Ratio (vs placebo) [1]	XX.XX	XX.XX	
95% CI	(XX.XX,XX.XX)	XX.XX,XX.XX)	
p-value	0.XXXX	0.XXXX	

Notes- Patient's global evaluation of study drug is measured on a scale of 0=poor, 1=fair, 2=good, 3=very good, 4=excellent.
[1] From a proportional odds model treatment group and baseline pain as covariates. An odds ratio > 1 means that patients rated active arm more highly than placebo

1.2. Planned Listing Shells

Listing 16.2.1
Subject Disposition
All Subjects

Subject Number	Randomized?	Patient Status	Date of Last Dose (Study Day)	Date of Completion/ Discontinuation (Study Day)	Reason for Discontinuation	Was blind broken? If yes, date and reason blind was broken
XXXXXX		Yes	DDMMMYYYY (XX)	DDMMMYYYY (XX)		XX
XXXXXX		Yes	DDMMMYYYY (XX)	DDMMMYYYY (XX)		XX
XXXXXX		Yes	DDMMMYYYY (XX)	DDMMMYYYY (XX)		XX
XXXXXX		No	DDMMMYYYY (X)	DDMMMYYYY (X)	XXXXXXXXXX: XXXXXXXXX	XX
XXXXXX		No	DDMMMYYYY (XX)	DDMMMYYYY (XX)	XXXXXXXXXXXXXXXXXXXXXX	XX

Abbreviation: NA=Not Applicable
Notes: Study day is calculated relative to the date of first dose of study drug
Programming Note: If reason for early termination is other, concatenate the specify text as follows: “Other: XXXXXXXXX”. If additional details about reason for discontinuation are present in DSREASSP, then concatenate reason for discontinuation with “DSREASSP”.
If reason for early termination is lost to follow-up, concatenate with date of last contact as follows: “Lost to follow-up: Lost-to follow-up comment (DSLFCOMT): date of last contact: DDMMMYYYY”. Lost to follow up comment DSLFCOMT will only be concatenated when present.
If reason for discontinuation is a PI decision, concatenate PI decision reason as follows: “PI Decision: XXXXXXXXXX

Listing 16.2.2.1
Inclusion/ Exclusion Criteria
All Subjects

Subject Number	Gender	Date (Study Day)		All Inclusion Criteria Met?	Any Exclusion Criteria Met?
		Screening	Informed Consent		
XXXXXX	XXXX	DDMMMYYYY (-X)	DDMMMYYYY (-X)	Yes	No
XXXXXX	XXXXXX	DDMMMYYYY (-X)	DDMMMYYYY (-X)	No: 02, 09	No
XXXXXX	XXXXXX	DDMMMYYYY (-X)	DDMMMYYYY (-X)	No: 06	No
XXXXXX	XXXX	DDMMMYYYY (-X)	DDMMMYYYY (-X)	Yes	Yes: 06
XXXXXX	XXXXXX	DDMMMYYYY (-X)	DDMMMYYYY (-X)	Yes	No
XXXXXX	XXXX	DDMMMYYYY (-X)	DDMMMYYYY (-X)	Yes	No

Notes: Study day is calculated relative to the date of first dose of study drug.
Programming note: If more than 1 inclusion or exclusion criterion number exists, concatenate with a comma. Decode any relevant criteria in the footnotes.

Listing 16.2.2.2
Screen Failures

Subject Number	Gender	Date of Birth	Age	Screen Fail Date	Screen Fail Reason
XXXXXX	XXXXXX	DDMMMYYYY	XX	DDMMMYYYY	Inclusion #2
XXXXXX	XXXXXX	DDMMMYYYY	XX	DDMMMYYYY	Inclusion #6
XXXXXX	XXXXXX	DDMMMYYYY	XX	DDMMMYYYY	Inclusion #4, Exclusion #6
XXXXXX	XXXXXX	DDMMMYYYY	XX	DDMMMYYYY	Other: XXXXXXXXXXXXX

Programming note: If more than 1 inclusion or exclusion criterion number exists, concatenate with a comma

Programming note: If additional details about reason for screen failure are present in, then concatenate reason for screen failure reason with “DSSFOTRN”.

Listing 16.2.2.3
Protocol Deviations
All Subjects

Subject Number	Treatment Group	Event Date (Study day)	Event Type	Violation Level	Description
XXXXXX	XXXX	XXXX(XXX)	XXXXXXXXXXX XXXXXXXXXXXXX	MAJOR MINOR	XXXXXXX XXXXXXXXXXXXXX
XXXXXX	XXXX	XXXX(XXX)	XXXXXXXXXXX XXXXXXXXXXXXXX	MINOR MINOR	XXXXXXXXXXXXXXXXXX XXXXXXXXXX
XXXXXX	XXXX	XXXX(XXX)	XXXXXXXXXXX	MAJOR	XXXXXXXXXXXXXXXXXXX

Notes: Study day is calculated relative to the date of first dose of study drug.

Listing 16.2.3
Analysis Populations
All Subjects

Subject Number	Treatment Group	SAF	PP	ITT	Primary Reason(s) for Exclusion
XXXXXX	XXX	Yes	No		XXXXXXXXXXXXXXXXXXXXXXXXXXXXXX.
XXXXXX	XXX	Yes	Yes		
XXXXXX	XXXX	No	No		

Abbreviations: PP = Per Protocol Population; SAF= Safety Population; ITT = Intent-to-treat population

Listing 16.2.4.1
Demographics and Baseline Characteristics
Safety Population

Subject Number	Gender	If Female, is she of childbearing potential?	Treatment Group	Age (years)	Ethnicity	Race	Weight (kg)	Height (cm)	BMI (kg/m2)	Duration of Surgery (hours)
XXXXXX	XX	XX	XX	XX	XXXXXXX	XXXXXXX	XX.X	XX.X	XX.XX	XX.XX
XXXXXX	XX	XX	XX	XX	XXXXXXX	XXXXXX	XX.X	XX.X	XX.XX	XX.XX
XXXXXX	XX	XX	XX	XX	XXXXXXX	XXXXXX	XX.X	XX.X	XX.XX	XX.XX
XXXXXX	XX	XX	XX	XX	XXXXXXX	XXXXX	XX.X	XX.X	XX.XX	XX.XX
XXXXXX	XX	XX	XX	XX	XXXXXXX	XXXXXX	XX.X	XX.X	XX.XX	XX.XX
XXXXXX	XX	XX	XX	XX	XXXXXX	XXXXXX	XX.X	XX.X	XX.XX	

Abbreviation: BMI = Body mass index
Notes: Height, weight, and BMI are the values at Screening.

Listing 16.2.4.2
Medical History
Safety Population

Subject Number	Treatment Group	Any Medical History	SOC/PT/VT	Start date(Study Day) / End Date(Study Day)	Ongoing?
XXX	XX	XX	XXXX/XXX/XXX	DDMMMYYYY/DDMMMYYYY(XXX)	
XXX	XX	XX	XXXX/XXX/XXX	DDMMMYYYY/DDMMMYYYY(XXX)	
XXX	XX	XX	XXXX/XXX/XXX	DDMMMYYYY/DDMMMYYYY(XXX)	
XXX	XX	XX	XXXX/XXX/XXX	DDMMMYYYY/DDMMMYYYY(XXX)	
XXX	XX	XX	XXXX/XXX/XXX	DDMMMYYYY/DDMMMYYYY(XXX)	
XXX	XX	XX	XXXX/XXX/XXX	DDMMMYYYY/DDMMMYYYY(XXX)	

SOC = System Organ Class; PT = Preferred Term; VT = Verbatim Term.

Notes: All medical history terms were coded using MedDRA dictionary version 21.1. Study day is calculated relative to the date of first dose of study drug

Listing 16.2.4.3
Listing of Subject Randomization
All Randomized Subjects

Subject Number	Randomization Date	Randomization Time	Randomization Number	Kit Number Assigned	Randomized Arm
XXX	DDMMMYYYY	hh:mm	XXX	XXX	XX
XXX	DDMMMYYYY	hh:mm	XXX	XXX	XX
XXX	DDMMMYYYY	hh:mm	XXX	XXX	XX
XXX	DDMMMYYYY	hh:mm	XXX	XXX	XX
XXX	DDMMMYYYY	hh:mm	XXX	XXX	XX

Listing 16.2.4.4
Study Drug Administration
Safety Population

Subject Number	Treatment Group	Timepoint	Was Study Drug Administered?	Reason Not Administered	Date of Administration	Time of Administration
XXX	XXX	0 hours	Yes/no	XXXXXXXXXXXX	DDMMMYYYY	hh:mm
XXX	XXX	8 hours	Yes/no	XXXXXXXXXXXX	DDMMMYYYY	hh:mm
XXX	XXX	12 hours	Yes/no	XXXXXXXXXXXX	DDMMMYYYY	hh:mm
XXX	XXX	16 hours	Yes/no	XXXXXXXXXXXX	DDMMMYYYY	hh:mm

Listing 16.2.7.1
Adverse Events
Safety Population

Subject Number	Gender	Treatment Group	Any AEs reported?	TEAE?	SOC/PT/VT	Start date time(Study Day) / End Date time(Study Day)	Severity/ Relationship	Medical Treatment Received?	Outcome/ Action Taken	Serious?
XXX	XXX	XX	XX	NO	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XX	XXXX/ XXXX	No
XXX	XXX	XX	XX	YES	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XX	XXXX/ XXXX	YES
XXX	XXX	XX	XX	NO	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XX	XXXX/ XXXX	No
XXX	XXX	XX	XX	YES	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XX	XXXX/ XXXX	No
XXX	XXX	XX	XX	YES	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XX	XXXX/ XXXX	YES
XXX	XXX	XX	XX	NO	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XX	XXXX/ XXXX	NO

Abbreviation: TEAE-Treatment Emergent Adverse Event, SOC = System Organ Class; PT = Preferred Term; VT = Verbatim Term.
Notes: AEs were coded using MedDRA dictionary version 21.1. TEAE is defined as any event that started or worsened in intensity or relationship to treatment on or after the first dose of study drug. Study day is calculated relative to the date of first dose of study drug.
Programming note= Fatal/hospitalization/life threatening/persistent/congenital/important medical event can be concatenated to SAE when SAE=Y. Concatenate an abbreviated version of the term. Example – For Fatal use F etc. Add term to list of abbreviations if such abbreviation is used.

Listing 16.2.7.2
Serious Adverse Events
Safety Population

(Same shell as Listing 16.2.7.1)

Listing 16.2.7.3
Treatment emergent Adverse Events Related to Study Drug
Safety Population

(Same shell as Listing 16.2.7.1)

Listing 16.2.7.4
Deaths
Safety Population

Subject Number	Gender	Treatment Group	Date of Death(Study Day)	Cause of Death (Specify if Other)
001-003			DDMMMYYYY(XX)	XXXXXXXXX

Notes-Study day is calculated relative to the date of first dose of study drug.

Listing 16.2.8.1
Clinical Laboratory Data: Serum Chemistry
Safety Population

Subject Number	Gender	Treatment Group	Was Sample Collected?	Date/Time of Assessment	Test Name	Standard Results	Units	Abnormal?/ If Yes, H or L	Comments/Reason not Done
XXX	XXX	XX		DDMMMYYYY(XX)		XX	XX	NO	
XXX	XXX	XX		DDMMMYYYY(XX)		XX	XX	NO	
XXX	XXX	XX		DDMMMYYYY(XX)		XX	XX	YES/ NO	
XXX	XXX	XX		DDMMMYYYY(XX)		XX	XX	YES/ YES	
XXX	XXX	XX		DDMMMYYYY(XX)		XX	XX	NO	

Abbreviation: H=High, L=Low
Notes: Study day is calculated relative to the date of first dose of study drug.

Listing 16.2.8.2
Clinical Laboratory Data: Hematology
Safety Population

(Same shell as Listing 16.2.8.1)

Listing 16.2.8.3
Clinical Laboratory Data: Urine
Safety Population

(Same shell as Listing 16.2.8.1)

Listing 16.2.8.4
Clinical Laboratory Data: Coagulation
Safety Population

(Same shell as Listing 16.2.8.1)

Listing 16.2.8.5
Serum and Urine Pregnancy Test
Safety Population

Subject Number	Treatment Group	Visit	Was Sample Collected?	Reason not collected	Date of Assessment	Time of Assessment	Serum or Urine Test ?	Result of Pregnancy Test
001-003					DDMMMYYYY		XXXXXXXXXX	

Listing 16.2.9.1
Prior and Concomitant Medications
Safety Population

Subject Number	Treatment Group	Prior, Concomitant or Both?	ATC Class (Level 4)/ /PT /VT	Start date time (Study Day)/ End date time(Study Day)	Dose Unit	Frequency	Route	Ongoing ?
XXX	XX	Prior	XXXX/XXX/XXX	DDMMMYYYY(XX)/ DDMMMYYYY(XX)	XXX	XXX		
XXX		Both	XXXX/XXX/XXX	DDMMMYYYY(XX) / DDMMMYYYY (XX)	XXX	XXX		
XXX		Concomitant	XXXX/XXX/XXX	DDMMMYYYY(XX) / DDMMMYYYY(XX)	XXX	XXX		
XXX			XXXX/XXX/XXX	DDMMMYYYY(XX) / DDMMMYYYY (XX)	XXX	XXX		
XXX			XXXX/XXX/XXX	DDMMMYYYY (XX)/ DDMMMYYYY(XX)	XXX	XXX		
XXX			XXXX/XXX/XXX	DDMMMYYYY(XX) / DDMMMYYYY (XX)	XXX	XXX		

ATC = Anatomic Therapeutic Chemical; PT = Preferred Term; VT = Verbatim Term.

Notes: Study day is calculated relative to the date of first dose of study drug.. Medications are coded using WHO-DD B2E version March 2020. . Medications that started prior to the first dose of study drug will be considered prior medications whether or not they were stopped prior to the first dose of study drug. Any medications continuing or starting post the first dose of study drug will be considered to be concomitant. If a medication starts prior to the first dose and continues after the first dose of study drug, it will be considered both prior and concomitant.

Listing 16.2.9.1.1
Rescue Medications
Safety Population

Subject Number	Treatment Group	Were any rescue medications reported ?	Medication	Date time for pain relief/pain intensity (Study Day)	NRS Pain intensity assessment	Pain Relief Assessment	ATC Class (Level 4)/ /PT /VT	Start date time (Study Day) / End date time(Study Day)	Dose Unit	Frequency	Route	Ongoing ?
XXX	XX	XX		XXXX (XX) / XXXX(XX)			XXXX/XXX/ XXX	XXXX (XX) / XXXX(XX)	XXX	XXX		
XXX		XX		XXXX (XX) / XXXX(XX)			XXXX/XXX/ XXX	XXXX (XX) / XXXX(XX)	XXX	XXX		
XXX		XX		XXXX (XX) / XXXX(XX)			XXXX/XXX/ XXX	XXXX (XX) / XXXX(XX)	XXX	XXX		
XXX				XXXX (XX) / XXXX(XX)			XXXX/XXX/ XXX	XXXX (XX) / XXXX(XX)	XXX	XXX		
XXX				XXXX (XX) / XXXX(XX)			XXXX/XXX/ XXX	XXXX (XX) / XXXX(XX)	XXX	XXX		
XXX				XXXX (XX) / XXXX(XX)			XXXX/XXX/ XXX	XXXX (XX) / XXXX(XX)	XXX	XXX		

Abbreviations: ATC = Anatomic Therapeutic Chemical; PT = Preferred Term; VT = Verbatim Term.

Notes: Study day is calculated relative to the date of first dose of study drug.. Medications are coded using WHO-DD B2E version March 2020. Pain assessments will be conducted immediately before each dose of rescue medication. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever and rate their pain relief relative to Time 0 using a 5-point categorical scale, none = 0, a little = 1, some = 2, a lot = 3, and complete = 4.

Listing 16.2.9.2
Vital Signs Measurements
Safety Population

Subject Number	Treatment Group	Visit	Timepoint	Were Vital Signs Collected?	Collection Date/Time (Study Day)	Temperature (Units)	Heart Rate (Units)	Respiration Rate (Units)	Systolic Blood Pressure (Units)	Diastolic Blood Pressure (Units)
XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX

Notes: Study day is calculated relative to the date of first dose of study drug.

Listing 16.2.9.2.1
Physical Examination Findings
Safety Population

Subject Number	Treatment Group	Was Exam Performed?	Visit	Date/Time of Assessment (Study Day)	Body System	Standard Results	If Abnormal, CS ?	Abnormal findings description	Were mouth and neck examined?	If no, reason	Any CS abnormal findings that have been newly diagnosed or have worsened since the previous assessment?
XXX	XX	Yes	XX	DDMMMYYYYThh:mm(XX)		XX			Yes	XX	Yes
XXX	XX	No	XX	DDMMMYYYYThh:mm (XX)		XX			No	XX	No
XXX	XX	Yes	XX	DDMMMYYYYThh:mm(XX)		XX	YES		Yes	XX	Yes
XXX	XX	No	XX	DDMMMYYYYThh:mm(XX)		XX			No	XX	No
XXX	XX	No	XX	DDMMMYYYYThh:mm(XX)		XX			No	XX	No

Abbreviation: CS: Clinically Significant

Notes: Study day is calculated relative to the date of first dose of study drug.

Programming note: In the 'If Abnormal, CS ?' column, 'Yes' will only be populated when we the abnormal value is CS.

Listing 16.2.9.3
12-Lead Electrocardiogram Measurements
Safety Population

Subject Number	Treatment Group	Was ECG Performed?	Date of Assessment (Study Day)	Time of Assessment	Heart Rate (Unit)	RR Interval (Unit)	PR Interval (Units)	QRS (Unit)	QT (Unit)	QTc Interval (Unit)	Investigator Interpretation
XXX	XXX	XXX	DDMMMYYYY(XX)	HH:MM	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	Normal
XXX	XXX	XXX	DDMMMYYYY (XX)	HH:MM	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	Abnormal-NCS
XXX	XXX	XXX	DDMMMYYYY (XX)	HH:MM	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	Abnormal-CS
XXX	XXX	XXX	DDMMMYYYY(XX)	HH:MM	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	Normal

Abbreviation: CS=Clinically Significant, NCS=Not Clinically Significant

Notes: Study day is calculated relative to the date of first dose of study drug

Listing 16.2.9.3.1
Alcohol Breathalyzer Test
Safety Population

Subject Number	Treatment	Was Alcohol Breathalyzer Test performed?	Test Date/Time (Study Day)	Alcohol Breathalyzer Test Result
XXXX	XX	Yes	DDMMMYYYYThh:mm(XX)	XXXXXXX

Notes: Study day is calculated relative to the date of first dose of study drug.

Listing 16.2.9.4
NRS Pain Intensity Assessment
Safety Population

Subject Number	Treatment Group	Was NRS Pain Assessment collected?	Reason not collected	Timepoint	Was Rescue Medication Taken? (Y/N)	Date time post dose	NRS Pain Intensity Score	NRS Pain Intensity Score when rescue medication was taken	Responder (Y/N)
XXXX	XX	Yes	XXXXXXXX	XXX		XXXX	XXX	XXX	

Notes- Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. A subject with ≥ 30% improvement in NRS pain intensity from T0 (predose) without rescue medication during the first 8 hours is considered a responder.

Programing Note- For those cases where "Was rescue medication taken?" is 'Yes', the datetime needs to be presented in the "Date time post dose" column.

Listing 16.2.9.5
Pain Relief Scores
Safety Population

Subject Number	Treatment Group	Was assessment completed?	Reason not collected	Date of Assessment	Date time pain relief collected	Timepoint	Was Rescue Medication Taken? (Y/N)	Date time post dose	How much relief have you had since your starting pain?	How much pain relief have you had since your starting pain when rescue medication was taken?
XXXX	XX	Yes	XXXXXXXX			XXX		XXXX	XXX	

Notes: Subjects rate their pain relief relative to Time 0 using a 5-point categorical scale, none = 0, a little = 1, some = 2, a lot = 3, and complete = 4.

Programing Note- For those cases where "Was rescue medication taken?" is 'Yes', the datetime needs to be presented in the "Date time post dose" column

Listing 16.2.9.6
Time to Pain Relief (Stopwatches)
Safety Population

Subject Number	Treatment Group	Which stopwatch pressed, perceptible or meaningful	Hours on Stopwatch	Minutes on stopwatch	Seconds on stopwatch
XXXX	XX	Perceptible/meaningful	XX	XXX	XXX

Notes: Perceptible pain relief stopwatch refers to the first stop watch and meaningful pain relief, the second stopwatch.

Listing 16.2.9.7
Subjects Global Evaluation of Study Drug
Safety Population

Subject Number	Treatment Group	Was Subject Global Evaluation of study drug completed	Date/Time of evaluation	Global evaluation score
XXXX	XX		XXXX	XX

Notes: Patient's global evaluation of study drug is measured on a scale of 0=poor, 1=fair, 2=good, 3=very good, 4=excellent

Figure 14.4.1.1
Kaplan-Meier plot of time to first perceptible pain relief

ITT Population

X-Axis- Time (hours)

Y-Axis- Proportion of patients experiencing first perceptible pain relief

Figure 14.4.1.2
Kaplan-Meier plot of time to Meaningful Pain Relief

ITT Population

X-Axis- Time (hours)

Y-Axis- Proportion of patients experiencing meaningful pain relief

Figure 14.4.1.3
Kaplan-Meier plot of time to onset of analgesia

ITT Population

X-Axis- Time (hours)

Y-Axis- Proportion of patients experiencing analgesia

Figure 14.4.1.4
Kaplan-Meier plot of time to peak pain relief

ITT Population

X-Axis- Time (hours)

Y-Axis- Proportion of patients experiencing peak pain relief

Figure 14.4.1.5
Kaplan-Meier plot of time to first use of rescue medication

ITT Population

X-Axis- Time (hours)

Y-Axis- Proportion of patients using rescue medication

Figure 14.4.1.6

Mean PID Scores versus Time

ITT Population

x-axis Time (hours)

y-axis- Mean PID score

Present with error bars of +/- 1 standard error.

Add footnote: For subjects who use rescue medication, windowed worst observation carried forward (WOCF) is used. Missing data due to missing intermediate assessments or premature discontinuation is not imputed.

Figure 14.4.1.7

Mean Pain Relief Scores versus Time

ITT Population

x-axis Time (hours)

y-axis- Mean pain relief score

Present with error bars of +/- 1 standard error.

Add footnote: For subjects who use rescue medication, windowed worst observation carried forward (WOCF) is used. Missing data due to missing intermediate assessments or premature discontinuation is not imputed.

Sponsor	Reckitt Benckiser
Protocol Title:	A Randomized, Double-Blind, Double-Dummy, Parallel-Group, Multiple-Dose, Active and Placebo-Controlled Efficacy Study of Ibuprofen Prolonged-Release Tablets for the Treatment of Pain after Surgical Removal of Impacted Third Molars
Protocol Number:	5003601
Premier Research PCN:	RECK.177035
Document Version:	Amendment 2.0
Document Date:	18-May-2020

Approvals

Role	Signatures	Date (dd-Mmm-yyyy)
Biostatistician Premier Research	Print Name: Raghu Vishnubhotla	19-May-2020 | 22:39:31 EDT
	Sign Name: DocuSigned by: Raghu Srinivas Vishnubhotla Signer Name: Raghu Srinivas Vishnubhotla Signing Reason: I am the author of this document Signing Time: 19-May-2020 | 22:39:14 EDT 46FE4F466250408E961764121635BB48	
Reckitt Benckiser Representative	Print Name: Darren Targett	19-MAY-2020
	Sign Name: [signature]	

Document History

Reasons for Amendment 1

The statistical analysis plan was amended in the following ways:

1. The sensitivity analyses for the primary efficacy endpoint has been updated. A pattern-mixture model with control-based pattern imputation will now be used.
2. A comparison of individual NRS pain intensity difference scores has been added. P-values comparing the treatment arms (PR vs Placebo, IR vs Placebo) has been added.
3. Pain relief scores at each time point will be summarized and by p-values will be added for treatment comparison.

Reasons for Amendment 2

The statistical analysis plan was amended in the following ways:

1. Add clarification for how pain assessments recorded within 4-hours of rescue medication and missing pain assessments are handled in the repeated measures analysis of pain intensity difference and pain relief scores.

2. The sensitivity analyses for the primary efficacy endpoint have been further updated. A multiple imputation model under a Missing at Random (MAR) assumption has been added to account for missing data due to patient withdrawal, missing intermediate pain assessments and pain assessments impacted by rescue medication.

3. Sensitivity analyses have been added for the key secondary endpoint SPID24.

4. Updated methodology for handling pain assessments post non-permitted rescue medications. Added imputation windows for non-permitted rescue medications.

Table of Contents

List of Tables

1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Reckitt Benckiser protocol number 5003601 (A Randomized, Double-Blind, Double-Dummy, Parallel-Group, Multiple-Dose, Active and Placebo-Controlled Efficacy Study of Ibuprofen Prolonged-Release Tablets for the Treatment of Pain after Surgical Removal of Impacted Third Molars), dated 19-Nov-2019, version 3.0. Reference materials for this statistical plan include the protocol and the accompanying sample data collection documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association[2] and the Royal Statistical Society[3], for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The statistical plan described hereafter is an *a priori* plan. It will be submitted to file prior to any unblinded inferential or descriptive analysis of data pertaining to Reckitt Benckiser's study 5003601.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective is:

- To evaluate the superiority of 2 x 300 mg ibuprofen PR tablets compared with placebo in subjects experiencing acute moderate to severe pain after third molar extraction over 12 hours post initial dose.

2.1.2. Secondary Objectives

The key secondary objectives are:

- To evaluate the analgesic performance of a total daily dose of 1200 mg of ibuprofen PR formulation compared to ibuprofen immediate release (IR) formulation over 24 hours post initial dose.
- To evaluate the safety and tolerability of 2 x 300 mg ibuprofen PR tablets.

Additional secondary objectives include:

- To evaluate the total analgesic effect, peak analgesic effect, onset and duration of action and the subject's overall assessment of the study medications.

2.2. Study Endpoints

2.2.1. Safety Endpoints

The safety endpoints of this study include the following:

- Incidence of treatment-emergent adverse events (TEAEs)
- Incidence of changes in vital sign measurements

2.2.2. Efficacy Endpoints

2.2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint of this study is the summed pain intensity difference (SPID) over 0 to 12 hours (SPID12).

2.2.2.2. Secondary Efficacy Endpoint(s)

The secondary efficacy endpoints of this study include the following:

- Summed pain intensity difference (SPID) over 0 to 24 hours (SPID24) after Time 0.
- SPID4, SPID8 and SPID12
- Sum of total pain relief (TOTPAR) over 0 to 4 hours (TOTPAR4), over 0 to 8 hours (TOTPAR8), over 0 to 12 hours (TOTPAR12) and over 0 to 24 hours (TOTPAR24) after Time 0.
- Summed pain relief and intensity difference (sum of TOTPAR and SPID [SPRID]) over 0 to 4 hours (SPRID4), over 0 to 8 hours (SPRID8), over 0 to 12 hours (SPRID12) and over 0 to 24 hours (SPRID24) after Time 0.
- Response to study drug
- Numeric rating scale (NRS) pain intensity difference (PID) at each scheduled timepoint after Time 0. NRS ranges from 0=no pain to 10=worst pain ever and pain relief is a 5 point categorical scale 0=none, 1=a little, 2=some, 3=a lot, 4=complete. PID is the difference in NRS pain intensity between each time point and Time 0.
- Pain intensity score at each scheduled time point after Time 0.
- Pain relief at each schedule time point after Time 0.
- Peak pain relief
- Time to onset of analgesia
- Time to first perceptible pain relief
- Time to meaningful pain relief

- Time to peak pain relief
- Proportion of subjects using rescue medication
- Time to first use of rescue medication

2.2.2.3. Exploratory Endpoint

- Patient's global evaluation of study drug. It is measured on a scale of 0=poor, 1=fair, 2=good, 3=very good, 4=excellent

3. Overall Study Design and Plan

3.1. Overall Design

3.2. Sample Size and Power

The sample size determination is based on the primary efficacy variable, SPID12. According to Farrar 2001, a clinically important improvement in pain is represented by a 2 point reduction on an 11-point NRS. Based on a baseline pain score of 7 this corresponds to an approximate 30% reduction in pain. An average 2 point difference in pain scores between ibuprofen PR and placebo across all 14 assessments up to 12 hours will correspond to a difference in SPID12 of 24 points. In a previous study, the pooled standard deviation (SD) for SPID12 was 31.65. Assuming the same variability in this study, a sample size of 40 subjects per group will have >90% power to detect a difference of 24 points in SPID12, between ibuprofen 2x300-mg PR tablets and placebo using a 2-sided test with an alpha level of 0.05. In order to provide a robust estimate of treatment effect differences between PR and IR, and to obtain a more precise estimate for this comparison, a 3:3:1 allocation ratio will be used, so that 120 subjects are randomized into each of the PR and IR groups. Thus 280 subjects will be enrolled in the study.

3.3. Study Population

Subjects with moderate to severe pain after extraction of 2 or more third molars will participate in this study.

3.4. Treatments Administered

Treatment A (test product): 2x300 mg ibuprofen PR tablets, BID (total daily dose 1200 mg)

Treatment B (reference product): 2x200 mg ibuprofen IR tablets, TID (total daily dose 1200 mg)

Treatment C: matching placebo tablets

3.5. Method of Assigning Subjects to Treatment Groups

Eligible subjects will be randomized in a 3:3:1 ratio to receive 2x300 mg ibuprofen PR tablets Q12h, 2x200 mg ibuprofen IR Q8h, or placebo using permuted blocks of fixed size. The randomization will be stratified by baseline pain category (moderate or severe) using a categorical scale that includes the categories of none (0), mild (1-4), moderate (5-7), and severe (8-10). The randomization schedule will be prepared by a statistician not otherwise involved in the study. Randomization will be performed using an interactive response system (IRT).

3.6. Blinding and Unblinding

This is a double-blind, double-dummy study. There will be two placebo tablets designed to be

comparable to each of the active products (PR and IR) in both shape, size, color and weight.

All subjects will receive 4 tablets at each dosing timepoint. All subject packs will be designed and labelled to ensure blinding is maintained.

Access to the unblinding codes will be restricted to personnel not otherwise involved in the study and will be available to the investigator only in the case of a subject requiring unblinding prior to database lock.

Unblinding will only occur after database lock or in the case of emergency unblinding.

3.7. Schedule of Events

A detailed schedule of events for the study is provided in Table 1.

Table 1: Schedule of Events

	Screening (Day -28 to Day -1)	Surgery (Day 1)						Day 2		Follow-up (Day 8 ±2 days) or ET[k]
			Post-op							
		Pre-Surgery	Pre-dose	0 h	15, 30, 45 min	1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 h	12 h	16 h	24h	
Written informed consent	X									
Assign a screening number	X									
Inclusion/exclusion criteria	X	X								
Demographics	X									
Medical history	X	X[b]								
Physical examination[c]	X									X
Vital signs[d]	X	X	X				X		X	X
Height, weight, and BMI	X									
Clinical laboratory tests (hematology, chemistry, urinalysis)	X									
Electrocardiogram	X									
Pregnancy test for female subjects of childbearing potential[e]	X	X								
Urine drug screen	X	X								
Alcohol breathalyzer test		X								
Oral radiography[f]	X									
Review study restrictions with subject	X									
Pain intensity (NRS)[g]			X		X	X	X	X	X	
Randomisation			X							
Dosing with study drug				0 h		8 h	12 h	16h		
Stopwatch assessment[h]				X						
Pain relief (5-point categorical scale)[g]					X	X	X		X	

	Screening (Day -28 to Day -1)	Surgery (Day 1)						Day 2		Follow-up (Day 8 ±2 days) or ET[k]
			Post-op							
		Pre-Surgery	Pre-dose	0 h	15, 30, 45 min	1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 h	12 h	16 h	24h	
Global evaluation of study drug[i]									X	
Concomitant medications		X[b]	X	X	X	X	X		X	X
Adverse events[j]		X	X	X	X	X	X		X	X
Dispense/prescribe pain medication for use at home, as needed									X	
Collect unused home pain medications, as needed										X
Discharge from study site									X	

Abbreviations: BMI=body mass index; ET=early termination; h=hour; min=minute; NRS=numeric rating scale; pre-op=pre-operative; post-op=post-operative.

a Times listed are relative to dosing with study drug.
b Medical history and concomitant medication use since Screening will be updated on Day 1 before surgery.
c A complete physical examination (excluding the genitourinary examination) will be performed at Screening. An abbreviated confirmatory physical assessment, including an examination of the subject's mouth and neck, will be performed at the Follow-up Visit (or Early Termination Visit).
d Vital signs will be recorded after the subject has been in a sitting position for 3 minutes at the following times: at Screening, before surgery, within 30 minutes before Time 0, 12 hours after Time 0, 24 hours after Time 0, and/or immediately before the first dose of rescue medication, and at the Follow-up Visit (or Early Termination Visit).
e Serum pregnancy test at Screening and urine pregnancy test before surgery on Day 1 (female subjects of childbearing potential only). Test results must be negative for the subject to continue in the study.
f Oral radiographs taken within 1 year before Screening will be acceptable and do not need to be repeated.
g Pain assessments will be conducted (pre-dose, if at one of the dosing timepoints of 0, 8, 12 or 16 hours) at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16 and 24 hours after Time 0 and immediately before each dose of rescue medication. Pain intensity will also be assessed pre-dose. At each assessment time point, the pain intensity assessment will be completed first and the pain relief assessment will be completed second. Subjects will not be able to compare their responses with their previous responses. Note for assessments less than 1 hour apart a window of +/-2 min is allowable whilst for assessments at least 1 hour apart a +/-5 min window is allowable.
h Two stopwatches will be started immediately after the subject has swallowed the first dose of study drug with 8 ounces of water (Time 0). Subjects will record the time to perceptible and meaningful pain relief, respectively, by stopping the stopwatches.

4. Statistical Analysis and Reporting

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher). If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

Continuous (quantitative) variable summaries will include the number of subjects (n) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum.

Categorical (qualitative) variable summaries will include the frequency and percentage of subjects who are in the particular category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population in each of the treatment arms, unless otherwise specified.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and measures of spread (SD) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified.

Unless otherwise indicated, all statistical tests will be conducted at the 0.05 significance level using 2-tailed tests, and P values will be reported. Corresponding 95% confidence intervals (CIs) will be presented for statistical tests. In addition to what is detailed in the SAP, other additional analyses may be conducted on the data which will only serve as exploratory evidence and the unplanned nature of these analyses will be made clear in the Clinical Study Report.

4.2. Interim Analysis

No interim analyses are planned.

5. Analysis Populations

The following analysis populations are planned for this study:

- **Safety Population (SAF):** The Safety Population includes all subjects who receive any amount of planned study medication. Subjects will be assigned to treatment received.
- **Intent-To-Treat Population (ITT):** The ITT population includes all subjects who are treated with study drug and who have at least 1 pain assessment after Time 0. The ITT population is the primary population for the efficacy analysis. Subjects will be assigned to treatment randomized.
- **Per Protocol (PP)**: The PP Population will consist of all ITT subjects who do not incur a major protocol violation that would challenge the validity of their data. This population will be determined at a data review meeting prior to database lock and used to evaluate the sensitivity of the primary efficacy analysis. Subjects will be assigned to treatment received.

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

The last observation recorded prior to the first dose of study drug will be used as the baseline observation for all calculations of change from baseline.

6.1.2. Adjustments for Covariates

For the primary endpoint analysis, the baseline NRS pain score will be included as a covariate.

For the secondary endpoint analyses, baseline pain will be included as a covariate for SPID, SPRID, and TOTPAR variables.

For the proportion of subjects who are responders and the proportion of subjects using rescue medication, logistic regression models will adjust for baseline pain.

For time to event endpoints, baseline pain will be included as a stratification factor.

6.1.3. Multiple Comparisons

No adjustment for multiplicity is required for the primary efficacy analysis – a single comparison of SPID12 for placebo versus SPID12 for ibuprofen PR.

No adjustments will be made for multiple comparisons for other endpoints.

6.1.4. Handling of Dropouts or Missing Data

Missing pain assessments for all efficacy analyses will be handled as follows:

- Missing pain assessments scheduled before the first observed assessment will be imputed with the subject's worst observed pain assessment.
- Missing intermediate pain assessments will be replaced by linear interpolation.
- Missing pain assessments at the end of the observation period due to premature discontinuation of pain assessments will be imputed by carrying forward the last observation prior to that missing.

All data for assessments other than pain assessments will be analyzed as collected; missing data due to premature termination or any other reason will be left as missing. Since this is a short-term study and subjects remain at the study site throughout the 24-hour pain assessment period, the discontinuation rate and the amount of missing data is expected to be minimal.

A number of sensitivity analyses will be performed in order to evaluate the efficacy under various different assumptions regarding missing data and are described in Section 6.1.6

The exceptions to the above data handling rules are the descriptive summaries and repeated measures analyses by timepoint for pain intensity difference and pain relief, described in sections 8.2.11 and 8.1.12. In these repeated measures analyses, missing values are indirectly imputed

under an assumption of missing at random, and so missing pain assessments will not be explicitly imputed prior to analysis.

6.1.5. Adjustment of Pain Scores for Rescue Medication Use

Subjects are required to record their pain assessment (NRS and pain relief) immediately prior to each dose of rescue medication permitted in the protocol (1000mg paracetamol/acetaminophen or 5mg oxycodone). The primary analysis will use windowed worst observation carried forward (WOCF) methodology for subjects who use rescue medication. If a subject received rescue medication at time x, for any time point within x + 4 hours, the highest pain score from time 0 up until time x will be used. If the pain score for the windowed observation is higher than the worst observed score, it will not be replaced. The same approach will be used for pain relief scores. Subject who received other drug and non-drug therapies during the treatment period will be evaluated on a case-by-case basis at a data review meeting, prior to database lock. If these therapies are considered to modulate the pain response, the same approach described above will be used to replace pain intensity and pain relief scores within a 4-hour time window after medication was taken. The windowed WOCF method to adjust pain scores for subjects who use rescue medication is consistent with the hypothetical strategy estimand, where the intercurrent event is use of rescue medication, and will be the approach used for the primary efficacy analysis [5].

6.1.6. Sensitivity Analysis of SPID12 and SPID24

The following sensitivity analyses will also be performed for the primary endpoint SPID12 if any pain assessments are missing or if subjects take rescue medication. Each of these are consistent with the hypothetical strategy estimand, with the exception of analysis number 3, which uses the treatment policy strategy estimand.

1. Missing data and values after rescue medication handled as per the main analysis but based on the PP population.

2. Missing data imputed using WOCF (worst observed pain score at any timepoint, including baseline). Values after rescue medication handled as per the main analysis.

3. Missing data handled as per the main analysis. Pain assessments are used regardless of whether rescue medication has been taken, and no adjustment is made for use of rescue medication. In this analysis, the pain assessment recorded at the time of rescue medication is disregarded (unless it coincides with a planned pain assessment).

4. Missing data handled as per the main analysis. All pain assessments recorded after the first dose of rescue medication has been taken will be disregarded. WOCF, LOCF (Last Observation Carried Forward) and multiple imputation methods will then be used to impute the disregarded data.

    a. WOCF - The worst (highest) pain assessment (including baseline) until first dose of rescue medication will be used to impute all subsequent pain assessments. In

other words, this method would be treating the subject as if they got no worse than their worst observed value prior to rescue medication.

b. LOCF - In this LOCF analysis, the pain assessment taken immediately prior to/at the time of rescue medication will be taken as the last observed score, i.e., this method would be treating the subject as if they got no worse than their last observed value prior to rescue medication.

c. Multiple Imputation under a MAR assumption. Data will be imputed separately for each treatment group, using a Markov Chain Monte Carlo (MCMC) method for full imputation, with covariates for baseline and pain scores observed at each assessment. The methodology described in sensitivity analysis 6 below will be used. In this analysis, the pain assessment recorded at the time of rescue medication is disregarded (unless it coincides with a planned pain assessment).

5. Missing data imputed using multiple imputation (methodology described below). Values after rescue medication handled as per the main analysis.

For sensitivity analysis 5, a pattern-mixture model with control-based pattern imputation will be used. This model assumes that after withdrawal from the study, subjects from the experimental group (no longer receiving active treatment) will exhibit the same future evolution of pain scores as subjects in the placebo group (who are also not exposed to active treatment). Subjects that discontinue from the placebo group are assumed to evolve in the same way as placebo subjects that remain in the study. This imputation assumes that intermittent missing values are missing at random (MAR), and that values that are missing due to withdrawal are missing not at random (MNAR). When data are MAR, the missingness of the data does not depend on the missing value after conditioning on the observed data (i.e., prior assessments and baseline covariates). Note that when the missingness of the data depends on the values of the missing variables after conditioning on the observed data, the data are called "missing not at random" (MNAR). In order to assess the MAR assumption, a placebo-based pattern mixture model (PMM) will be utilized following the steps outlined in Ratitch B and O'Kelly, M.J. (2011) for SPID-12.

Briefly, the strategy for implementing this approach is as follows for subjects with missing data:

i. Impute all non-monotone (intermittent) missing data using the MCMC method of PROC MI. Note that this imputation will sample data within each treatment group. Note that PI_i is the NRS pain intensity at time T_i as mentioned in Section 6.1.7. SAS pseudo code is provided below. With MCMC option, SAS does 200 burn-in iterations (default) before each imputation.

```
PROC MI DATA=example seed = xxxx NIMPUTE = 20 OUT = outdata1 minimum=0 maximum=10;
        by <treatment>;
        MCMC chain=multiple impute=monotone;
        VAR  <PI0> <PI0.25> <PI0.5> <PI0.75><PI1> …..<PI12>;
RUN;
```

ii. Using the imputed datasets from Step #1 that are now monotone missing (no intermittent missing data), a single call to PROC MI (including the MNAR statement) will be utilized to impute the monotone missing data. Additional details are provided below.

a. Within the call to PROC MI, one timepoint is imputed at a time. The order in which pain scores are imputed will be PI_0, then $PI_{0.25}$...,PI_{12}

b. When imputing at timepoint t, the imputation step will include all placebo subjects, but only those from the active arms that have a value missing at timepoint t. Subjects with non-missing data that are on active arms will not contribute to the estimation for this step.

c. Repeat the above step for all timepoints *t*. Thus, the data for timepoint *t+1* uses the data imputed from previous timepoints.

SAS pseudo code is provided below. SAS accomplishes this iterative process in one step. Note that the treatment level 3 is the placebo treatment group. The MNAR statement imputes missing values for scenarios under the MNAR assumption. The MODEL option specifies that only observations in which treatment=3 are used to derive the imputation model for the pain score that time point. The minimum and maximum options are used to ensure that every pain score imputed ranges from 0-10.

```
PROC MI DATA=OUTDATA1 seed = xxxx NIMPUTE = 1 OUT = outdata2 MINIMUM=. 0..0
MAXIMUM=. 10 10…10;
BY _IMPUTATION_;
CLASS <treatment>;
MONOTONE REG (/ details);
MNAR MODEL (PI0.25> <PI0.5> <PI0.75><PI1> …..<PI12>/ modelobs=(<treatment='3'>));
        VAR  <PI0> <PI0.25> <PI0.5> <PI0.75><PI1> …..<PI12>;
RUN;
```

iii. When all missing PI scores are imputed, SPID12 will be derived as described in 6.1.7 and analyzed using the ANCOVA models as described in Section 8.1. PROC MIANALYZE will be used to combine the parameters from the analyses for inference.

6. Missing data and values within the defined window after rescue medication are imputed using multiple imputation (methodology described below).

For sensitivity analysis 6, a multiple imputation model under a MAR assumption will be used. This assumes that the missingness of the data does not depend on the missing observations after conditioning on the observed data (i.e., prior assessments and baseline as covariates). This is considered a reasonable assumption since patients are encouraged to use rescue medication only if needed (i.e. high pain scores), and thus it can be expected that the intercurrent event of rescue medication depends on the observed data (i.e. rescue medication likely to be taken when the preceding pain scores were high). It can then be inferred that the pain scores post-rescue can be predicted from the observed variables, and therefore the response can be estimated without bias

using the observed data. In this analysis, the pain assessment recorded at the time of rescue medication is disregarded (unless it coincides with a planned pain assessment).

The strategy to be used is as follows:

i. Set pain scores recorded within the defined window after rescue medication to missing. Impute all missing data (due to subject withdrawal, missing intermittent values and that set to missing due to rescue medication) using the MCMC method of PROC MI. Note that this imputation will sample data within each treatment group. Note that PIi is the NRS pain intensity at time Ti as mentioned in Section 6.1.7. SAS pseudo code is provided below. With the MCMC option, SAS does 200 burn-in iterations (default) before each imputation. Twenty imputations will be performed.

```
PROC MI DATA=example seed = xxxx NIMPUTE = 20 OUT = outdata1 minimum=0 … 0
maximum=10 … 10;
        by <treatment>;
        MCMC chain=multiple;
        VAR  <PI0> <PI0.25> <PI0.5> <PI0.75><PI1> …..<PI12>;
RUN;
```

ii. When all missing PI scores are imputed, SPID12 will be derived as described in 6.1.7 and analyzed using the ANCOVA models as described in Section 8.1. PROC MIANALYZE will be used to combine the parameters from the analyses for inference

Sensitivity analyses 3 and 6 will also be performed for SPID24, with the necessary modifications to the SAS pseudo code in sensitivity analysis 6 to incorporate a covariate for PI_{24}.

6.1.7. Derived Variables

At each assessment time point, subjects will complete the pain intensity NRS assessment first and the pain relief assessment second.

Planned assessment time points are as follows: 0 (predose), 15, 30, and 45 minutes, and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hours after Time 0. Please see Table 2 below.

Table 2 Planned Assessment Times

i	T_i (hours)
0	0 (predose)
1	0.25
2	0.5
3	0.75

4	1
5	1.5
6	2
7	3
8	4
9	5
10	6
11	7
12	8
13	10
14	12
15	16
16	24

- SPID-12 = summed pain intensity difference (change from Time 0) under the numeric rating scale (NRS)-time curve from 15 min through 12 hours calculated using the linear trapezoidal rule and the actual time points, where Time 0 is the time of the first dose of study drug. Scheduled time points in Table 2 will be used when actual time is missing.

$$SPID_{12} = \sum_{i=1}^{14} (T_i - T_{i-1}) * PID_i$$

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

PID is defined as

$$PID_i = PI_i - PI_0$$

Where PI is the pain intensity as measured by the NRS scale.

- SPID-x = summed pain intensity difference (change from Time 0) under the numeric rating scale (NRS)-time curve from 15 min through x hours calculated using the linear trapezoidal rule and the actual time points, where Time 0 is the time of the first dose of study drug. Scheduled time points in Table 2 will be used when actual time is missing. X = 4, 8, and 24.

$$SPID_x = \sum_{i=1}^{y} (T_i - T_{i-1}) * PID_i$$

For x=4 y=8; x=8 y=12; x=24 y=16.

- TOTPAR-x = total pain relief under the Pain Relief Scale (0 – 4) from 15 min through x hours calculated using the linear trapezoidal rule and actual time points, where Time 0 is the time of the first dose of study drug. Scheduled time points in Table 2 will be used when actual time is missing. x = 4, 8, 12, and 24.

$$TOTPAR_x = \sum_{i=1}^{y} (T_i - T_{i-1}) * PAR_i$$

For x=4 y=8; x=8 y=12; x=12 y=14; x=24 y=16. PAR_i is the pain relief score on the Pain Relief Scale (0-4) at time T_i

- SPRID-x = summed pain relief (TOTPAR) and intensity difference (SPID) from 15 min through x hours calculated using the linear trapezoidal rule and actual time points, where Time 0 is the time of the first dose of study drug. Scheduled time points in Table 2 will be used when actual time is missing. X = 4, 8, 12, and 24.

$$SPRID_x = SPID_x + TOTPAR_x$$

- Responder: subject with ≥ 30% improvement in NRS pain intensity from T_0 (predose) without rescue medication during the first 8 hours. If a subject takes rescue medication prior to the 8-hour pain assessment or if the 8-hour assessment is not performed they will be considered a non-responder. i.e.,

$$\frac{(PI_0 - PI_8)}{PI_0} * 100 \geq 30$$

Where PI_0 and PI_8 are the predose and 8-hour NRS pain intensity measurements respectively.

- Time to onset of analgesia = If the subject has had meaningful pain relief (i.e., presses both stopwatches) then time to onset of analgesia is date/time of perceptible pain relief – date/time of the first dose of study drug. If subjects don't experience both perceptible pain relief and meaningful pain relief during the 8-hour interval after Time 0, time to onset to analgesia will be right censored at the time of their last pain assessment in the first 8 hours. For subjects who take rescue medication prior to onset of analgesia during the 8-hour interval after Time 0, time to onset of analgesia will be right censored at the time rescue medication was taken.

- Time to first perceptible pain relief = date/time of the first reported pain relief (any) as assessed by the subject (i.e. subject stops the first stopwatch (irrespective of the second stopwatch)) – date/time of the first dose of study drug. If subjects don't experience perceptible pain relief during the 8-hour interval after Time 0, time to first perceptible pain relief will be right censored at the time of their last pain assessment in the first 8 hours. If the first stopwatch is not stopped but the second stopwatch is stopped, time will be left censored at the time that the second stopwatch is stopped. In other words, it is assumed that the first stopwatch measurement has already occurred but was missed/not recorded. For subjects who take rescue medication prior to first perceptible pain relief during the 8-hour interval after Time 0, time to first perceptible pain relief will be right censored at the time rescue medication was taken.

- Time to meaningful pain relief = date/time of the first reported meaningful (subjective) pain relief as assessed by the subject (i.e. the subject stops the second stopwatch) – date/time of the first dose of study drug. If subjects don't experience meaningful pain relief during the 8-hour interval after Time 0, time to meaningful pain relief will be right censored at the time of their last pain assessment in the first 8 hours. If the subject stops the second stopwatch but doesn't stop the first stopwatch or the first stopwatch assessment is missing, then time to meaningful pain relief will be right censored at the time of their last pain assessment in the first 8 hours. For subjects who take rescue medication prior to achieving meaningful pain relief during the 8-hour interval after Time 0, time to meaningful pain relief will be right censored at the time rescue medication was taken.

- Peak pain relief- Pain relief is measured on a scale from 0 (None) to 4 (Complete). If PR_i is the pain relief measurement at time T_i , peak pain relief PPR is defined as

$$PPR = \max\{PR_1, PR_2, PR_3, \ldots, PR_{16}\}$$

- Time to first use of rescue medication = date/time to the first dose of rescue medication – date/time of the first dose of study drug. If subjects don't take rescue medication, subjects will be right censored at the time of their last pain assessment.

- Time to peak pain relief = date/time of peak pain relief– date/time of the first dose of study drug. Time of peak pain relief is the time T_i when peak pain relief (PPR) first occurs. If no

pain relief is observed then the time to peak pain relief will be right censored at the time of their last pain assessment.

- Change from baseline = value at current time point – value at baseline.
- TEAE = TEAE is defined as any event that started or worsened in intensity or relationship to treatment on or after the first dose of study drug.

6.1.8. Data Adjustments/Handling/Conventions

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included only in the data listings.

All *P* values will be displayed in four decimals and rounded using standard scientific notation (e.g., 0.XXXX). If a *P* value less than 0.0001 occurs it will be shown in tables as <0.0001.

Adverse events will be coded using the MedDRA version 23.0 thesaurus.

A treatment related AE is any AE with a relationship to the study drug with possible, probable or certain causality to the study drug as determined by the Investigator.

If partial dates occur, the convention for replacing missing dates for the purpose of statistical analysis is as follows: if just day is missing then the day assigned is the first day of the month or the date of first dose (if in the same month), whichever is later; if just month is missing then the month assigned is the month of the first dose, unless that results in a date prior to the first dose in which case the month after the first dose is used; and if both month and day are missing then the month assigned is the month of the first dose and the day assigned is either the first day of the month or the first dose date, whichever is later.

If partial times occur, the convention is as follows: if the missing time occurs on the day of the first dose and both the hour and minute are missing then the time assigned is the time of the first dose, otherwise if both the hour and minute are missing and the date is not the date of first dose the time assigned is 12:00; if the date is the same as the date of the first dose and only hour is missing the hour assigned is 12 or the hour of first dose, whichever is later, and if the date is the same as the date of first dose and only the minute is missing the minute assigned is 30 or the minute of first dose, whichever is later. Otherwise the hour assigned is 12 if the hour is missing and the date is not the same as the date of first dose and the minute assigned is 30 is the the date is not the same as the date of first dose.

These conventions will be applied only to adverse event onset dates and times with the following precaution: if the missing date and time reflect the date and time of onset of an adverse event, the modified date and time will be constructed to match the first documented date/time post drug administration while preserving the order in which the AE was reported in the CRF.

7. Study Patients/Subjects and Demographics

7.1. Disposition of Patients/Subjects and Withdrawals

Disposition will include tabulations of the number of subjects screened, number of subjects randomized into each treatment group, the number of subjects who received treatment, tabulated reasons for discontinuation from the study, and number of subjects in each analysis population.

7.2. Protocol Violations and Deviations

Protocol deviations will be listed.

7.3. Demographics and Other Baseline Characteristics

Summary statistics for age, gender, race, ethnicity, height, weight, BMI, baseline pain category and baseline pain (continuous) will be presented by treatment groups and overall. For the continuous variables, the number of non-missing values and the mean, standard deviation, minimum, median and maximum will be tabulated.

For the categorical variables, the counts and proportions of each value will be tabulated.

These analyses will be conducted for the ITT, PP, and Safety populations.

The number and percent of subjects reporting various medical histories, grouped by MedDRA system organ class and preferred term (coded using MedDRA v23.0), will be tabulated by treatment group. This analysis will be conducted for the Safety Population. Physical examination findings will also be summarized by body system and examination result- Normal, Abnormal – Clinically Significant, Abnormal-Not Clinically Significant.

7.4. Exposure and Compliance

The number of doses taken and treatment duration will be summarized by descriptive statistics. All study drug will be administered in clinic. The total number of tablets taken, and the number of tablets with active ingredient taken at each time point will be summarized. The dosage (in mg) of active ingredient taken and duration of exposure, from first dose to last dose of the study treatment will be summarized using descriptive statistics. Any deviations from the planned dose should be reported.

8. Efficacy Analysis

8.1. Primary Efficacy Analysis

The primary efficacy endpoint is the summed pain intensity difference (SPID) over 0 to 12 hours (SPID12). The primary endpoint will be used to compare the test product (2x300 mg ibuprofen PR tablets) against placebo.

The primary efficacy hypothesis is that SPID12 for placebo is equal to SPID12 for ibuprofen 2x300 mg PR tablets. The primary analysis will be an ANCOVA model that includes the main effect of treatment and a covariate of the baseline NRS pain score and will use windowed worst

observation carried forward (WOCF) imputation for subjects who use rescue medication. The primary analysis will be based on a 2-sided test at the significance level of 0.05. The treatment difference will be presented with a 95% confidence interval.

Normality assumptions will be tested. If the data is considered non-normal, the Wilcoxon rank sum test will be used for the comparison between treatments, and the point estimate and 95% confidence interval will be calculated using the Hodges-Lehmann estimator.

The primary efficacy analysis will be based on the ITT population. These analyses will be repeated for the PP population. SPID-12 scores will also be summarized by baseline pain category (moderate or severe).

8.2. Secondary Efficacy Analysis

8.2.1. SPID

Summed Pain Intensity Difference (SPID) will be calculated for secondary efficacy analysis as described in Section 6.1.7 at 4, 8, and 24 hours. Descriptive statistics by treatment regimen will be produced.

ANCOVA models for comparing placebo with other treatment regimens with SPID as the dependent variable and treatment group and baseline pain as covariates will be generated. These models will be computed for SPID4, SPID8 and SPID12. The least square (LS) mean and standard error (SE) for each treatment group will be estimated and the difference in LS means and 95% confidence interval (CI) for the comparison of placebo with the IR and PR treatment regimens will be estimated. P-values will be reported but no formal statistical inferences will be made on the basis of these tests. In addition, for the SPID24 endpoint, the difference in LS means and 95% CI for the IR versus PR groups will be presented. In the event that normality assumptions are violated for a parameter, non-parametric analysis methods will be used.

8.2.2. TOTPAR

Total pain relief (TOTPAR) will be calculated as described in Section 6.1.7 at 4, 8, 12 and 24 hours. Descriptive statistics by treatment regimen will be produced.

ANCOVA models for comparing placebo with other treatment regimens with TOTPAR as the dependent variable and treatment group and baseline pain as covariates will be generated. These models will be generated at TOTPAR4, TOTPAR8, TOTPAR12 and TOTPAR24. The LS mean and SE for each treatment group will be estimated and the difference in LS means and 95% CI for the comparison of placebo with the IR and PR treatment regimens will be estimated. P-values will be reported but no formal statistical inferences will be made on the basis of these tests. In the event that normality assumptions are violated for a parameter, non-parametric analysis methods will be used.

8.2.3. SPRID

Summed pain relief and intensity difference is the sum of TOTPAR and SPID and will be calculated at 4, 8, and 12 and 24 hours as described in Section 6.1.7.

Descriptive statistics by treatment regimen will be produced for SPRID at each planned assessment time point.

ANCOVA models for comparing placebo with other treatment regimens with SPRID as the dependent variable and treatment group and baseline pain as covariates will be generated. The LS mean and SE for each treatment group will be estimated and the difference in LS means and 95% CI for the comparison of placebo with the IR and PR treatment regimens will be estimated. P-values will be reported but no formal statistical inferences will be made on the basis of these tests. In the event that normality assumptions are violated for a parameter, non-parametric analysis methods will be used.

8.2.4. Peak Pain Relief

Peak pain relief will be calculated as described in Section 6.1.7 and will be summarized by counts (and percentages) for each pain relief score. It 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 a factor for treatment and baseline pain intensity as a continuous covariate. For each of the PR and IR treatment regimens, the odds of being in a higher (better) pain relief category compared to placebo (odds ratio) will be presented with a 95% CI and associated p-value.

8.2.5. 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 6.1.7. With baseline pain as a stratification factor, treatments will be compared to placebo using a stratified log-rank test or a stratified Wilcoxon test as appropriate. Summary tables will provide the number of subjects analyzed, the number of subjects censored, estimates for the 25th, 75th percentiles and median (including 95% CI), and associated p-value for comparisons versus placebo.

A measure of the treatment effect comparing each of the active arms with placebo will be obtained by calculating a hazard ratio and 95% CI by fitting a Cox proportional hazards model with a factor for treatment group and baseline pain as a continuous covariate. The assumption of proportional hazards will first be evaluated.

8.2.6. Time to Meaningful Pain Relief

Time to first meaningful pain relief will be summarized using Kaplan-Meier methods. The definition and censoring rules are described in Section 6.1.7. With baseline pain as a stratification factor, treatments will be compared to placebo using a stratified log-rank test or a stratified Wilcoxon test. Summary tables will provide the number of subjects analyzed, the number of subjects censored, estimates for the 25th, 75th percentiles and median (including 95% CI), and associated p-value for comparisons versus placebo.

A measure of the treatment effect comparing each of the active arms with placebo will be obtained by calculating a hazard ratio and 95% CI by fitting a Cox proportional hazards model with a factor for treatment group and baseline pain as a continuous covariate. The assumption of proportional hazards will first be evaluated.

8.2.7. Time to onset of Analgesia

Time to onset of analgesia will be summarized using Kaplan-Meier methods. The definition and censoring rules are described in Section 6.1.7. With baseline pain as a stratification factor, treatments will be compared to placebo and with each other (IR vs PR) using a stratified log-rank test or a stratified Wilcoxon test. The summary tables will provide the number of subjects analyzed, the number of subjects censored, estimates for the 25th, 75th percentiles and median (including 95% CI), and associated p-value for treatment comparisons.

A measure of the treatment effect comparing each of the active arms with placebo and with each other (IR vs PR) will be obtained by calculating a hazard ratio and 95% CI by fitting a Cox proportional hazards model with a factor for treatment group and baseline pain as a continuous covariate. The assumption of proportional hazards will first be evaluated.

8.2.8. 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 6.1.7. With baseline pain as a stratification factor, treatments will be compared to placebo using a stratified log-rank test or a stratified Wilcoxon test. The summary tables will provide the number of subjects analyzed, the number of subjects censored, estimates for the 25th, 75th percentiles and median (including 95% CI), and associated p-value for comparisons versus placebo.

A measure of the treatment effect comparing each of the active arms with placebo will be obtained by calculating a hazard ratio and 95% CI by fitting a Cox proportional hazards model with a factor for treatment group and baseline pain as a continuous covariate. The assumption of proportional hazards will first be evaluated.

8.2.9. Time to first use of Rescue Medication

Time to first use of rescue medication will be summarized using Kaplan-Meier methods. The definition of time to first use of rescue medication and censoring rules for subjects who don't take rescue medication are described in Section 6.1.7. With baseline pain as stratification factor, treatments will be compared to placebo using a stratified log-rank test or a stratified Wilcoxon test. The summary tables will provide the number of subjects analyzed, the number of subjects censored, estimates for the 25th, 75th percentiles and median (including 95% CI), and associated p-value for comparisons versus placebo.

A measure of the treatment effect comparing each of the active arms with placebo will be obtained by calculating a hazard ratio and 95% CI by fitting a Cox proportional hazards model with a factor for treatment group and baseline pain as a continuous covariate. The assumption of proportional hazards will first be evaluated.

8.2.10. Proportion of Responders

For the proportion of subjects who are responders, a logistic regression model that adjusts for baseline pain (as a continuous covariate) and treatment arm will be used to evaluate the treatment effect. As a measure of treatment effect for each of the PR and IR groups versus placebo, odds

ratios together with a 95% CI and p-values will be presented.

8.2.11. Numeric rating scale (NRS) pain intensity difference (PID)

PID at each time point will be calculated using the formula specified in Section 6.1.7, with pain scores recorded after rescue medication handled using the windowed WOCF method described in Section 6.1.5. Pain scores that are missing (assessment not performed or subject withdrew) will not be replaced. PID at each timepoint will be analyzed in a mixed model for repeated measures (MMRM) ANCOVA analysis. The model will include treatment, timepoint, treatment by timepoint, baseline and baseline by timepoint as fixed effects, and subject as a random effect. An unstructured covariance matrix will be used to model the within-subject correlations by timepoint. If the model fails to converge, alternative covariance structures, such as compound symmetry, will be tried instead. The model will be used to show estimated treatment effects at each timepoint. The LS mean and SE for each treatment group will be estimated and the difference in LS means and 95% CI for the comparison of placebo with the IR and PR treatment regimens will be estimated. P-values will be reported but no formal statistical inferences will be made on the basis of these tests. Descriptive summaries (including mean, SD, median, minimum and maximum) will be presented by treatment group.

Pain intensity is measured using NRS at planned assessment time points. Descriptive summaries (including mean, SD, median, minimum and maximum) will also be presented by treatment group. Pain scores recorded after rescue medication will be handled using the windowed WOCF method described in Section 6.1.5. Pain scores that are missing (assessment not performed or subject withdrew) will not be replaced.

8.2.12. Pain relief at each scheduled time point

Pain relief scores at each scheduled time point will be summarized using descriptive statistics (including mean, SD, median, minimum and maximum) as well as counts (and percentages) for each pain relief score by treatment group. Pain relief scores recorded after rescue medication will be handled using the windowed WOCF method described in Section 6.1.5. Pain relief scores that are missing (assessment not performed or subject withdrew) will not be replaced. Treatment comparison will be done in the following way:

- Pain relief category at each timepoint will also be analyzed using a repeated measures proportional odds model (an extension of the logistic regression). This method allows for an ordinal response variable with more than two categories. Here the categories none = 0, a little = 1, some = 2, a lot = 3, and complete = 4.This model will include the following covariate terms- treatment and baseline pain intensity (as a continuous covariate) timepoint, baseline by timepoint and treatment by timepoint. Subject will be the repeated measure in this model. For each of the PR and IR treatment regimens, the odds of being in a higher (better) pain relief category compared to placebo (odds ratio) will be presented with a 95% CI and associated p-value.

8.2.13. Proportion of Subjects Rescue Medication

The definition of rescue medication use is presented in Section 6.1.5. The proportion of subjects using rescue medication for pain will be analyzed using logistic regression. The logistic regression model will include treatment arm and baseline pain (as a continuous covariate) as covariates. As a measure of treatment effect for each of the PR and IR groups versus placebo, odds ratios together with a 95% CI and p-values will be presented.

8.3. Exploratory Efficacy Analysis

8.3.1. 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 a factor for treatment group and baseline pain intensity as a continuous covariate. For each of the PR and IR treatment regimens, the odds of being in a higher (better) evaluation category compared to placebo (odds ratio) will be presented with a 95% CI and associated p-value.

9. Safety and Tolerability Analysis

Safety will be evaluated from reported AEs, and changes in vital signs.

All safety analyses will be performed on the Safety population.

9.1. Adverse Events

> The number and percent of subjects reporting treatment emergent AEs, grouped by MedDRA system organ class and preferred term (coded using MedDRA v21.1), will be tabulated by severity and treatment group. In the case of multiple occurrences of the same TEAE within the same subject, each subject will only be counted once for each preferred term.

The frequency and percentage of subjects reporting TEAEs, grouped by MedDRA SOC and PT, will be tabulated by treatment group for the SAF. Such summaries will be displayed for the following:

- TEAEs by SOC and PT
- TEAEs by SOC, PT, and severity
- TEAEs by SOC, PT, and relationship to the study medication
- TEAEs leading to death by SOC, and PT
- Serious TEAEs other than deaths by SOC, and PT
- TEAEs leading to premature discontinuation by SOC, and PT
- Listing of non-TEAEs

In the case of multiple occurrences of the same AE within the same subject, each subject will only be counted once for each preferred term. In summaries of AE by SOC and PT, along with the number (%) of subjects with at least 1 AE in the category, the number of events will be

displayed. In the summaries showing severity and relationship to study medication the event with the maximum severity or strongest relationship will be reported. If a particular event is missing the severity and/or relationship, then the strongest possible severity or relationship will be assumed for analysis (severity = severe, relationship = certain).

Missing and partially missing AE start and/or stop dates will be imputed for the purpose of statistical analysis, according to the specifications described in Section 6.1.7.

In the AE data listings, all AEs will be displayed. AEs that are not treatment-emergent will be flagged.

9.1.1. Adverse Events Leading to Withdrawal

A summary of incidence rates (frequencies and percentages) of TEAEs leading to withdrawal of study drug, by treatment group, SOC, and preferred term will be prepared for the Safety Population. No inferential statistical tests will be performed.

A data listing of AEs leading to withdrawal of study drug will also be provided, displaying details of the event(s) captured on the CRF.

9.1.2. Deaths and Serious Adverse Events

Any deaths that occur during the study will be listed.

Serious adverse events will be listed and also tabulated by system organ class and preferred term and presented by treatment.

9.2. Clinical Safety Laboratory Data

Descriptive statistics for clinical safety laboratory data (laboratory data) recorded at screening will be presented overall and by treatment regimen. Summary tables by treatment regimen will be presented for each category of data separately. Routine clinical laboratory data will include hematology, serum chemistry, and urinalysis. Quantitative laboratory test result summaries will include N (population count for each regimen), n (number of subjects with non-missing values), mean, SD, median, and range. Qualitative tests (e.g., some urinalysis assessments) will be categorized accordingly. The set of laboratory parameters included in each table will correspond to those requested in the study protocol. Urine drug screen, alcohol breath analyzer and urine pregnancy test results will be presented in listings.

9.3. Vital Signs

Descriptive summaries of actual values and changes from baseline will be calculated for supine systolic blood pressure, supine diastolic blood pressure, heart rate, respiratory rate, and oral body temperature, and will be presented by treatment regimen. Summary statistics for 12-lead ECG parameters and counts for ECG interpretations at screening will be presented.

9.4. Concomitant Medication

Prior and concomitant medications will be summarized descriptively by treatment using counts and percentages.

Prior medications will be presented separately from concomitant medications. Medications that started prior to the first dose of study drug will be considered prior medications whether or not they were stopped prior to the first dose of study drug. Any medications continuing or starting post the first dose of study drug will be considered to be concomitant. If a medication starts prior to the first dose and continues after the first dose of study drug, it will be considered both prior and concomitant. Medications will be coded using March 2020 version of World Health Organization Drug Coding Dictionary (WHODD).

9.5. Rescue Medication use

The number of subjects taking rescue medication will be summarized by treatment group at the following post dose times -1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 10 hours, 12 hours, 16 hours and 24 hours. This will be done on the safety population.

10. Changes to analysis planned in the protocol

For the time to event endpoints an additional measure of the treatment effect comparing each of the active arms with placebo will be obtained by calculating a hazard ratio and 95% CI by fitting a Cox proportional hazards model with a factor for treatment group and baseline pain as a continuous covariate. The assumption of proportional hazards will first be evaluated.

There has been a clarification to the definition of the ITT population to that stated in the protocol. The ITT population is defined as all subjects who are treated with study drug and who have at least 1 pain assessment after Time 0. In the protocol the ITT population was defined as subjects who have at least 1 pain relief assessment.

11. References

1. ASA. (2016) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April 2016. http://www.amstat.org/about/ethicalguidelines.cfm
2. RSS. (2014) The Royal Statistical Society: Code of Conduct, 2014. http://www.rss.org.uk/Images/PDF/join-us/RSS-Code-of-Conduct-2014.pdf.
3. US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.
4. Ratitich, B. and O'Kelly, M.J. (2011). Implementation of Pattern-Mixture Models Using Standard SAS / STAT Procedures.
5. E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials

12. Tables, Listings, and Figures

All listings, tables, and graphs will have a header showing the sponsor company name and protocol and a footer showing the version of SAS, the file name and path, and the source of the data (CRF page or listing number).

12.1. Planned Table Descriptions

The following are planned summary tables for protocol number 5003601. The table numbers and page numbers are place holders only and will be determined when the tables are produced.

Table 3: Demographic Data Summary Tables

Table Number	Population	Table Title/Summary
14.1 Displays of Demographics and Disposition Data		
Table 14.1.1	All Subjects	Subject Disposition
Table 14.1.2	Safety Population	Demographics and Baseline Characteristics
Table 14.1.2.1	ITT Population	Demographics and Baseline Characteristics
Table 14.1.3	Safety Population	Medical History
Table 14.1.4	Safety Population	Prior Medications
Table 14.1.5	Safety Population	Concomitant Medications
Table 14.1.6	All Enrolled Subjects	Summary of Protocol Deviations
Table 14.1.7	Safety Population	Summary of Study Drug Exposure

12.2. Efficacy Data

Table 4: Efficacy Tables

Table Number	Population	Table Title/Summary
14.2.1	ITT Population	Analysis of SPID-12 Scores
14.2.1.1	PP Population	Analysis of SPID-12 Scores- Sensitivity Analysis 1
14.2.1.2	ITT Population	Analysis of SPID-12 Scores- Sensitivity Analysis 2-WOCF
14.2.1.3	ITT Population	Analysis of SPID-12 Scores- Sensitivity Analysis 3-No Rescue Adjustment
14.2.1.	ITT Population	Analysis of SPID-12 Scores- Sensitivity Analysis 4a-Rescue WOCF
14.2.1.5	ITT Population	Analysis of SPID-12 Scores- Sensitivity Analysis 4b-Rescue LOCF
14.2.1.6	ITT Population	Analysis of SPID-12 Scores- Sensitivity Analysis 4c-Multiple Imputation-Rescue Medication-MAR
14.2.1.7	ITT Population	Analysis of SPID-12 Scores- Sensitivity Analysis 5-Multiple Imputation-PMM
14.2.1.8	ITT Population	Analysis of SPID-12 Scores- Sensitivity Analysis 6-Multiple Imputation-MAR
14.2.1.9	ITT Population	Summary of SPID-12 Scores by Baseline Pain Category
14.2.2	ITT Population	Analysis of Summed Pain Intensity Difference Scores
14.2.2.1	ITT Population	Analysis of SPID-24 Scores- Sensitivity Analysis 7-No Rescue Adjustment
14.2.2.2	ITT Population	Analysis of SPID-24 Scores- Sensitivity Analysis 8-Multiple Imputation-MAR
14.2.3	ITT Population	Analysis of Total Pain Relief Scores
14.2.4	ITT Population	Analysis of Summed Pain Relief and Intensity Difference Scores
14.2.5	ITT Population	Comparison of SPID-24 in Ibuprofen PR and IR arms
14.2.5.1	ITT Population	Comparison of SPID-24 in Ibuprofen PR and IR arms-Sensitivity Analysis 7-No Rescue Adjustment
14.2.5.2	ITT Population	Comparison of SPID-24 in Ibuprofen PR and IR arms- Sensitivity Analysis 8-Multiple Imputation-MAR
14.2.6	ITT Population	Summary of Peak Pain Relief
14.2.7	ITT Population	Time to First Perceptible Pain Relief
14.2.8	ITT Population	Time to Meaningful Pain Relief
14.2.9	ITT Population	Time to Onset of Analgesia
14.2.10	ITT Population	Time to Peak Pain Relief
14.2.11	ITT Population	Time to First use of Rescue Medication
14.2.12	ITT Population	Proportion of Subjects Using Rescue Medication
14.2.13	ITT Population	Proportion of Responders

14.2.14	ITT Population	Summary of NRS Pain Intensity Difference Score
14.2.15	ITT Population	Summary of Pain Intensity Score at each Scheduled Time Point
14.2.16	ITT Population	Summary of Pain Relief at each Scheduled Time Point
14.2.17	ITT Population	Analysis of Patient Global Evaluation of Study Drug

12.3. Safety Data

Table 5: Safety Tables

Table Number	Population	Table Title/Summary
14.3.1 Summary of Treatment Emergent Adverse Events		
Table 14.3.1.1	Safety Population	Overall Summary of Treatment-Emergent Adverse Events
Table 14.3.1.2	Safety Population	Summary of Treatment-Emergent Adverse Events
Table 14.3.1.3	Safety Population	Summary of Treatment-Emergent Adverse Events by Maximum Severity
Table 14.3.1.4	Safety Population	Summary of Treatment-Emergent Adverse Events by Relationship to Study Drug
Table 14.3.1.5	Safety Population	Summary of Non-Serious Treatment-Emergent Adverse Events
14.3.2 Summary of Deaths, Other Serious and Significant Adverse Events		
Table 14.3.2.1	Safety Population	Summary of Serious Adverse Events
Table 14.3.2.2	Safety Population	Summary of Treatment Emergent Adverse Events Leading to Discontinuation
14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events		
Table 14.3.3.1	Safety Population	Listing of Serious Adverse Events
Table 14.3.3.2	Safety Population	Listing of Treatment Emergent Adverse Events Leading to Study Drug Discontinuation
14.3.4 Abnormal Laboratory Value		
Table 14.3.4.1	Safety Population	Listing of Potentially Clinically Significant Abnormal Laboratory Values
14.3.5 Laboratory Data Summary Tables		
Table 14.3.5.1	Safety Population	Summary of Serum Chemistry Laboratory Results
14.3.6 Other Safety Data Summary Tables		
Table 14.3.6.1	Safety Population	Summary of Vital Signs
Table 14.3.6.2	Safety Population	Summary of Electrocardiogram (ECG) Interpretations
Table 14.3.6.3	Safety Population	Summary of 12-Lead Electrocardiogram (ECG) Parameters
Table 14.3.6.4	Safety Population	Summary of Physical Examination Findings
Table 14.3.6.5	Safety Population	Rescue Medication use

12.4. Planned Listing Descriptions

The following are planned data and patient/subject data listings for protocol number 5003601.

In general, one listing will be produced per CRF domain. All listings will be sorted by treatment, site, and subject number. All calculated variables will be included in the listings.

In all listings a blank line will be placed between each subject. Within a data listing, if an item appears line after line (e.g., repetition of subject number), then only the first occurrence will be displayed.

In data listings, the information for one subject will be kept on one page if at all possible, rather than splitting a subject's information across pages.

Table 6: Planned Listings

Data Listing Number	Population	Data Listing Title / Summary
16.2.1 Subject Discontinuations/Completions		
Listing 16.2.1	All Subjects	Subject Disposition
16.2.2 Protocol Deviations		
Listing 16.2.2.1	All Subjects	Eligibility Criteria Not Met
Listing 16.2.2.2	All Subjects	Screen Failures
Listing 16.2.2.3	All Subjects	Protocol Deviations
16.2.3 Subjects in Analysis Populations		
Listing 16.2.3	All Subjects	Analysis Populations
16.2.4 Demographic Data and Other Baseline Characteristics		
Listing 16.2.4.1	Safety Population	Demographics and Baseline Characteristics
Listing 16.2.4.2	Safety Population	Medical History
Listing 16.2.4.3	All Randomized Subjects	Listing of Subject Randomization
Listing 16.2.4.4	Safety Population	Study Drug Administration
16.2.7 Adverse Event Listings (by Subject)		
Listing 16.2.7.1	Safety Population	Adverse Events
Listing 16.2.7.2	Safety Population	Serious Adverse Events
Listing 16.2.7.3	Safety Population	Treatment emergent Adverse Events Related to Study Drug
Listing 16.2.7.4	Safety Population	Deaths
16.2.8 Laboratory Values by Subject		
Listing 16.2.8.1	Safety Population	Clinical Laboratory Data: Serum Chemistry
Listing 16.2.8.2	Safety Population	Clinical Laboratory Data: Hematology
Listing 16.2.8.3	Safety Population	Clinical Laboratory Data: Urine
Listing 16.2.8.4	Safety Population	Clinical Laboratory Data: Coagulation
Listing 16.2.8.5	Safety Population	Serum and Urine Pregnancy Test
16.2.9 Other Clinical Observations and Measurements (by Subject)		
Listing 16.2.9.1	Safety Population	Prior and Concomitant Medications
Listing 16.2.9.1.1	Safety Population	Rescue Medications
Listing 16.2.9.2	Safety Population	Vital Signs Measurements
Listing 16.2.9.2.1	Safety Population	Physical Examination Findings
Listing 16.2.9.3	Safety Population	12-lead Electrocardiogram Measurements
Listing 16.2.9.3.1	Safety Population	Alcohol Breathalyzer Test
Listing 16.2.9.4	Safety Population	NRS Pain Intensity Assessment

Data Listing Number	Population	Data Listing Title / Summary
Listing 16.2.9.5	Safety Population	Pain Relief Scores
Listing 16.2.9.6	Safety Population	Time to Pain Relief (Stopwatches)
Listing 16.2.9.7	Safety Population	Subjects Global Evaluation of Study Drug

12.5. Planned Figure Descriptions

The following are planned summary figures for protocol number 5003601. The figure numbers and page numbers are place holders only and will be determined when the figures are produced.

Table 7: Planned Figures

Figure Number	Population	Figure Title / Summary
Figure 14.4.1.1	ITT Population	Kaplan-Meier Plot of Time to First Perceptible Pain Relief
Figure 14.4.1.2	ITT Population	Kaplan-Meier Plot of Time to Meaningful Pain Relief
Figure 14.4.1.3	ITT Population	Kaplan-Meier Plot of Time to Onset Of Analgesia
Figure 14.4.1.4	ITT Population	Kaplan-Meier Plot of Time to Peak Pain Relief
Figure 14.4.1.5	ITT Population	Kaplan-Meier Plot of Time to First Use Of Rescue Medication
Figure 14.4.1.6	ITT Population	Mean Pid Scores versus Time
Figure 14.4.1.7	ITT Population	Mean Pain Relief Scores versus Time

Appendix 1: Premier Research Library of Abbreviations

Abbreviation	Definition
aCRF	annotated case report form
AE	adverse event
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
BMI	body mass index
BSL	biostatistician lead
CCGs	CRF completion guidelines
CDISC	clinical data interchange standards consortium
CEC	central ethics committee
CFR	code of federal regulations
CI	confidence intervals
CM	clinical manager
CMP	clinical monitoring plan
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CS	clinically significant
CSR	clinical study report

Abbreviation	Definition
CTA	clinical trial administrator
CTM	clinical trial manager
CTMS	clinical trial management system
DB	database
DBL	database lock
DM	data management
DMB	data monitoring board
DMC	data monitoring committee
DMP	data management plan
DSMB	data safety monitoring board
DSP	data safety plan
DSUR	development safety update report
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
eTMF	electronic trial master file
EU	European Union
FDA	food and drug administration
FPI	first patient in
GCP	good clinical practice
HR	heart rate

Abbreviation	Definition
IB	investigator's brochure
IC or ICF	informed consent or informed consent form
ICH	international council for harmonization
IP	investigational product
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LPI	last patient in
LPLV	last patient last visit
LPO	last patient out
MedDRA	medical dictionary for regulatory activities
MHRA	medicines and healthcare products regulatory agency
MM	medical monitor
MMP	medical monitoring plan
MMRM	mixed effect model repeat measurement
N	number
NA	not applicable
NCS	non-clinically significant
NF	non-functional

Abbreviation	Definition
PD	protocol deviation
PDGP	protocol deviation guidance plan
PE	physical examination
PI	principal investigator
PK	pharmacokinetic
PKAP	pharmacokinetic analysis plan
PM	project manager
PMP	project management plan
PP	per-protocol
PS	project specialist
PV	pharmacovigilance
PVG	pharmacovigilance group
QA	quality assurance
QARC	quality assurance, risk and compliance
QC	quality control
QOL	quality of life
SAE	serious adverse event
SAF	Safety Population
SAP	statistical analysis plan
SAS®	a software system used for data analysis
SBP	systolic blood pressure

Abbreviation	Definition
SD	standard deviation
SDS	study design specifications
SDTM	study data tabulation model
SF	screen failure
SFT or SFTP	secure file transfer or secure file transfer plan
SIV	site initiation visit
SMP	safety management plan
SOC	system organ class
TEAE	treatment-emergent adverse event
TMF	trial master file
UAT	user acceptance testing
WHO	world health organization
WHO-DD	world health organization drug dictionary
WOCF	worst observation carried forward

Sponsor	Reckitt Benckiser
Protocol Title:	A Randomized, Double-Blind, Double-Dummy, Parallel-Group, Multiple-Dose, Active and Placebo-Controlled Efficacy Study of Ibuprofen Prolonged-Release Tablets for the Treatment of Pain after Surgical Removal of Impacted Third Molars
Protocol Number:	5003601
Premier Research PCN:	RECK.177035
Document Version:	Amendment 2.0
Document Date:	18-May-2020

Approvals

Role	Signatures	Date (dd-Mmm-yyyy)
Biostatistician Premier Research	Print Name: Raghu Vishnubhotla Sign Name: DocuSigned by: Raghu Srinivas Vishnubhotla Signer Name: Raghu Srinivas Vishnubhotla Signing Reason: I am the author of this document Signing Time: 19-May-2020 | 22:39:24 EDT 46FE4E466250408E961764121635BB48	19-May-2020 | 22:39:31 EDT
Reckitt Benckiser Representative	Print Name: Darren Targett Sign Name: DTargett	19-MAY-2020

1.1. Planned Table Shells

Table 14.1.1
Subject Disposition
All Randomized Subjects

Disposition	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Study Populations [1]				
Screened				XXX
Safety Population	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
ITT Population	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Per-Protocol Population	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Completion Status [2]				
Completed Study	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Prematurely Discontinued Study Medication	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Prematurely Discontinued Study	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Reasons for discontinuation from Study				
Lost to Follow-up	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Protocol Violation	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Adverse Event	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Non-Compliance with Study Drug	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Death	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Lack of Efficacy	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Withdrawal by Subject	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Pregnancy	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Physician Decision	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Study Terminated by Sponsor	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Other	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Abbreviation: ITT= Intent-to-Treat
[1] Percentages are based on the number of randomized subjects.
[2] Percentages are based on the number of subjects in the Safety Population.
Source: Listing 16.2.1

Table 14.1.2
Demographics and Baseline Characteristics
Safety Population

Variable Statistic or Category	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Age (years)				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
Gender				
Male	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Female	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Ethnicity				
Hispanic or Latino	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Not Hispanic or Latino	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Missing/Not Answered	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Race				
American Indian/Alaska Native	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Asian	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Black or African-American	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Native Hawaiian or Other Pacific Islander	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
White	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Missing/Not Answered	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Baseline Pain [1]				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
Baseline Pain Category [2]				
Moderate	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Severe	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Height (cm)				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X

Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
Weight (kg)				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
BMI (kg/m2)				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
Surgery Duration (min)				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX

Abbreviation: BMI=Body Mass Index
Note: Percentage are based on the number of subjects in the Safety Population.
[1] Subjects rate their pain using a numeric rating scale (NRS) from 0 (no pain) to 10 (worst pain ever).
[2] NRS pain scores at baseline are categorized as moderate (5-7), and severe (8-10).

Source: Listing 16.2.4.1

Table 14.1.2.1
Demographics and Baseline Characteristics
ITT Population
Use Same Shell as Table 14.1.2
Programming Note- Update footnote Note: Percentage are based on the number of subjects in the ITT Population.

Table 14.1.3
Medical History
Safety Population

System Organ Class Preferred Term	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with at least One Recorded Medical History	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 1				
Preferred Term 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Notes: Percentages are based on number of subjects in the Safety Population.
Medical conditions were coded using MedDRA version 23.0 or later. Subjects were counted once for each system organ class (SOC) and once for each preferred term (PT). Medical history terms are displayed by descending frequency of SOC, then PT within SOC, and then alphabetically by PT.
SOURCE: Listing 16.2.4.2
Programming Note- Uncoded terms, if any, will be at the bottom of the table. They will have labels' Not Coded' for SOC and PT

Table 14.1.4
Prior Medications
Safety Population

ATC Class Level 4 Preferred Term (ATC Class Level 5)	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with at least one Prior Medication	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
ATC Class 1				
Preferred Term 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
ATC Class 2				
Preferred Term 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Notes: Percentages are on number of subjects in the Safety Population.
Medications are coded using WHO-DD B2E version March 2020.
Medications that started prior to the first dose of study drug will be considered prior medications whether or not they were stopped prior to the first dose of study drug.. Medications are displayed by descending frequency of Anatomic Therapeutic Chemical (ATC) Level 4 classification, by Preferred Term (PT) within ATC and then alphabetically.
Subjects were counted only once for each ATC and PT.
SOURCE: Listing 16.2.9.1

Table 14.1.5
Concomitant Medications
Safety Population
Use same shell as Table 14.1.4
Use this footnote for definition of concomitant medications- Any medications continuing or starting post the first dose of study drug will be considered as concomitant medications.

Table 14.1.6
Summary of Protocol Deviations
All Enrolled Subjects

Deviation Category Type of Deviation	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with any Protocol Deviation	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Subjects with Major Protocol Deviations	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Type of Protocol Deviation				
Deviation type 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Deviation type 2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
.....				
Subjects with Minor Protocol Deviations	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Type of Protocol Deviation				
Deviation type 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Deviation type 2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
....				

Notes: Subjects with one or more deviations within a deviation category (Major/Minor) or type of deviation were counted only once.
Percentages are based on number of all enrolled subjects.
SOURCE: Listing 16.2.2.3

Table 14.1.7
Summary of Study Drug Exposure
Safety Population

Category Statistic	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
Number of Tables Taken			
n	XX	XX	XX
Mean	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX
Number of Active Doses Taken [1]			
n	XX	XX	
Mean	XX.X	XX.X	
Std Dev	XX.XX	XX.XX	
Median	XX.X	XX.X	
Min, Max	XX, XX	XX, XX	
Quantity of Active Drug Taken (mg)			
n			
Mean	XX.X	XX.X	
Std Dev	XX.XX	XX.XX	
Median	XX.X	XX.X	
Min, Max	XX, XX	XX, XX	
Treatment Duration (Hours) [2]			
n	XX	XX	XX
Mean	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX

Note: Percentages are based on number of all enrolled subjects.
[1] Active dose is a dose where the tablet taken has an active ingredient
[2] Duration = date/time of last dose administered – date/time of first dose administered
SOURCE: Listing 16.2.4.4.1

Table 14.3.1.1
Overall Summary of Treatment Emergent Adverse Events
Safety Population

	Ibuprofen PR (N=XX)	Ibuprofen PR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with at least one TEAE	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
TEAE by Maximum Severity				
Mild	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Moderate	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Severe	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
TEAE by Strongest Relationship				
Unassessable/Unclassifiable	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Conditional/Unclassified	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unrelated	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unlikely	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Possible	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Probable	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Certain	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
AE leading to Discontinuation	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
SAE	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
AE leading to Death	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Abbreviations: TEAE = Treatment Emergent Adverse Event; SAE = Serious Adverse Event.
Notes: Percentages are based on number of subjects in the safety population..
TEAE is defined as any event that started or worsened in intensity or relationship to treatment on or after the first dose of study drug. Strongest possible severity or relationship will be assumed for TEAES with missing severity and/or relationship (severity=severe, relationship=certain)

SOURCE: Listing 16.2.7.1

Table 14.3.1.2
Summary of Treatment Emergent Adverse Events
Safety Population

System Organ Class Preferred Term	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with at least One TEAE	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]
System Organ Class 1				
Preferred Term 1	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]
Preferred Term 2	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]
Preferred Term 3	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]
System Organ Class 2				
Preferred Term 1	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]
Preferred Term 2	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]
Preferred Term 3	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]

Abbreviations: TEAE = Treatment Emergent Adverse Event.
Notes: The first number (n) corresponds to the count of unique subjects and percentage, while the second is the count of the number of events.

Percentages are based on number of subjects in the safety population. Subjects were counted only once for each System Organ Class (SOC) or Preferred Term.
TEAE is defined as any event that started or worsened in intensity or relationship to treatment on or after the first dose of study drug.
AEs were coded using MedDRA version 23.0.

SOURCE: Listing 16.2.7.1
Programmers Note- Ensure there is some space between the Number of subject (%) count and the number of events in the table

Table 14.3.1.3
Summary of Treatment Emergent Adverse Events by Maximum Severity
Safety Population

System Organ Class Preferred Term Maximum Severity [1]	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with at least One TEAE				
Mild	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Moderate	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Severe	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 1				
Mild	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Moderate	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Severe	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 1				
Mild	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Moderate	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Severe	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Abbreviations: TEAE = Treatment Emergent Adverse Event; SAE = Serious Adverse Event.
[1] The severity shown is the greatest severity reported for a particular subject (Severe > Moderate > Mild). AEs with missing severity have been classified as Severe.
Notes: Percentages are based on number of subjects in the safety population. Subjects were counted only once for each System Organ Class (SOC) or Preferred Term. TEAE is defined as any event that started or worsened in intensity or relationship to treatment on or after the first dose of study drug. AEs were coded using MedDRA version 23.0.
SOURCE: Listing 16.2.7.1

Table 14.3.1.4
Summary of Treatment Emergent Adverse Events by Relationship to Study Drug
Safety Population

System Organ Class Preferred Term Greatest Relationship [1]	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with at least One TEAE	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unassessable/Unclassifiable	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Conditional/Unclassified	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unrelated	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unlikely	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Possible	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Probable	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Certain	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unassessable/Unclassifiable	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Conditional/Unclassified	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unrelated	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unrelated	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unlikely	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Possible	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Probable	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Certain	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unassessable/Unclassifiable	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Conditional/Unclassified	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unrelated	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unrelated	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unlikely	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Possible	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Probable	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Certain	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

[1] AE relation is marked in the CRF. The relationship shown is the strongest relationship reported for a particular subject. AEs with missing relationship have been classified as Certain.
Abbreviations: TEAE = Treatment Emergent Adverse Event.
Notes: Percentages are based on number of subjects in the safety population.. Subjects were counted only once for each System Organ Class (SOC) or Preferred Term. TEAE is defined as any event that started or worsened in intensity or relationship to treatment on or after the first dose of study drug.. AEs were coded using MedDRA version 23.0.
SOURCE: Listing 16.2.7.1

Table 14.3.1.5
Summary of Non-Serious Treatment Emergent Adverse Events
Safety Population

System Organ Class Preferred Term	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with at least one non-serious TEAE	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
System Organ Class 1				
Preferred Term 1	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 2	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 3	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
System Organ Class 2				
Preferred Term 1	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 2	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 3	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X

Abbreviations: TEAE = Treatment Emergent Adverse Event.

Notes: The first number (n) corresponds to the count of unique subjects and percentage, while the second is the count of the number of events. Percentages are based on number of subjects in the safety population.. Subjects were counted only once for each System Organ Class (SOC) or Preferred Term.. TEAE is defined as any event that started or worsened in intensity or relationship to treatment on or after the first dose of study drug. AEs were coded using MedDRA version 23.0.

SOURCE: Listing 16.2.7.1
Programmers Note- Ensure there is some space between the Number of subject (%) count and the number of events in the table

Table 14.3.2.1
Summary of Serious Adverse Events
Safety Population

System Organ Class Preferred Term	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with at least one SAE	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
System Organ Class 1				
Preferred Term 1	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 2	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 3	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
System Organ Class 2				
Preferred Term 1	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 2	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 3	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X

Abbreviation: SAE = Serious Adverse Event.
Notes: The first number (n) corresponds to the count of unique subjects and percentage, while the second is the count of the number of events.
Percentages are based on number of subjects in the safety population. Subjects were counted only once for each System Organ Class (SOC) or Preferred Term.

AEs were coded using MedDRA version 23.0.
SOURCE: Listing 16.2.7.1

Programmers Note- Ensure there is some space between the Number of subject (%) count and the number of events in the table

Table 14.3.2.2
Summary of Treatment Emergent Adverse Events Leading to Study Drug Discontinuation
Safety Population

System Organ Class Preferred Term	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with at least one TEAE that led to study drug discontinuation	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
System Organ Class 1				
Preferred Term 1	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 2	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 3	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
System Organ Class 2				
Preferred Term 1	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 2	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 3	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X

Abbreviation: TEAE = Treatment Emergent Adverse Event.

Notes: The first number (n) corresponds to the count of unique subjects and percentage, while the second is the count of the number of events.
Percentages are based on number of subjects in the safety population. Subjects were counted only once for each System Organ Class (SOC) or Preferred Term.
TEAE is defined as any event that started or worsened in intensity or relationship to treatment on or after the first dose of study drug.
AEs were coded using MedDRA version 23.0.

SOURCE: Listing 16.2.7.1

Programmers Note- Ensure there is some space between the Number of subject (%) count and the number of events in the table

Table 14.3.3.1
Listing of Serious Adverse Events
Safety Population

Subject ID	Treatment Group	Gender	Age (years)	SAE	System Organ Class/ Preferred Term/ Verbatim Term	Start Date/Time (Study Day)/ End Date/Time (Study Day)	Severity/ Causality	Outcome/ Action Taken
XXXX		M	XX	XXXX XXXX	XXXX/XXX/XXX	DDMMMYYYY/THH:MM (XX)/ DDMMMYYYY/THH:MM (XX)	MILD/Related	XXX/XXX

Abbreviation: SAE = Serious adverse event.
Note: AEs were coded using MedDRA version 23.0.
Study day is calculated relative to the date of first dose of study drug.
Source: Listing 16.2.7.2

Table 14.3.3.2
Listing of Treatment Emergent Adverse Events Leading to Study Drug Discontinuation
Safety Population

Subject ID	Treatment Group	Gender	Age (Years)	TEAE	System Organ Class/ Preferred Term/ Verbatim Term	Start Date/Time (Study Day)/ End Date/Time(Study Day)	Severity/ Causality	Outcome/ Action Taken
XXXX	XX	F	XX	XXXX	XXXX/XXX/XXX	DDMMMYYYYTHH:MM (XX)/ DDMMMYYYYTHH:MM (XX)	MILD/Related	XXX/XXX
XXXX	XX	M		XXXX	XXXX/XXX/XXX	DDMMMYYYYTHH:MM (XX)/ DDMMMYYYYTHH:MM (XX)	MILD/Related	XXX/XXX

Abbreviations: TEAE = Treatment Emergent Adverse Event.
Notes: AEs were coded using MedDRA version 23.0.
TEAE is defined as any event that started or worsened in intensity or relationship to treatment on or after the first dose of study drug. Study day is calculated relative to the date of first dose of study drug.

Source: Listing 16.2.7.1

Table 14.3.4.1
Listing of Potentially Clinically Significant Abnormal Laboratory Values
Safety Population

Subject Number	Treatment Group	Gender	Age (Years)	Lab Category	Lab Parameter (Units)	Parameter Value	Reference Range	Test Result Assessment	Date/Time of Collection (Study Day)
XXXX	XX	M	XX	Hematology	Hemoglobin	XXXXX	XX-XX	High/Low	XXXXX(XX)
					Haematocrit	XXXX			

Abbreviation: NA=Not ApplicableNotes: Study day is calculated relative to the date of first dose of study drug.
Source: Listings 16.2.8.1, 16.2.8.2, 16.2.8.3, 16.2.8.4
Programming note- Category will be Hematology/Chemistry/Urinalysis/Coagulation. Sort by subject id, treatment group, and paramn.

Table 14.3.5.1
Summary of Clinical Laboratory Results
Safety Population

Lab Category: Chemistry/Hematology/Urinalysis

Parameter:XXXX Visit/ Statistic	Iburprofen PR (N=XX)	Iburprofen PR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Lab Parameter: XXXXX				
Screening				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX

Notes- Clinical laboratory tests (hematology, chemistry, urinalysis) tests are only done at Screening.

SOURCE: Listing 16.2.8.1, 16.2.8.2, 16.2.8.3, 16.2.8.4
Programming Note- Lab Category is Hematology or Chemistry or Urinalysis or Coagulation

Table 14.3.6.1
Summary of Vital Signs
Safety Population

Parameter:XXXXX

Visit/ Statistic	Iburprofen PR (N=XX)	Iburprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Baseline				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
12 hours				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
Change from Baseline to 12 hours				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
…….				

Notes- Baseline is defined as the last observation recorded prior to the first dose.
Programming Note- Calculate summary stats and change from baseline for 12 hours, 24 hours and Day 8/ET visit.
Source:Listing 16.2.9.2

Table 14.3.6.2
Summary of Electrocardiogram (ECG) Interpretations
Safety Population

Visit Category	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Screening				
Normal	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Abnormal - CS	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Abnormal - NCS	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Abbreviations: CS = clinically significant; NCS = not clinically significant

SOURCE: Listing 16.2.9.3

Table 14.3.6.3
Summary of 12-Lead Electrocardiogram (ECG) Parameters
Safety Population

Parameter: XXXXXX

Visit/ Statistic	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Screening				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX

SOURCE: Listing 16.2.9.3.

Table 14.3.6.4
Summary of Physical Examination Findings
Safety Population

Body System=XXXXXX

Visit Category	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Visit				
Normal	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Abnormal - CS	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Abnormal - NCS	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
.....				

Abbreviations: CS = clinically significant; NCS = not clinically significant ET: end of treatment

SOURCE: Listing 16.2.9.3

Table 14.3.6.5
Rescue Medication Use
Safety Population

Any rescue medication	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Total
At Any time	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
In the first 1 hour after dosing	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
In the first 2 hours after dosing	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
.....				

Note: At each level of summarization subjects taking multiple rescue medication are counted only once. Percentage is based on number of subjects in the safety population.
Programming note- Please complete table for the following time points 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 10 hours, 12 hours, 16 hours and 24 hours.

Table 14.2.1
Analysis of SPID-12 Scores
ITT Population

Statistics	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
n	XX	XX	XX
Mean	XX.XX	XX.XX	XX.XX
Std Dev	XX.XXX	XX.XXX	XX.XXX
Median	XX.XX	XX.XX	XX.XX
Min, Max	XX.X,XX.X	XX.X,XX.X	XX.X,XX.X
ANCOVA Statistics[1]			
LS Mean (SE)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)
LS Mean Difference from Placebo (95% CI)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	
p-value	0.XXXX	0.XXXX	
.....			

Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error.
[1] Estimates are from an analysis of covariance model with SPID-12 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.
Notes: SPID-12 is summed pain intensity difference (SPID) over 0 to 12 hours. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Baseline pain is also recorded using the NRS scale. For subjects who use rescue medication, windowed worst observation carried forward (WOCF) is used. Missing intermediate pain assessments imputed by linear interpolation. Missing pain assessments due to premature discontinuation imputed by LOCF.

Source: Listing 16.x.xx

Table 14.2.1.1
Analysis of SPID-12 Scores – Sensitivity Analysis 1
PP Population

(Same Shell as Table 14.2.1)

Table 14.2.1.2
Analysis of SPID-12 Scores- Sensitivity Analysis 2-WOCF
ITT Population
(Same Shell as Table 14.2.1)

Please add these footnotes: Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error.

[1] Estimates are from an analysis of covariance model with SPID-12 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.

Note: SPID-12 is summed pain intensity difference (SPID) over 0 to 12 hours. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Baseline pain is also recorded using the NRS scale. For subjects who use rescue medication, windowed worst observation carried forward (WOCF) is used. Missing pain assessments imputed by WOCF

(Programming Note-This is sensitivity analysis # 2 in section 6.1.6 of the SAP.)

Table 14.2.1.3
Analysis of SPID-12 Scores- Sensitivity Analysis 3-No Rescue Adjustment
ITT Population
(Same Shell as Table 14.2.1)

Please add these footnotes: Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error.

[1] Estimates are from an analysis of covariance model with SPID-12 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.

Note: SPID-12 is summed pain intensity difference (SPID) over 0 to 12 hours. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Baseline pain is also recorded using the NRS scale. No adjustment made to pain scores after use of rescue medication. Missing intermediate pain assessments imputed by linear interpolation. Missing pain assessments due to premature discontinuation imputed by LOCF.

(Programming Note-This is sensitivity analysis # 3 in section 6.1.6 of the SAP.)

Table 14.2.1.4
Analysis of SPID-12 Scores- Sensitivity Analysis 4a-Rescue WOCF
ITT Population
(Same Shell as Table 14.2.1)

Please add these footnotes: Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error.

[1] Estimates are from an analysis of covariance model with SPID-12 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.

Note: SPID-12 is summed pain intensity difference (SPID) over 0 to 12 hours. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Baseline pain is also recorded using the NRS scale. Worst observation carried forward (WOCF) is used to impute all subsequent pain scores after first use of rescue medication. Missing intermediate pain assessments imputed by linear interpolation. Missing pain assessments due to premature discontinuation imputed by LOCF.

(Programming Note-This is sensitivity analysis # 4a in section 6.1.6 of the SAP.)

Table 14.2.1.5
Analysis of SPID-12 Scores- Sensitivity Analysis 4b-Rescue LOCF
ITT Population
(Same Shell as Table 14.2.1)

Please add these footnotes: Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error.
[1] Estimates are from an analysis of covariance model with SPID-12 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.
Note: SPID-12 is summed pain intensity difference (SPID) over 0 to 12 hours. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Baseline pain is also recorded using the NRS scale. Last observation carried forward (LOCF) is used to impute all subsequent pain scores after first use of rescue medication. Missing intermediate pain assessments imputed by linear interpolation. Missing pain assessments due to premature discontinuation imputed by LOCF.

(Programming Note-This is sensitivity analysis # 4b in section 6.1.6 of the SAP.)

Table 14.2.1.6
Analysis of SPID-12 Scores- Sensitivity Analysis 4c-Multiple Imputation-Rescue Medication-MAR
ITT Population
(Same Shell as Table 14.2.1)

Footnotes: Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error.
[1] Estimates are from an analysis of covariance model with SPID-12 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.
Note: SPID-12 is summed pain intensity difference (SPID) over 0 to 12 hours. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Baseline pain is also recorded using the NRS scale. All pain scores after rescue medication are imputed using an MCMC method under missing at random assumption. Intermediate pain assessments imputed by linear interpolation. Missing pain assessments due to premature discontinuation imputed by LOCF.

(Programming Note-This is sensitivity analysis # 4c in section 6.1.6 of the SAP.)

Table 14.2.1.7
Analysis of SPID-12 Scores- Sensitivity Analysis 5-Multiple Imputation-PMM
ITT Population
(Same Shell as Table 14.2.1)

Footnotes: Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error.
[1] Estimates are from an analysis of covariance model with SPID-12 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.
Note: SPID-12 is summed pain intensity difference (SPID) over 0 to 12 hours. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Baseline pain is also recorded using the NRS scale. For subjects who use rescue medication, windowed worst observation carried forward (WOCF) is used. Intermittent missing values are replaced by an MCMC method under a missing at random assumption. Missing pain assessments due to premature discontinuation are replaced using a pattern-mixture model with control-based imputation.

(Programming Note-This is sensitivity analysis # 5 in section 6.1.6 of the SAP.)

Table 14.2.1.8
Analysis of SPID-12 Scores- Sensitivity Analysis 6-Multiple Imputation-MAR
ITT Population
(Same Shell as Table 14.2.1)

Footnotes: Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error.
[1] Estimates are from an analysis of covariance model with SPID-12 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.
Note: SPID-12 is summed pain intensity difference (SPID) over 0 to 12 hours. Subjects rate their pain intensity using a numeric rating (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Baseline pain is also recorded using the NRS scale. Missing pain scores and values within the defined window after rescue medication are imputed using multiple imputation under the MAR assumption.

(Programming Note-This is sensitivity analysis # 5 in section 6.1.6 of the SAP.)

Table 14.2.1.9
Summary of SPID-12 Scores by Baseline Pain Category
ITT Population

Category/Statistic	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
Baseline Pain Category-Moderate			
n	XX	XX	XX
Mean	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX
Median	XX	XX	XX
Min, Max	XX,XX	XX,XX	XX,XX
.....			

Notes- SPID-12 is summed pain intensity difference (SPID) over 0 to 12 hours. Subjects will rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Baseline pain using a categorical scale that includes moderate (5-7), and severe (8-10). For subjects who use rescue medication, windowed worst observation carried forward (WOCF) is used. Missing intermediate pain assessments imputed by linear interpolation. Missing pain assessments due to premature discontinuation imputed by LOCF.

Programming Note- Please complete table for all baseline pain categories.

Table 14.2.2
Analysis of Summed Pain Intensity Difference Scores
ITT Population

Category/Statistics	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
SPID-4			
n	XX	XX	XX
Mean	XX.XX	XX.XX	XX.XX
Std Dev	XX.XXX	XX.XXX	XX.XXX
Median	XX.XX	XX.XX	XX.XX
Min, Max	XX.X,XX.X	XX.X,XX.X	XX.X,XX.X
ANCOVA Statistics[1]			
LS Mean (SE)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)
LS Mean Difference from Placebo (95% CI)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	
p-value	0.XXXX	0.XXXX	
.....			

Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error.
[1] Estimates are from an analysis of covariance model with SPID score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.
Notes: SPID-4/8/12 is summed pain intensity difference (SPID) over 0 to 4/8/12 hours. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Baseline pain is also recorded using the NRS scale. For subjects who use rescue medication, windowed worst observation carried forward (WOCF) is used. Missing intermediate pain assessments imputed by linear interpolation. Missing pain assessments due to premature discontinuation imputed by LOCF.

Programming Note- Please program for SPID-4 SPID-8 and SPID-24.

Source: Listing 16.x.xx

Table 14.2.2.1
Analysis of SPID-24 Scores- Sensitivity Analysis 7-No Rescue Adjustment
ITT Population
(Same Shell as Table 14.2.1)

Please add these footnotes: Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error.
[1] Estimates are from an analysis of covariance model with SPID-12 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.
Note: SPID-12 is summed pain intensity difference (SPID) over 0 to 12 hours. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Baseline pain is also recorded using the NRS scale. No adjustment made to pain scores after use of rescue medication. Missing intermediate pain assessments imputed by linear interpolation. Missing pain assessments due to premature discontinuation imputed by LOCF.

Table 14.2.2.2
Analysis of SPID-24 Scores- Sensitivity Analysis 8-Multiple Imputation-MAR
ITT Population
(Same Shell as Table 14.2.1)

Footnotes: Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error.
[1] Estimates are from an analysis of covariance model with SPID-12 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.
Note: SPID-24 is summed pain intensity difference (SPID) over 0 to 24 hours. Subjects rate their pain intensity using a numeric rating (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Baseline pain is also recorded using the NRS scale. Missing pain scores and values within the defined window after rescue medication are imputed using multiple imputation under the MAR assumption

Table 14.2.3
Analysis of Total Pain Relief Scores
ITT Population

(Programming Note- Use same shell as Table 14.2.2. Please add the following footnote defining sum of total pain relief (TOTPAR) Note- Total pain relief (TOTPAR) is summed total pain relief under the Pain Relief Scale (0 – 4) from 15 min through 4/8/12/24 hours)

Table 14.2.4
Analysis of Summed Pain Relief and Intensity Difference Scores
ITT Population
(Use same shell as Table 14.2.2)

Table 14.2.5
Comparison of SPID-24 in Ibuprofen PR and IR arms
ITT Population

Category/Statistics	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)
SPID-24		
ANCOVA Statistics[1]		
LS Mean (SE)	XX.XX (XX.XX)	XX.XX (XX.XX)
LS Mean Difference (95% CI)	XX.XX (XX.XX, XX.XX)	
p-value	0.XXXX	
…..		

Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error, SPID=summed pain intensity difference.
[1] Estimates are from an analysis of covariance model with SPID-24/TOTPAR-24/SPRID-24 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.
Notes-SPID-24 is summed pain intensity difference (SPID) over 0 to 24 hours. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. For subjects who use rescue medication, windowed worst observation carried forward (WOCF) is used. Missing intermediate pain assessments imputed by linear interpolation. Missing pain assessments due to premature discontinuation imputed by LOCF.

Table 14.2.5.1
Comparison of SPID-24 in Ibuprofen PR and IR arms-Sensitivity Analysis 7-No Rescue Adjustment
ITT Population

Use same shell as Table 14.2.5
Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error, SPID=summed pain intensity difference.
[1] Estimates are from an analysis of covariance model with SPID-24 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.
Notes-SPID-24 is summed pain intensity difference (SPID) over 0 to 24 hours. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. No adjustment made to pain scores after use of rescue medication. Missing intermediate pain assessments imputed by linear interpolation. Missing pain assessments due to premature discontinuation imputed by LOCF.

Table 14.2.5.2
Comparison of SPID-24 in Ibuprofen PR and IR arms-Sensitivity Analysis 8- Multiple Imputation
ITT Population

Use same shell as Table 14.2.5
Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error, SPID=summed pain intensity difference.
[1] Estimates are from an analysis of covariance model with SPID-24 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.
Notes-SPID-24 is summed pain intensity difference (SPID) over 0 to 24 hours. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10

= worst pain ever. No adjustment made to pain scores after use of rescue medication. Missing pain scores and values within the defined window after rescue medication are imputed using multiple imputation under the MAR assumption

Table 14.2.6
Summary of Peak Pain Relief
ITT Population

Category/Statistics	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
None	X (XX.X%)	X (XX.X%)	X (XX.X%)
A Little Relief	X (XX.X%)	X (XX.X%)	X (XX.X%)
Some Relief	X (XX.X%)	X (XX.X%)	X (XX.X%)
A lot of Relief	X (XX.X%)	X (XX.X%)	X (XX.X%)
Complete Relief	X (XX.X%)	X (XX.X%)	X (XX.X%)
Odds Ratio (vs placebo) [1]	XX.XX	XX.XX	
95% CI	(XX.XX,XX.XX)	XX.XX,XX.XX)	
p-value	0.XXXX	0.XXXX	

Abbreviations: CI=Confidence Interval
[1] From a proportional odds model treatment group and baseline pain as covariates. An odds ratio > 1 means that patients experienced higher pain relief than the placebo.
Notes- Subjects rate their pain relief relative to Time 0 using a 5-point categorical scale, none = 0, a little = 1, some = 2, a lot = 3, and complete = 4.

SOURCE: Listing 16.x.xx

Table 14.2.7
Time to First Perceptible Pain Relief
ITT Population

Category/Statistic	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
Number of Subjects with First Perceptible Pain Relief	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of Subjects Censored	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Time to first perceptible pain relief (hours) [1]			
Median (95% CI)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)
Q1	XX.XX	XX.XX	XX.XX
Q3	XX.XX	XX.XX	XX.XX
Range (Min-Max)	XX.X-XX.X	XX.X-XX.X	XX-XX
p-value (vs placebo) [2]	0.XXXX	0.XXXX	
Hazard Ratio (vs placebo) [3]	XX.XX	XX.XX	
95% CI	(XX.XX,XX.XX)	(XX.XX,XX.XX)	

Abbreviation- Q1- 25th Percentile, Q3- 75th Percentile
[1] From Kaplan-Meier Estimates
[2] From Log-rank/Wilcoxon test stratified by baseline pain
[3] Hazard Ratio calculated from Cox proportional hazards model with treatment group as a categorical factor and baseline pain as a continuous covariate. A hazard ratio of <1 means that patients in the Ibuprofen groups achieved pain relief faster than the placebo.
Notes- Time of first perceptible pain relief is the time of first reported pain relief as assessed by the subject (i.e. subject stops the first stopwatch (irrespective of the second stopwatch)). Pain scores at baseline are categorized as moderate (5-7), and severe (8-10).

Table 14.2.8
Time to Meaningful Pain Relief
ITT Population

Use same shell as Table 14.2.7
(Programmers Note- Please add the following footnote- Abbreviation- Q1- 25th Percentile, Q3- 75th Percentile
[1] From Kaplan-Meier Estimates.
[2] From Log-rank/Wilcoxon test stratified by baseline pain.
[3] Hazard Ratio calculated from Cox proportional hazards model with treatment group as a categorical factor and baseline pain as a continuous covariate. A hazard ratio of <1 means that patients in the Ibuprofen groups achieved pain relief faster than the placebo.
Notes- Time of meaningful pain relief is the time of the first reported meaningful (subjective) pain relief assessed by stopping the second stopwatch. Pain scores at baseline pain) are categorized as moderate (5-7), and severe (8-10

Table 14.2.9
Time to Onset of Analgesia
ITT Population

Category/Statistic	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
Number of Subjects with First Perceptible Pain Relief and Meaningful Pain Relief	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of Subjects Censored	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Time to onset of analgesia (hours) [1]			
Median (95% CI)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)
Q1	XX.XX	XX.XX	XX.XX
Q3	XX.XX	XX.XX	XX.XX
p-value (vs placebo) [2]	0.XXXX	0.XXXX	
p-value (PR vs IR) [2]	0.XXXX		
Range (Min-Max)	XX.X-XX.X	XX.X-XX.X	XX.X-XX.X
Hazard Ratio (95% CI) (vs placebo) [3]	XX.XX (XX.XX,XX.XX)	XX.XX (XX.XX,XX.XX)	
Hazard Ratio (95% CI) (PR vs IR) [4]	XX.XX (XX.XX,XX.XX)		

(Programmers Note- Please add the following footnote- Abbreviation- Q1- 25th Percentile, Q3- 75th Percentile
[1] From Kaplan-Meier Estimates
[2] From Log-rank/Wilcoxon test stratified by baseline pain.
[3] Hazard Ratio calculated from Cox proportional hazards model with treatment group as a categorical factor and baseline pain as a continuous covariate. If hazard ratio <1 means that patients in the Ibuprofen groups achieved pain relief faster than the placebo
[4] Hazard Ratio calculated from Cox proportional hazards model with treatment group as a categorical factor and baseline pain as a continuous covariate. If hazard ratio <1 means that patients in the PR group achieved pain relief faster than the IR.
Notes- If the subject has had meaningful pain relief (i.e., presses both stopwatches) then time to onset of analgesia is date/time when the first stopwatch is stopped. Pain scores at baseline are categorized as moderate (5-7), and severe (8-10).

Table 14.2.10
Time to Peak Pain Relief
ITT Population
Use same shell as Table 14.2.7

(Programmers Note- Please add the following footnote- Abbreviation- Q1- 25th Percentile, Q3- 75th Percentile
[1] From Kaplan-Meier Estimates
[2] From Log-rank/Wilcoxon test stratified by baseline pain.
[3] Hazard Ratio calculated from Cox proportional hazards model with treatment group as a categorical factor and baseline pain as a continuous covariate. A hazard ratio of <1 means

that patients in the Ibuprofen groups achieved pain relief faster than the placebo.
Note- Time of peak pain relief is the time when pain relief, which is measured on a scale from 0 (none)-4 (complete), is maximum. Subjects who do not experience any pain relief are censored at the time of their last pain assessment.

Table 14.2.11
Time to First use of Rescue Medication
ITT Population

Use same shell as Table 14.2.7

(Programmers Note- Please add the following footnote- Abbreviation- Q1- 25th Percentile, Q3- 75th Percentile
[1] From Kaplan-Meier Estimates
[2] From Log-rank/Wilcoxon test stratified by baseline pain.
[3] Hazard Ratio calculated from Cox proportional hazards model with treatment group as a categorical factor and baseline pain as a continuous covariate. A hazard ratio of >1 means that patients in the Ibuprofen groups refrained from taking rescue medication for longer than the placebo.

Notes- Subjects who do not take rescue medication are censored at the time of their last pain assessment.

Table 14.2.12
Proportion of Subjects Using Rescue Medication
ITT Population

Category/Statistic	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
Number of subjects using Rescue Medication	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Odds Ratio for Rescue Medication (Active/Placebo) [1]	XX.XX	XX.XX	
(95% CI)	(XX.XX,XX.XX)	(XX.XX,XX.XX)	
p-value	0.XXXX	0.XXXX	

Abbreviation: CI= Confidence Interval
[1] Odds ratio, CI, and p-value are from a logistic regression model estimating the probability of using rescue medication with baseline pain and treatment arm as covariates in the model. An odds ratio < 1 means patients in the Ibuprofen groups are less likely to have used rescue medication compared to those in placebo.

Table 14.2.13
Proportion of Responders
ITT Population

(Use same shell as 14.2.12. Please use footnote below.)

Abbreviation: CI=Confidence Interval
Notes- A subject with ≥ 30% improvement in NRS pain intensity from T0 (predose) without rescue medication during the first 8 hours is considered a responder.
[1] Odds ratio, CI, and p-value are from a logistic regression model estimating the probability of being a responder with baseline pain and treatment arm as covariates in the model. An odds ratio > 1 means patients in the Ibuprofen groups are more likely to be responders compared to those in placebo.

Table 14.2.14
Summary of NRS Pain Intensity Difference Score
ITT Population

	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
PID 15 mins after Time 0			
n	XX	XX	XX
Mean	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX
Median	XX	XX	XX
Min, Max	XX,XX	XX,XX	XX,XX
LS Mean Difference from Placebo (95% CI)[1]	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	
p-value (vs Placebo)	0.XXXX	0.XXXX	

Abbreviations: PID= Pain Intensity Difference NRS- Numeric Rating Scale.
Notes- Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Pain intensity difference score at a time point is the difference in NRS pain intensity from baseline to that time point. For subjects who use rescue medication, windowed worst observation carried forward (WOCF) is used. Missing data due to missing intermediate assessments or premature discontinuation is not imputed.
[1] From a repeated measures mixed model with treatment, timepoint, treatment by timepoint, baseline and baseline by timepoint as fixed effects, and subject as a random effect.

Programming Note- Please complete table for all scheduled time assessments. Only impute using wWOCF for assessments after rescue medication. Do not impute for missing data.

Table 14.2.15
Summary of Pain Intensity Score at each Scheduled Time Point
ITT Population
Use same shell as Table 14.2.14

(Programmers please add the following footnote-
Note- Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. For subjects who use rescue medication, windowed worst observation carried forward (WOCF) is used. Missing data due to missing intermediate assessments or premature discontinuation is not imputed.
Programming Note- Please complete table for all scheduled time assessments. No need for LS mean difference 95%CI and p value from 14.2.14 shell). Only impute using wWOCF for assessments after rescue medication. Do not impute for missing data.

Table 14.2.16
Summary of Pain Relief at each Scheduled Time Point
ITT Population

	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
Pain Relief 5 mins after Time 0			
n	XX	XX	XX
Mean	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX
Median	XX	XX	XX
Min, Max	XX,XX	XX,XX	XX,XX
None	X (XX.X%)	X (XX.X%)	X (XX.X%)
A Little Relief	X (XX.X%)	X (XX.X%)	X (XX.X%)
Some Relief	X (XX.X%)	X (XX.X%)	X (XX.X%)
A lot of Relief	X (XX.X%)	X (XX.X%)	X (XX.X%)
Complete Relief	X (XX.X%)	X (XX.X%)	X (XX.X%)
Odds Ratio (vs placebo) [1]	XX.XX	XX.XX	
95% CI	(XX.XX,XX.XX)	XX.XX,XX.XX)	
p-value	0.XXXX	0.XXXX	

(Programmers please add the following footnote-
1] From a repeated measures proportional odds model with treatment, timepoint, treatment by timepoint, baseline and baseline by timepoint as fixed effects, and subject as a random effect. An odds ratio > 1 means that patients experienced higher pain relief than the placebo.
Notes- Subjects rate their pain relief relative to Time 0 using a 5-point categorical scale, none = 0, a little = 1, some = 2, a lot = 3, and complete = 4. For subjects who use rescue medication, windowed worst observation carried forward (WOCF) is used. Missing data due to missing intermediate assessments or premature discontinuation is not imputed.

Programming Note- Please complete table for all scheduled time assessments. Only impute using wWOCF for assessments after rescue medication. Do not impute for missing data.

Table 14.2.17
Analysis of Patient Global Evaluation of Study Drug
ITT Population

Category/Statistics	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
Poor	X (XX.X%)	X (XX.X%)	X (XX.X%)
Fair	X (XX.X%)	X (XX.X%)	X (XX.X%)
Good	X (XX.X%)	X (XX.X%)	X (XX.X%)
Very Good	X (XX.X%)	X (XX.X%)	X (XX.X%)
Excellent	X (XX.X%)	X (XX.X%)	X (XX.X%)
Odds Ratio (vs placebo) [1]	XX.XX	XX.XX	
95% CI	(XX.XX,XX.XX)	XX.XX,XX.XX)	
p-value	0.XXXX	0.XXXX	

Notes- Patient's global evaluation of study drug is measured on a scale of 0=poor, 1=fair, 2=good, 3=very good, 4=excellent.
[1] From a proportional odds model treatment group and baseline pain as covariates. An odds ratio > 1 means that patients rated active arm more highly than placebo

1.2. Planned Listing Shells

Listing 16.2.1
Subject Disposition
All Subjects

Subject Number	Randomized?	Patient Status	Date of Last Dose (Study Day)	Date of Completion/ Discontinuation (Study Day)	Reason for Discontinuation	Was blind broken? If yes, date and reason blind was broken
XXXXXX		Yes	DDMMMYYYY (XX)	DDMMMYYYY (XX)		XX
XXXXXX		Yes	DDMMMYYYY (XX)	DDMMMYYYY (XX)		XX
XXXXXX		Yes	DDMMMYYYY (XX)	DDMMMYYYY (XX)		XX
XXXXXX		No	DDMMMYYYY (X)	DDMMMYYYY (X)	XXXXXXXXXX: XXXXXXXXX	XX
XXXXXX		No	DDMMMYYYY (XX)	DDMMMYYYY (XX)	XXXXXXXXXXXXXXXXXXXXXX	XX

Abbreviation: NA=Not Applicable
Notes: Study day is calculated relative to the date of first dose of study drug
Programming Note: If reason for early termination is other, concatenate the specify text as follows: “Other: XXXXXXXXX”. If additional details about reason for discontinuation are present in DSREASSP, then concatenate reason for discontinuation with “DSREASSP”.
If reason for early termination is lost to follow-up, concatenate with date of last contact as follows: “Lost to follow-up: Lost-to follow-up comment (DSLFCOMT): date of last contact: DDMMMYYYY”. Lost to follow up comment DSLFCOMT will only be concatenated when present.
If reason for discontinuation is a PI decision, concatenate PI decision reason as follows: “PI Decision: XXXXXXXXXX

Listing 16.2.2.1
Inclusion/ Exclusion Criteria
All Subjects

Subject Number	Gender	Date (Study Day)		All Inclusion Criteria Met?	Any Exclusion Criteria Met?
		Screening	Informed Consent		
XXXXXX	XXXX	DDMMMYYYY (-X)	DDMMMYYYY (-X)	Yes	No
XXXXXX	XXXXXX	DDMMMYYYY (-X)	DDMMMYYYY (-X)	No: 02, 09	No
XXXXXX	XXXXXX	DDMMMYYYY (-X)	DDMMMYYYY (-X)	No: 06	No
XXXXXX	XXXX	DDMMMYYYY (-X)	DDMMMYYYY (-X)	Yes	Yes: 06
XXXXXX	XXXXXX	DDMMMYYYY (-X)	DDMMMYYYY (-X)	Yes	No
XXXXXX	XXXX	DDMMMYYYY (-X)	DDMMMYYYY (-X)	Yes	No

Notes: Study day is calculated relative to the date of first dose of study drug.
Programming note: If more than 1 inclusion or exclusion criterion number exists, concatenate with a comma. Decode any relevant criteria in the footnotes.

Listing 16.2.2.2
Screen Failures

Subject Number	Gender	Date of Birth	Age	Screen Fail Date	Screen Fail Reason
XXXXXX	XXXXXX	DDMMMYYYY	XX	DDMMMYYYY	Inclusion #2
XXXXXX	XXXXXX	DDMMMYYYY	XX	DDMMMYYYY	Inclusion #6
XXXXXX	XXXXXX	DDMMMYYYY	XX	DDMMMYYYY	Inclusion #4, Exclusion #6
XXXXXX	XXXXXX	DDMMMYYYY	XX	DDMMMYYYY	Other: XXXXXXXXXXXXX

Programming note: If more than 1 inclusion or exclusion criterion number exists, concatenate with a comma

Programming note: If additional details about reason for screen failure are present in, then concatenate reason for screen failure reason with “DSSFOTRN”.

Listing 16.2.2.3
Protocol Deviations
All Subjects

Subject Number	Treatment Group	Event Date (Study day)	Event Type	Violation Level	Description
XXXXXX	XXXX	XXXX(XXX)	XXXXXXXXXXX XXXXXXXXXXXXX	MAJOR MINOR	XXXXXXX XXXXXXXXXXXXXX
XXXXXX	XXXX	XXXX(XXX)	XXXXXXXXXXX XXXXXXXXXXXXXX	MINOR MINOR	XXXXXXXXXXXXXXXXXX XXXXXXXXXX
XXXXXX	XXXX	XXXX(XXX)	XXXXXXXXXXX	MAJOR	XXXXXXXXXXXXXXXXXXX

Notes: Study day is calculated relative to the date of first dose of study drug.

Listing 16.2.3
Analysis Populations
All Subjects

Subject Number	Treatment Group	SAF	PP	ITT	Primary Reason(s) for Exclusion
XXXXXX	XXX	Yes	No		XXXXXXXXXXXXXXXXXXXXXXXXXXXXXX.
XXXXXX	XXX	Yes	Yes		
XXXXXX	XXXX	No	No		

Abbreviations: PP = Per Protocol Population; SAF= Safety Population; ITT = Intent-to-treat population

Listing 16.2.4.1
Demographics and Baseline Characteristics
Safety Population

Subject Number	Gender	If Female, is she of childbearing potential?	Treatment Group	Age (years)	Ethnicity	Race	Weight (kg)	Height (cm)	BMI (kg/m2)	Duration of Surgery (hours)
XXXXXX	XX	XX	XX	XX	XXXXXXX	XXXXXXX	XX.X	XX.X	XX.XX	XX.XX
XXXXXX	XX	XX	XX	XX	XXXXXXX	XXXXXX	XX.X	XX.X	XX.XX	XX.XX
XXXXXX	XX	XX	XX	XX	XXXXXXX	XXXXXX	XX.X	XX.X	XX.XX	XX.XX
XXXXXX	XX	XX	XX	XX	XXXXXXX	XXXXX	XX.X	XX.X	XX.XX	XX.XX
XXXXXX	XX	XX	XX	XX	XXXXXXX	XXXXXX	XX.X	XX.X	XX.XX	XX.XX
XXXXXX	XX	XX	XX	XX	XXXXXX	XXXXXX	XX.X	XX.X	XX.XX	

Abbreviation: BMI = Body mass index
Notes: Height, weight, and BMI are the values at Screening.

Listing 16.2.4.2
Medical History
Safety Population

Subject Number	Treatment Group	Any Medical History	SOC/PT/VT	Start date(Study Day) / End Date(Study Day)	Ongoing?
XXX	XX	XX	XXXX/XXX/XXX	DDMMMYYYY/DDMMMYYYY(XXX)	
XXX	XX	XX	XXXX/XXX/XXX	DDMMMYYYY/DDMMMYYYY(XXX)	
XXX	XX	XX	XXXX/XXX/XXX	DDMMMYYYY/DDMMMYYYY(XXX)	
XXX	XX	XX	XXXX/XXX/XXX	DDMMMYYYY/DDMMMYYYY(XXX)	
XXX	XX	XX	XXXX/XXX/XXX	DDMMMYYYY/DDMMMYYYY(XXX)	
XXX	XX	XX	XXXX/XXX/XXX	DDMMMYYYY/DDMMMYYYY(XXX)	

SOC = System Organ Class; PT = Preferred Term; VT = Verbatim Term.

Notes: All medical history terms were coded using MedDRA dictionary version 21.1. Study day is calculated relative to the date of first dose of study drug

Listing 16.2.4.3
Listing of Subject Randomization
All Randomized Subjects

Subject Number	Randomization Date	Randomization Time	Randomization Number	Kit Number Assigned	Randomized Arm
XXX	DDMMMYYYY	hh:mm	XXX	XXX	XX
XXX	DDMMMYYYY	hh:mm	XXX	XXX	XX
XXX	DDMMMYYYY	hh:mm	XXX	XXX	XX
XXX	DDMMMYYYY	hh:mm	XXX	XXX	XX
XXX	DDMMMYYYY	hh:mm	XXX	XXX	XX

Listing 16.2.4.4
Study Drug Administration
Safety Population

Subject Number	Treatment Group	Timepoint	Was Study Drug Administered?	Reason Not Administered	Date of Administration	Time of Administration
XXX	XXX	0 hours	Yes/no	XXXXXXXXXXXX	DDMMMYYYY	hh:mm
XXX	XXX	8 hours	Yes/no	XXXXXXXXXXXX	DDMMMYYYY	hh:mm
XXX	XXX	12 hours	Yes/no	XXXXXXXXXXXX	DDMMMYYYY	hh:mm
XXX	XXX	16 hours	Yes/no	XXXXXXXXXXXX	DDMMMYYYY	hh:mm

Listing 16.2.7.1
Adverse Events
Safety Population

Subject Number	Gender	Treatment Group	Any AEs reported?	TEAE?	SOC/PT/VT	Start date time(Study Day) / End Date time(Study Day)	Severity/ Relationship	Medical Treatment Received?	Outcome/ Action Taken	Serious?
XXX	XXX	XX	XX	NO	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XX	XXXX/ XXXX	No
XXX	XXX	XX	XX	YES	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XX	XXXX/ XXXX	YES
XXX	XXX	XX	XX	NO	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XX	XXXX/ XXXX	No
XXX	XXX	XX	XX	YES	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XX	XXXX/ XXXX	No
XXX	XXX	XX	XX	YES	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XX	XXXX/ XXXX	YES
XXX	XXX	XX	XX	NO	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XX	XXXX/ XXXX	NO

Abbreviation: TEAE-Treatment Emergent Adverse Event, SOC = System Organ Class; PT = Preferred Term; VT = Verbatim Term.
Notes: AEs were coded using MedDRA dictionary version 21.1. TEAE is defined as any event that started or worsened in intensity or relationship to treatment on or after the first dose of study drug. Study day is calculated relative to the date of first dose of study drug.
Programming note= Fatal/hospitalization/life threatening/persistent/congenital/important medical event can be concatenated to SAE when SAE=Y. Concatenate an abbreviated version of the term. Example – For Fatal use F etc. Add term to list of abbreviations if such abbreviation is used.

Listing 16.2.7.2
Serious Adverse Events
Safety Population

(Same shell as Listing 16.2.7.1)

Listing 16.2.7.3
Treatment emergent Adverse Events Related to Study Drug
Safety Population

(Same shell as Listing 16.2.7.1)

Listing 16.2.7.4
Deaths
Safety Population

Subject Number	Gender	Treatment Group	Date of Death(Study Day)	Cause of Death (Specify if Other)
001-003			DDMMMYYYY(XX)	XXXXXXXXXX

Notes-Study day is calculated relative to the date of first dose of study drug.

Listing 16.2.8.1
Clinical Laboratory Data: Serum Chemistry
Safety Population

Subject Number	Gender	Treatment Group	Was Sample Collected?	Date/Time of Assessment	Test Name	Standard Results	Units	Abnormal?/ If Yes, H or L	Comments/Reason not Done
XXX	XXX	XX		DDMMMYYYY(XX)		XX	XX	NO	
XXX	XXX	XX		DDMMMYYYY(XX)		XX	XX	NO	
XXX	XXX	XX		DDMMMYYYY(XX)		XX	XX	YES/ NO	
XXX	XXX	XX		DDMMMYYYY(XX)		XX	XX	YES/ YES	
XXX	XXX	XX		DDMMMYYYY(XX)		XX	XX	NO	

Abbreviation: H=High, L=Low
Notes: Study day is calculated relative to the date of first dose of study drug.

Listing 16.2.8.2
Clinical Laboratory Data: Hematology
Safety Population

(Same shell as Listing 16.2.8.1)

Listing 16.2.8.3
Clinical Laboratory Data: Urine
Safety Population

(Same shell as Listing 16.2.8.1)

Listing 16.2.8.4
Clinical Laboratory Data: Coagulation
Safety Population

(Same shell as Listing 16.2.8.1)

Listing 16.2.8.5
Serum and Urine Pregnancy Test
Safety Population

Subject Number	Treatment Group	Visit	Was Sample Collected?	Reason not collected	Date of Assessment	Time of Assessment	Serum or Urine Test ?	Result of Pregnancy Test
001-003					DDMMMYYYY		XXXXXXXXXX	

Listing 16.2.9.1
Prior and Concomitant Medications
Safety Population

Subject Number	Treatment Group	Prior, Concomitant or Both?	ATC Class (Level 4)/ /PT /VT	Start date time (Study Day)/ End date time(Study Day)	Dose Unit	Frequency	Route	Ongoing ?
XXX	XX	Prior	XXXX/XXX/XXX	DDMMMYYYY(XX)/ DDMMMYYYY(XX)	XXX	XXX		
XXX		Both	XXXX/XXX/XXX	DDMMMYYYY(XX) / DDMMMYYYY (XX)	XXX	XXX		
XXX		Concomitant	XXXX/XXX/XXX	DDMMMYYYY(XX) / DDMMMYYYY(XX)	XXX	XXX		
XXX			XXXX/XXX/XXX	DDMMMYYYY(XX) / DDMMMYYYY (XX)	XXX	XXX		
XXX			XXXX/XXX/XXX	DDMMMYYYY (XX)/ DDMMMYYYY(XX)	XXX	XXX		
XXX			XXXX/XXX/XXX	DDMMMYYYY(XX) / DDMMMYYYY (XX)	XXX	XXX		

ATC = Anatomic Therapeutic Chemical; PT = Preferred Term; VT = Verbatim Term.

Notes: Study day is calculated relative to the date of first dose of study drug.. Medications are coded using WHO-DD B2E version March 2020. . Medications that started prior to the first dose of study drug will be considered prior medications whether or not they were stopped prior to the first dose of study drug. Any medications continuing or starting post the first dose of study drug will be considered to be concomitant. If a medication starts prior to the first dose and continues after the first dose of study drug, it will be considered both prior and concomitant.

Listing 16.2.9.1.1
Rescue Medications
Safety Population

Subject Number	Treatment Group	Were any rescue medications reported ?	Medication	Date time for pain relief/pain intensity (Study Day)	NRS Pain intensity assessment	Pain Relief Assessment	ATC Class (Level 4)/ /PT /VT	Start date time (Study Day) / End date time(Study Day)	Dose Unit	Frequency	Route	Ongoing ?
XXX	XX	XX		XXXX (XX) / XXXX(XX)			XXXX/XXX/ XXX	XXXX (XX) / XXXX(XX)	XXX	XXX		
XXX		XX		XXXX (XX) / XXXX(XX)			XXXX/XXX/ XXX	XXXX (XX) / XXXX(XX)	XXX	XXX		
XXX		XX		XXXX (XX) / XXXX(XX)			XXXX/XXX/ XXX	XXXX (XX) / XXXX(XX)	XXX	XXX		
XXX				XXXX (XX) / XXXX(XX)			XXXX/XXX/ XXX	XXXX (XX) / XXXX(XX)	XXX	XXX		
XXX				XXXX (XX) / XXXX(XX)			XXXX/XXX/ XXX	XXXX (XX) / XXXX(XX)	XXX	XXX		
XXX				XXXX (XX) / XXXX(XX)			XXXX/XXX/ XXX	XXXX (XX) / XXXX(XX)	XXX	XXX		

Abbreviations: ATC = Anatomic Therapeutic Chemical; PT = Preferred Term; VT = Verbatim Term.

Notes: Study day is calculated relative to the date of first dose of study drug.. Medications are coded using WHO-DD B2E version March 2020. Pain assessments will be conducted immediately before each dose of rescue medication. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever and rate their pain relief relative to Time 0 using a 5-point categorical scale, none = 0, a little = 1, some = 2, a lot = 3, and complete = 4.

Listing 16.2.9.2
Vital Signs Measurements
Safety Population

Subject Number	Treatment Group	Visit	Timepoint	Were Vital Signs Collected?	Collection Date/Time (Study Day)	Temperature (Units)	Heart Rate (Units)	Respiration Rate (Units)	Systolic Blood Pressure (Units)	Diastolic Blood Pressure (Units)
XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX

Notes: Study day is calculated relative to the date of first dose of study drug.

Listing 16.2.9.2.1
Physical Examination Findings
Safety Population

Subject Number	Treatment Group	Was Exam Performed?	Visit	Date/Time of Assessment (Study Day)	Body System	Standard Results	If Abnormal, CS ?	Abnormal findings description	Were mouth and neck examined?	If no, reason	Any CS abnormal findings that have been newly diagnosed or have worsened since the previous assessment?
XXX	XX	Yes	XX	DDMMMYYYYThh:mm(XX)		XX			Yes	XX	Yes
XXX	XX	No	XX	DDMMMYYYYThh:mm (XX)		XX			No	XX	No
XXX	XX	Yes	XX	DDMMMYYYYThh:mm(XX)		XX	YES		Yes	XX	Yes
XXX	XX	No	XX	DDMMMYYYYThh:mm(XX)		XX			No	XX	No
XXX	XX	No	XX	DDMMMYYYYThh:mm(XX)		XX			No	XX	No

Abbreviation: CS: Clinically Significant

Notes: Study day is calculated relative to the date of first dose of study drug.

Programming note: In the 'If Abnormal, CS ?' column, 'Yes' will only be populated when we the abnormal value is CS.

Listing 16.2.9.3
12-Lead Electrocardiogram Measurements
Safety Population

Subject Number	Treatment Group	Was ECG Performed?	Date of Assessment (Study Day)	Time of Assessment	Heart Rate (Unit)	RR Interval (Unit)	PR Interval (Units)	QRS (Unit)	QT (Unit)	QTc Interval (Unit)	Investigator Interpretation
XXX	XXX	XXX	DDMMMYYYY(XX)	HH:MM	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	Normal
XXX	XXX	XXX	DDMMMYYYY (XX)	HH:MM	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	Abnormal-NCS
XXX	XXX	XXX	DDMMMYYYY (XX)	HH:MM	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	Abnormal-CS
XXX	XXX	XXX	DDMMMYYYY(XX)	HH:MM	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	Normal

Abbreviation: CS=Clinically Significant, NCS=Not Clinically Significant

Notes: Study day is calculated relative to the date of first dose of study drug

Listing 16.2.9.3.1
Alcohol Breathalyzer Test
Safety Population

Subject Number	Treatment	Was Alcohol Breathalyzer Test performed?	Test Date/Time (Study Day)	Alcohol Breathalyzer Test Result
XXXX	XX	Yes	DDMMMYYYYThh:mm(XX)	XXXXXXX

Notes: Study day is calculated relative to the date of first dose of study drug.

Listing 16.2.9.4
NRS Pain Intensity Assessment
Safety Population

Subject Number	Treatment Group	Was NRS Pain Assessment collected?	Reason not collected	Timepoint	Was Rescue Medication Taken? (Y/N)	Date time post dose	NRS Pain Intensity Score	NRS Pain Intensity Score when rescue medication was taken	Responder (Y/N)
XXXX	XX	Yes	XXXXXXXX	XXX		XXXX	XXX	XXX	

Notes- Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. A subject with ≥ 30% improvement in NRS pain intensity from T0 (predose) without rescue medication during the first 8 hours is considered a responder.

Programing Note- For those cases where "Was rescue medication taken?" is 'Yes', the datetime needs to be presented in the "Date time post dose" column.

Listing 16.2.9.5
Pain Relief Scores
Safety Population

Subject Number	Treatment Group	Was assessment completed?	Reason not collected	Date of Assessment	Date time pain relief collected	Timepoint	Was Rescue Medication Taken? (Y/N)	Date time post dose	How much relief have you had since your starting pain?	How much pain relief have you had since your starting pain when rescue medication was taken?
XXXX	XX	Yes	XXXXXXXX			XXX		XXXX	XXX	

Notes: Subjects rate their pain relief relative to Time 0 using a 5-point categorical scale, none = 0, a little = 1, some = 2, a lot = 3, and complete = 4.

Programing Note- For those cases where "Was rescue medication taken?" is 'Yes', the datetime needs to be presented in the "Date time post dose" column

Listing 16.2.9.6
Time to Pain Relief (Stopwatches)
Safety Population

Subject Number	Treatment Group	Which stopwatch pressed, perceptible or meaningful	Hours on Stopwatch	Minutes on stopwatch	Seconds on stopwatch
XXXX	XX	Perceptible/meaningful	XX	XXX	XXX

Notes: Perceptible pain relief stopwatch refers to the first stop watch and meaningful pain relief, the second stopwatch.

Listing 16.2.9.7
Subjects Global Evaluation of Study Drug
Safety Population

Subject Number	Treatment Group	Was Subject Global Evaluation of study drug completed	Date/Time of evaluation	Global evaluation score
XXXX	XX		XXXX	XX

Notes: Patient's global evaluation of study drug is measured on a scale of 0=poor, 1=fair, 2=good, 3=very good, 4=excellent

Figure 14.4.1.1
Kaplan-Meier plot of time to first perceptible pain relief

ITT Population

X-Axis- Time (hours)

Y-Axis- Proportion of patients experiencing first perceptible pain relief

Figure 14.4.1.2
Kaplan-Meier plot of time to Meaningful Pain Relief

ITT Population

X-Axis- Time (hours)

Y-Axis- Proportion of patients experiencing meaningful pain relief

Figure 14.4.1.3
Kaplan-Meier plot of time to onset of analgesia

ITT Population

X-Axis- Time (hours)

Y-Axis- Proportion of patients experiencing analgesia

Figure 14.4.1.4
Kaplan-Meier plot of time to peak pain relief

ITT Population

X-Axis- Time (hours)

Y-Axis- Proportion of patients experiencing peak pain relief

Figure 14.4.1.5
Kaplan-Meier plot of time to first use of rescue medication

ITT Population

X-Axis- Time (hours)

Y-Axis- Proportion of patients using rescue medication

Figure 14.4.1.6

Mean PID Scores versus Time

ITT Population

x-axis Time (hours)

y-axis- Mean PID score

Present with error bars of +/- 1 standard error.

Add footnote: For subjects who use rescue medication, windowed worst observation carried forward (WOCF) is used. Missing data due to missing intermediate assessments or premature discontinuation is not imputed.

Figure 14.4.1.7

Mean Pain Relief Scores versus Time

ITT Population

x-axis Time (hours)

y-axis- Mean pain relief score

Present with error bars of +/- 1 standard error.

Add footnote: For subjects who use rescue medication, windowed worst observation carried forward (WOCF) is used. Missing data due to missing intermediate assessments or premature discontinuation is not imputed.

Sponsor	Reckitt Benckiser
Protocol Title:	A Randomized, Double-Blind, Double-Dummy, Parallel-Group, Multiple-Dose, Active and Placebo-Controlled Efficacy Study of Ibuprofen Prolonged-Release Tablets for the Treatment of Pain after Surgical Removal of Impacted Third Molars
Protocol Number:	5003601
Premier Research PCN:	RECK.177035
Document Version:	Amendment 1.0
Document Date:	24-Feb-2020

Approvals

Role	Signatures	Date (dd-Mmm-yyyy)
Biostatistician Premier Research	Print Name: Raghu Vishnubhotla Sign Name: DocuSigned by: Signer Name: Raghu Srinivas Vishnubhotla Signing Reason: I am the author of this document Signing Time: 25-Feb-2020 | 10:22:34 EST 46FE4E466250408E961764121635BB48	25-Feb-2020 | 10:23:40 EST
Reckitt Benckiser Representative	Print Name: Darren Targett Sign Name:	25 FEB 2020.

Document History

Reasons for Amendment 1

The statistical analysis plan was amended in the following ways:

1. The sensitivity analyses for the primary efficacy endpoint has been updated. A pattern-mixture model with control-based pattern imputation will now be used.
2. A comparison of individual NRS pain intensity difference scores has been added. P-values comparing the treatment arms (PR vs Placebo, IR vs Placebo) has been added.
3. Pain relief scores at each time point will be summarized and by p-values will be added for treatment comparison.

Table of Contents

List of Tables

1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Reckitt Benckiser protocol number 5003601 (A Randomized, Double-Blind, Double-Dummy, Parallel-Group, Multiple-Dose, Active and Placebo-Controlled Efficacy Study of Ibuprofen Prolonged-Release Tablets for the Treatment of Pain after Surgical Removal of Impacted Third Molars), dated 19-Nov-2019, version 3.0. Reference materials for this statistical plan include the protocol and the accompanying sample data collection documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association[2] and the Royal Statistical Society[3], for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The statistical plan described hereafter is an *a priori* plan. It will be submitted to file prior to any unblinded inferential or descriptive analysis of data pertaining to Reckitt Benckiser's study 5003601.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective is:

- To evaluate the superiority of 2 x 300 mg ibuprofen PR tablets compared with placebo in subjects experiencing acute moderate to severe pain after third molar extraction over 12 hours post initial dose.

2.1.2. Secondary Objectives

The key secondary objectives are:

- To evaluate the analgesic performance of a total daily dose of 1200 mg of ibuprofen PR formulation compared to ibuprofen immediate release (IR) formulation over 24 hours post initial dose.
- To evaluate the safety and tolerability of 2 x 300 mg ibuprofen PR tablets.

Additional secondary objectives include:

- To evaluate the total analgesic effect, peak analgesic effect, onset and duration of action and the subject's overall assessment of the study medications.

2.2. Study Endpoints

2.2.1. Safety Endpoints

The safety endpoints of this study include the following:

- Incidence of treatment-emergent adverse events (TEAEs)
- Incidence of changes in vital sign measurements

2.2.2. Efficacy Endpoints

2.2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint of this study is the summed pain intensity difference (SPID) over 0 to 12 hours (SPID12).

2.2.2.2. Secondary Efficacy Endpoint(s)

The secondary efficacy endpoints of this study include the following:

- Summed pain intensity difference (SPID) over 0 to 24 hours (SPID24) after Time 0.
- SPID4, SPID8 and SPID12
- Sum of total pain relief (TOTPAR) over 0 to 4 hours (TOTPAR4), over 0 to 8 hours (TOTPAR8), over 0 to 12 hours (TOTPAR12) and over 0 to 24 hours (TOTPAR24) after Time 0.
- Summed pain relief and intensity difference (sum of TOTPAR and SPID [SPRID]) over 0 to 4 hours (SPRID4), over 0 to 8 hours (SPRID8), over 0 to 12 hours (SPRID12) and over 0 to 24 hours (SPRID24) after Time 0.
- Response to study drug
- Numeric rating scale (NRS) pain intensity difference (PID) at each scheduled timepoint after Time 0. NRS ranges from 0=no pain to 10=worst pain ever and pain relief is a 5 point categorical scale 0=none, 1=a little, 2=some, 3=a lot, 4=complete. PID is the difference in NRS pain intensity between each time point and Time 0.
- Pain intensity score at each scheduled time point after Time 0.
- Peak pain relief
- Time to onset of analgesia
- Time to first perceptible pain relief
- Time to peak pain relief
- Proportion of subjects using rescue medication

- Time to first use of rescue medication

2.2.2.3. Exploratory Endpoint

- Patient's global evaluation of study drug. It is measured on a scale of 0=poor, 1=fair, 2=good, 3=very good, 4=excellent

3. Overall Study Design and Plan

3.1. Overall Design

3.2. Sample Size and Power

The sample size determination is based on the primary efficacy variable, SPID12. According to Farrar 2001, a clinically important improvement in pain is represented by a 2 point reduction on an 11-point NRS. Based on a baseline pain score of 7 this corresponds to an approximate 30% reduction in pain. An average 2 point difference in pain scores between ibuprofen PR and placebo across all 14 assessments up to 12 hours will correspond to a difference in SPID12 of 24 points. In a previous study, the pooled standard deviation (SD) for SPID12 was 31.65. Assuming the same variability in this study, a sample size of 40 subjects per group will have >90% power to detect a difference of 24 points in SPID12, between ibuprofen 2x300-mg PR tablets and placebo using a 2-sided test with an alpha level of 0.05. In order to provide a robust estimate of treatment effect differences between PR and IR, and to obtain a more precise estimate for this comparison, a 3:3:1 allocation ratio will be used, so that 120 subjects are randomized into each of the PR and IR groups. Thus 280 subjects will be enrolled in the study.

3.3. Study Population

Subjects with moderate to severe pain after extraction of 2 or more third molars will participate in this study.

3.4. Treatments Administered

Treatment A (test product): 2x300 mg ibuprofen PR tablets, BID (total daily dose 1200 mg)

Treatment B (reference product): 2x200 mg ibuprofen IR tablets, TID (total daily dose 1200 mg)

Treatment C: matching placebo tablets

3.5. Method of Assigning Subjects to Treatment Groups

Eligible subjects will be randomized in a 3:3:1 ratio to receive 2x300 mg ibuprofen PR tablets Q12h, 2x200 mg ibuprofen IR Q8h, or placebo using permuted blocks of fixed size. The randomization will be stratified by baseline pain category (moderate or severe) using a categorical scale that includes the categories of none (0), mild (1-4), moderate (5-7), and severe (8-10). The randomization schedule will be prepared by a statistician not otherwise involved in the study. Randomization will be performed using an interactive response system (IRT).

3.6. Blinding and Unblinding

This is a double-blind, double-dummy study. There will be two placebo tablets designed to be comparable to each of the active products (PR and IR) in both shape, size, color and weight.

All subjects will receive 4 tablets at each dosing timepoint. All subject packs will be designed and labelled to ensure blinding is maintained.

Access to the unblinding codes will be restricted to personnel not otherwise involved in the study and will be available to the investigator only in the case of a subject requiring unblinding prior to database lock.

Unblinding will only occur after database lock or in the case of emergency unblinding.

3.7. Schedule of Events

A detailed schedule of events for the study is provided in Table 1.

Table 1: Schedule of Events

	Screening (Day -28 to Day -1)	Surgery (Day 1)						Day 2		Follow-up (Day 8 ±2 days) or ET[k]
			Post-op							
		Pre-Surgery	Pre-dose	0 h	15, 30, 45 min	1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 h	12 h	16 h	24h	
Written informed consent	X									
Assign a screening number	X									
Inclusion/exclusion criteria	X	X								
Demographics	X									
Medical history	X	X[b]								
Physical examination[c]	X									X
Vital signs[d]	X	X	X				X		X	X
Height, weight, and BMI	X									
Clinical laboratory tests (hematology, chemistry, urinalysis)	X									
Electrocardiogram	X									
Pregnancy test for female subjects of childbearing potential[e]	X	X								
Urine drug screen	X	X								
Alcohol breathalyzer test		X								
Oral radiography[f]	X									
Review study restrictions with subject	X									
Pain intensity (NRS)[g]			X		X	X	X	X	X	
Randomisation			X							
Dosing with study drug				0 h		8 h	12 h	16h		
Stopwatch assessment[h]				X						
Pain relief (5-point categorical scale)[g]					X	X	X		X	

	Screening (Day -28 to Day -1)	Surgery (Day 1)						Day 2		Follow-up (Day 8 ±2 days) or ET[k]
			Post-op							
		Pre-Surgery	Pre-dose	0 h	15, 30, 45 min	1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 h	12 h	16 h	24h	
Global evaluation of study drug[i]									X	
Concomitant medications		X[b]	X	X	X	X	X		X	X
Adverse events[j]		X	X	X	X	X	X		X	X
Dispense/prescribe pain medication for use at home, as needed									X	
Collect unused home pain medications, as needed										X
Discharge from study site									X	

Abbreviations: BMI=body mass index; ET=early termination; h=hour; min=minute; NRS=numeric rating scale; pre-op=pre-operative; post-op=post-operative.

a Times listed are relative to dosing with study drug.
b Medical history and concomitant medication use since Screening will be updated on Day 1 before surgery.
c A complete physical examination (excluding the genitourinary examination) will be performed at Screening. An abbreviated confirmatory physical assessment, including an examination of the subject's mouth and neck, will be performed at the Follow-up Visit (or Early Termination Visit).
d Vital signs will be recorded after the subject has been in a sitting position for 3 minutes at the following times: at Screening, before surgery, within 30 minutes before Time 0, 12 hours after Time 0, 24 hours after Time 0, and/or immediately before the first dose of rescue medication, and at the Follow-up Visit (or Early Termination Visit).
e Serum pregnancy test at Screening and urine pregnancy test before surgery on Day 1 (female subjects of childbearing potential only). Test results must be negative for the subject to continue in the study.
f Oral radiographs taken within 1 year before Screening will be acceptable and do not need to be repeated.
g Pain assessments will be conducted (pre-dose, if at one of the dosing timepoints of 0, 8, 12 or 16 hours) at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16 and 24 hours after Time 0 and immediately before each dose of rescue medication. Pain intensity will also be assessed pre-dose. At each assessment time point, the pain intensity assessment will be completed first and the pain relief assessment will be completed second. Subjects will not be able to compare their responses with their previous responses. Note for assessments less than 1 hour apart a window of +/-2 min is allowable whilst for assessments at least 1 hour apart a +/-5 min window is allowable.
h Two stopwatches will be started immediately after the subject has swallowed the first dose of study drug with 8 ounces of water (Time 0). Subjects will record the time to perceptible and meaningful pain relief, respectively, by stopping the stopwatches.

4. Statistical Analysis and Reporting

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher). If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

Continuous (quantitative) variable summaries will include the number of subjects (n) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum.

Categorical (qualitative) variable summaries will include the frequency and percentage of subjects who are in the particular category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population in each of the treatment arms, unless otherwise specified.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and measures of spread (SD) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified.

Unless otherwise indicated, all statistical tests will be conducted at the 0.05 significance level using 2-tailed tests, and P values will be reported. Corresponding 95% confidence intervals (CIs) will be presented for statistical tests. In addition to what is detailed in the SAP, other additional analyses may be conducted on the data which will only serve as exploratory evidence and the unplanned nature of these analyses will be made clear in the Clinical Study Report.

4.2. Interim Analysis

No interim analyses are planned.

5. Analysis Populations

The following analysis populations are planned for this study:

- **Safety Population (SAF):** The Safety Population includes all subjects who receive any amount of planned study medication. Subjects will be assigned to treatment received.
- **Intent-To-Treat Population (ITT):** The ITT population includes all subjects who are treated with study drug and who have at least 1 pain assessment after Time 0. The ITT population is the primary population for the efficacy analysis. Subjects will be assigned to treatment randomized.
- **Per Protocol (PP)**: The PP Population will consist of all ITT subjects who do not incur a major protocol violation that would challenge the validity of their data. This population will be determined at a data review meeting prior to database lock and used to evaluate the sensitivity of the primary efficacy analysis. Subjects will be assigned to treatment received.

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

The last observation recorded prior to the first dose of study drug will be used as the baseline observation for all calculations of change from baseline.

6.1.2. Adjustments for Covariates

For the primary endpoint analysis, the baseline NRS pain score will be included as a covariate.

For the secondary endpoint analyses, baseline pain will be included as a covariate for SPID, SPRID, and TOTPAR variables.

For the proportion of subjects who are responders and the proportion of subjects using rescue medication, logistic regression models will adjust for baseline pain.

For time to event endpoints, baseline pain will be included as a stratification factor.

6.1.3. Multiple Comparisons

No adjustment for multiplicity is required for the primary efficacy analysis – a single comparison of SPID12 for placebo versus SPID12 for ibuprofen PR.

No adjustments will be made for multiple comparisons for other endpoints.

6.1.4. Handling of Dropouts or Missing Data

Missing pain assessments for all efficacy analyses will be handled as follows:

- Missing pain assessments scheduled before the first observed assessment will be imputed with the subject's worst observed pain assessment.
- Missing intermediate pain assessments will be replaced by linear interpolation.
- Missing pain assessments at the end of the observation period due to premature discontinuation of pain assessments will be imputed by carrying forward the last observation prior to that missing.

All data for assessments other than pain assessments will be analyzed as collected; missing data due to premature termination or any other reason will be left as missing. Since this is a short-term study and subjects remain at the study site throughout the 24-hour pain assessment period, the discontinuation rate and the amount of missing data is expected to be minimal.

A number of sensitivity analyses will be performed in order to evaluate the efficacy under various different assumptions regarding missing data and are described in Section 6.1.6

6.1.5. Adjustment of Pain Scores for Rescue Medication Use

Subjects are required to record their pain assessment (NRS and pain relief) immediately prior to each dose of rescue medication. The primary analysis will use windowed worst observation carried forward (WOCF) methodology for subjects who use rescue medication. If a subject received rescue medication at time x, for any time point within x + 4 hours, the highest pain score from time 0 up until time x will be used. If the pain score for the windowed observation is higher than the worst observed score, it will not be replaced. The same approach will be used for pain relief scores.

6.1.6. Sensitivity Analysis of SPID12

The following sensitivity analyses will also be performed for the primary endpoint SPID12 if any pain assessments are missing or if subjects take rescue medication:

1. Missing data and values after rescue medication handled as per the main analysis but based on the PP population.

2. Missing data imputed using WOCF (worst observed pain score at any timepoint, including baseline). Values after rescue medication handled as per the main analysis.

3. Missing data handled as per the main analysis. Pain assessments are used regardless of whether rescue medication has been taken, and no adjustment is made for use of rescue medication. In this analysis, the pain assessment recorded at the time of rescue medication is disregarded (unless it coincides with a planned pain assessment).

4. Missing data handled as per the main analysis. All pain assessments recorded after the first dose of rescue medication has been taken will be disregarded. WOCF and LOCF (Last Observation Carried Forward) imputation methods will then be used to impute the disregarded data.

    a. WOCF - The worst (highest) pain assessment (including baseline) until first dose of rescue medication will be used to impute all subsequent pain assessments. In other words, this method would be treating the subject as if they got no worse than their worst observed value prior to rescue medication.

    b. LOCF - In this LOCF analysis, the pain assessment taken immediately prior to/at the time of rescue medication will be taken as the last observed score, i.e., this method would be treating the subject as if they got no worse than their last observed value prior to rescue medication.

5. Missing data imputed using multiple imputation (methodology described below). Values after rescue medication handled as per the main analysis.

For sensitivity analysis 5, a pattern-mixture model with control-based pattern imputation will be used. This model assumes that after withdrawal from the study, subjects from the experimental

group (no longer receiving active treatment) will exhibit the same future evolution of pain scores as subjects in the placebo group (who are also not exposed to active treatment). Subjects that discontinue from the placebo group are assumed to evolve in the same way as placebo subjects that remain in the study. This imputation assumes that intermittent missing values are missing at random (MAR), and that values that are missing due to withdrawal are missing not at random (MNAR). When data are MAR, the missingness of the data does not depend on the missing value after conditioning on the observed data (i.e., prior assessments and baseline covariates). Note that when the missingness of the data depends on the values of the missing variables after conditioning on the observed data, the data are called "missing not at random" (MNAR). In order to assess the MAR assumption, a placebo-based pattern mixture model (PMM) will be utilized following the steps outlined in Ratitch B and O'Kelly, M.J. (2011) for SPID-12.

Briefly, the strategy for implementing this approach is as follows for subjects with missing data:

i. Impute all non-monotone (intermittent) missing data using the MCMC method of PROC MI. Note that this imputation will sample data within each treatment group. Note that PI_i is the NRS pain intensity at time T_i as mentioned in Section 6.1.7. SAS pseudo code is provided below. With MCMC option, SAS does 200 burn-in iterations (default) before each imputation.

```
PROC MI DATA=example seed = xxxx NIMPUTE = 20 OUT = outdata1 minimum=0 maximum=10;
        by <treatment>;
        MCMC chain=multiple impute=monotone;
        VAR  <PI0> <PI0.25> <PI0.5> <PI0.75><PI1> …..<PI12>;
RUN;
```

ii. Using the imputed datasets from Step #1 that are now monotone missing (no intermittent missing data), a single call to PROC MI (including the MNAR statement) will be utilized to impute the monotone missing data. Additional details are provided below.

   a. Within the call to PROC MI, one timepoint is imputed at a time. The order in which pain scores are imputed will be PI_0, then $PI_{0.25}$...,PI_{12}

   b. When imputing at timepoint t, the imputation step will include all placebo subjects, but only those from the active arms that have a value missing at timepoint t. Subjects with non-missing data that are on active arms will not contribute to the estimation for this step.

   c. Repeat the above step for all timepoints *t*. Thus, the data for timepoint *t+1* uses the data imputed from previous timepoints.

SAS pseudo code is provided below. SAS accomplishes this iterative process in one step. Note that the treatment level 3 is the placebo treatment group. The MNAR statement imputes missing values for scenarios under the MNAR assumption. The MODEL option specifies that only observations in which treatment=3 are used to derive the imputation

model for the pain score that time point. The minimum and maximum options are used to ensure that every pain score imputed ranges from 0-10.

```
PROC MI DATA=OUTDATA1 seed = xxxx NIMPUTE = 1 OUT = outdata2 MINIMUM=. 1..1 MAXIMUM=. 10 10…10;
              BY _IMPUTATION_;
              CLASS <treatment>;
              MONOTONE REG (/ details);
              MNAR MODEL (PI0.25> <PI0.5> <PI0.75><PI1> …..<PI12>/ modelobs=(<treatment='3'>));
                     VAR  <PI0> <PI0.25> <PI0.5> <PI0.75><PI1> …..<PI12>;
RUN;
```

iii. When all missing PI scores are imputed, SPID12 will be derived as described in 6.1.7 and analyzed using the ANCOVA models as described in Section 8.1. PROC MIANALYZE will be used to combine the parameters from the analyses for inference.

6.1.7. Derived Variables

At each assessment time point, subjects will complete the pain intensity NRS assessment first and the pain relief assessment second.

Planned assessment time points are as follows: 0 (predose), 15, 30, and 45 minutes, and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hours after Time 0. Please see Table 2 below.

Table 2: Planned Assessment Times

i	T_i (hours)
0	0 (predose)
1	0.25
2	0.5
3	0.75
4	1
5	1.5
6	2
7	3
8	4
9	5

10	6
11	7
12	8
13	10
14	12
15	16
16	24

- SPID-12 = summed pain intensity difference (change from Time 0) under the numeric rating scale (NRS)-time curve from 15 min through 12 hours calculated using the linear trapezoidal rule and the actual time points, where Time 0 is the time of the first dose of study drug. Scheduled time points in Table 2 will be used when actual time is missing.

$$SPID_{12} = \sum_{i=1}^{14} (T_i - T_{i-1}) * PID_i$$

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

PID is defined as

$$PID_i = PI_i - PI_0$$

Where PI is the pain intensity as measured by the NRS scale.

- SPID-x = summed pain intensity difference (change from Time 0) under the numeric rating scale (NRS)-time curve from 15 min through x hours calculated using the linear trapezoidal rule and the actual time points, where Time 0 is the time of the first dose of study drug. Scheduled time points in Table 2 will be used when actual time is missing. X = 4, 8, and 24.

$$SPID_x = \sum_{i=1}^{y} (T_i - T_{i-1}) * PID_i$$

For x=4 y=8; x=8 y=12; x=24 y=16.

- TOTPAR-x = total pain relief under the Pain Relief Scale (0 – 4) from 15 min through x hours calculated using the linear trapezoidal rule and actual time points, where Time 0 is the time of the first dose of study drug. Scheduled time points in Table 2 will be used when actual time is missing. x = 4, 8, 12, and 24.

$$TOTPAR_x = \sum_{i=1}^{y} (T_i - T_{i-1}) * PAR_i$$

For x=4 y=8; x=8 y=12; x=12 y=14; x=24 y=16. PAR_i is the pain relief score on the Pain Relief Scale (0-4) at time T_i

- SPRID-x = summed pain relief (TOTPAR) and intensity difference (SPID) from 15 min through x hours calculated using the linear trapezoidal rule and actual time points, where Time 0 is the time of the first dose of study drug. Scheduled time points in Table 2 will be used when actual time is missing. X = 4, 8, 12, and 24.

$$SPRID_x = SPID_x + TOTPAR_x$$

- Responder: subject with ≥ 30% improvement in NRS pain intensity from T_0 (predose) without rescue medication during the first 8 hours. If a subject takes rescue medication prior to the 8-hour pain assessment or if the 8-hour assessment is not performed they will be considered a non-responder. i.e.,

$$\frac{(PI_0 - PI_8)}{PI_0} * 100 \geq 30$$

Where PI_0 and PI_8 are the predose and 8-hour NRS pain intensity measurements respectively.

- Time to onset of analgesia = If the subject has had meaningful pain relief (i.e., presses both stopwatches) then time to onset of analgesia is date/time of perceptible pain relief – date/time of the first dose of study drug. If subjects don't experience both perceptible pain relief and meaningful pain relief during the 8-hour interval after Time 0, time to onset to analgesia will be right censored at the time of their last pain assessment in the first 8 hours. For subjects who take rescue medication prior to onset of analgesia during the 8-hour interval after Time 0, time to onset of analgesia will be right censored at the time rescue medication was taken.

- Time to first perceptible pain relief = date/time of the first reported pain relief (any) as assessed by the subject (i.e. subject stops the first stopwatch (irrespective of the second

stopwatch)) – date/time of the first dose of study drug. If subjects don't experience perceptible pain relief during the 8-hour interval after Time 0, time to first perceptible pain relief will be right censored at the time of their last pain assessment in the first 8 hours. If the first stopwatch is not stopped but the second stopwatch is stopped, time will be left censored at the time that the second stopwatch is stopped. In other words, it is assumed that the first stopwatch measurement has already occurred but was missed/not recorded. For subjects who take rescue medication prior to first perceptible pain relief during the 8-hour interval after Time 0, time to first perceptible pain relief will be right censored at the time rescue medication was taken.

- Time to meaningful pain relief = date/time of the first reported meaningful (subjective) pain relief as assessed by the subject (i.e. the subject stops the second stopwatch) – date/time of the first dose of study drug. If subjects don't experience meaningful pain relief during the 8-hour interval after Time 0, time to meaningful pain relief will be right censored at the time of their last pain assessment in the first 8 hours. If the subject stops the second stopwatch but doesn't stop the first stopwatch or the first stopwatch assessment is missing, then time to meaningful pain relief will be right censored at the time of their last pain assessment in the first 8 hours. For subjects who take rescue medication prior to achieving meaningful pain relief during the 8-hour interval after Time 0, time to meaningful pain relief will be right censored at the time rescue medication was taken.

- Peak pain relief- Pain relief is measured on a scale from 0 (None) to 4 (Complete). If PR_i is the pain relief measurement at time T_i , peak pain relief PPR is defined as

$$PPR = \max\{PR_1, PR_2, PR_3, \dots, PR_{16}\}$$

- Time to first use of rescue medication = date/time to the first dose of rescue medication – date/time of the first dose of study drug. If subjects don't take rescue medication, subjects will be right censored at the time of their last pain assessment.

- Time to peak pain relief = date/time of peak pain relief– date/time of the first dose of study drug. Time of peak pain relief is the time T_i when peak pain relief (PPR) first occurs. If no pain relief is observed then the time to peak pain relief will be right censored at the time of their last pain assessment.

- Change from baseline = value at current time point – value at baseline.

- TEAE = TEAE is defined as any event that started or worsened in intensity or relationship to treatment on or after the first dose of study drug.

6.1.8. Data Adjustments/Handling/Conventions

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included only in the data listings.

All *P* values will be displayed in four decimals and rounded using standard scientific notation (e.g., 0.XXXX). If a *P* value less than 0.0001 occurs it will be shown in tables as <0.0001.

Adverse events will be coded using the MedDRA version 21.1 thesaurus.

A treatment related AE is any AE with a relationship to the study drug with possible, probable or certain causality to the study drug as determined by the Investigator.

If partial dates occur, the convention for replacing missing dates for the purpose of statistical analysis is as follows: if just day is missing then the day assigned is the first day of the month or the date of first dose (if in the same month), whichever is later; if just month is missing then the month assigned is the month of the first dose, unless that results in a date prior to the first dose in which case the month after the first dose is used; and if both month and day are missing then the month assigned is the month of the first dose and the day assigned is either the first day of the month or the first dose date, whichever is later.

If partial times occur, the convention is as follows: if the missing time occurs on the day of the first dose and both the hour and minute are missing then the time assigned is the time of the first dose, otherwise if both the hour and minute are missing and the date is not the date of first dose the time assigned is 12:00; if the date is the same as the date of the first dose and only hour is missing the hour assigned is 12 or the hour of first dose, whichever is later, and if the date is the same as the date of first dose and only the minute is missing the minute assigned is 30 or the minute of first dose, whichever is later. Otherwise the hour assigned is 12 if the hour is missing and the date is not the same as the date of first dose and the minute assigned is 30 is the the date is not the same as the date of first dose.

These conventions will be applied only to adverse event onset dates and times with the following precaution: if the missing date and time reflect the date and time of onset of an adverse event, the modified date and time will be constructed to match the first documented date/time post drug administration while preserving the order in which the AE was reported in the CRF.

7. Study Patients/Subjects and Demographics

7.1. Disposition of Patients/Subjects and Withdrawals

Disposition will include tabulations of the number of subjects screened, number of subjects randomized into each treatment group, the number of subjects who received treatment, tabulated reasons for discontinuation from the study, and number of subjects in each analysis population.

7.2. Protocol Violations and Deviations

Protocol deviations will be listed.

7.3. Demographics and Other Baseline Characteristics

Summary statistics for age, gender, race, ethnicity, height, weight, BMI, baseline pain category and baseline pain (continuous) will be presented by treatment groups and overall. For the

continuous variables, the number of non-missing values and the mean, standard deviation, minimum, median and maximum will be tabulated.

For the categorical variables, the counts and proportions of each value will be tabulated.

These analyses will be conducted for the ITT, PP, and Safety populations.

The number and percent of subjects reporting various medical histories, grouped by MedDRA system organ class and preferred term (coded using MedDRA v21.1), will be tabulated by treatment group. This analysis will be conducted for the Safety Population. Physical examination findings will also be summarized by body system and examination result- Normal, Abnormal – Clinically Significant, Abnormal-Not Clinically Significant.

7.4. Exposure and Compliance

The number of doses taken and treatment duration will be summarized by descriptive statistics. All study drug will be administered in clinic. The total number of tablets taken, and the number of tablets with active ingredient taken at each time point will be summarized. The dosage (in mg) of active ingredient taken and duration of exposure, from first dose to last dose of the study treatment will be summarized using descriptive statistics. Any deviations from the planned dose should be reported.

8. Efficacy Analysis

8.1. Primary Efficacy Analysis

The primary efficacy endpoint is the summed pain intensity difference (SPID) over 0 to 12 hours (SPID12). The primary endpoint will be used to compare the test product (2x300 mg ibuprofen PR tablets) against placebo.

The primary efficacy hypothesis is that SPID12 for placebo is equal to SPID12 for ibuprofen 2x300 mg PR tablets. The primary analysis will be an ANCOVA model that includes the main effect of treatment and a covariate of the baseline NRS pain score and will use windowed worst observation carried forward (WOCF) imputation for subjects who use rescue medication. The primary analysis will be based on a 2-sided test at the significance level of 0.05. The treatment difference will be presented with a 95% confidence interval.

Normality assumptions will be tested. If the data is considered non-normal, the Wilcoxon rank sum test will be used for the comparison between treatments, and the point estimate and 95% confidence interval will be calculated using the Hodges-Lehmann estimator.

The primary efficacy analysis will be based on the ITT population. These analyses will be repeated for the PP population. SPID-12 scores will also be summarized by baseline pain category (moderate or severe).

8.2. Secondary Efficacy Analysis

8.2.1. SPID

Summed Pain Intensity Difference (SPID) will be calculated for secondary efficacy analysis as

described in Section 6.1.7 at 4, 8, and 24 hours. Descriptive statistics by treatment regimen will be produced.

ANCOVA models for comparing placebo with other treatment regimens with SPID as the dependent variable and treatment group and baseline pain as covariates will be generated. These models will be computed for SPID4, SPID8 and SPID12. The least square (LS) mean and standard error (SE) for each treatment group will be estimated and the difference in LS means and 95% confidence interval (CI) for the comparison of placebo with the IR and PR treatment regimens will be estimated. P-values will be reported but no formal statistical inferences will be made on the basis of these tests. In addition, for the SPID24 endpoint, the difference in LS means and 95% CI for the IR versus PR groups will be presented. In the event that normality assumptions are violated for a parameter, non-parametric analysis methods will be used.

8.2.2. TOTPAR

Total pain relief (TOTPAR) will be calculated as described in Section 6.1.7 at 4, 8, 12 and 24 hours. Descriptive statistics by treatment regimen will be produced.

ANCOVA models for comparing placebo with other treatment regimens with TOTPAR as the dependent variable and treatment group and baseline pain as covariates will be generated. These models will be generated at TOTPAR4, TOTPAR8, TOTPAR12 and TOTPAR24. The LS mean and SE for each treatment group will be estimated and the difference in LS means and 95% CI for the comparison of placebo with the IR and PR treatment regimens will be estimated. P-values will be reported but no formal statistical inferences will be made on the basis of these tests. In the event that normality assumptions are violated for a parameter, non-parametric analysis methods will be used.

8.2.3. SPRID

Summed pain relief and intensity difference is the sum of TOTPAR and SPID and will be calculated at 4, 8, and 12 and 24 hours as described in Section 6.1.7.

Descriptive statistics by treatment regimen will be produced for SPRID at each planned assessment time point.

ANCOVA models for comparing placebo with other treatment regimens with SPRID as the dependent variable and treatment group and baseline pain as covariates will be generated. The LS mean and SE for each treatment group will be estimated and the difference in LS means and 95% CI for the comparison of placebo with the IR and PR treatment regimens will be estimated. P-values will be reported but no formal statistical inferences will be made on the basis of these tests. In the event that normality assumptions are violated for a parameter, non-parametric analysis methods will be used.

8.2.4. Peak Pain Relief

Peak pain relief will be calculated as described in Section 6.1.7 and will be summarized by counts (and percentages) for each pain relief score. It 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 a factor for treatment and

baseline pain intensity as a continuous covariate. For each of the PR and IR treatment regimens, the odds of being in a higher (better) pain relief category compared to placebo (odds ratio) will be presented with a 95% CI and associated p-value.

8.2.5. 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 6.1.7. With baseline pain as a stratification factor, treatments will be compared to placebo using a stratified log-rank test or a stratified Wilcoxon test as appropriate. Summary tables will provide the number of subjects analyzed, the number of subjects censored, estimates for the 25th, 75th percentiles and median (including 95% CI), and associated p-value for comparisons versus placebo.

A measure of the treatment effect comparing each of the active arms with placebo will be obtained by calculating a hazard ratio and 95% CI by fitting a Cox proportional hazards model with a factor for treatment group and baseline pain as a continuous covariate. The assumption of proportional hazards will first be evaluated.

8.2.6. Time to Meaningful Pain Relief

Time to first meaningful pain relief will be summarized using Kaplan-Meier methods. The definition and censoring rules are described in Section 6.1.7. With baseline pain as a stratification factor, treatments will be compared to placebo using a stratified log-rank test or a stratified Wilcoxon test. Summary tables will provide the number of subjects analyzed, the number of subjects censored, estimates for the 25th, 75th percentiles and median (including 95% CI), and associated p-value for comparisons versus placebo.

A measure of the treatment effect comparing each of the active arms with placebo will be obtained by calculating a hazard ratio and 95% CI by fitting a Cox proportional hazards model with a factor for treatment group and baseline pain as a continuous covariate. The assumption of proportional hazards will first be evaluated.

8.2.7. Time to onset of Analgesia

Time to onset of analgesia will be summarized using Kaplan-Meier methods. The definition and censoring rules are described in Section 6.1.7. With baseline pain as a stratification factor, treatments will be compared to placebo and with each other (IR vs PR) using a stratified log-rank test or a stratified Wilcoxon test. The summary tables will provide the number of subjects analyzed, the number of subjects censored, estimates for the 25th, 75th percentiles and median (including 95% CI), and associated p-value for treatment comparisons.

A measure of the treatment effect comparing each of the active arms with placebo and with each other (IR vs PR) will be obtained by calculating a hazard ratio and 95% CI by fitting a Cox proportional hazards model with a factor for treatment group and baseline pain as a continuous covariate. The assumption of proportional hazards will first be evaluated.

8.2.8. 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 6.1.7. With baseline pain as a stratification factor, treatments will be compared to placebo using a stratified log-rank test or a stratified Wilcoxon test. The summary tables will provide the number of subjects analyzed, the number of subjects censored, estimates for the 25th, 75th percentiles and median (including 95% CI), and associated p-value for comparisons versus placebo.

A measure of the treatment effect comparing each of the active arms with placebo will be obtained by calculating a hazard ratio and 95% CI by fitting a Cox proportional hazards model with a factor for treatment group and baseline pain as a continuous covariate. The assumption of proportional hazards will first be evaluated.

8.2.9. Time to first use of Rescue Medication

Time to first use of rescue medication will be summarized using Kaplan-Meier methods. The definition of time to first use of rescue medication and censoring rules for subjects who don't take rescue medication are described in Section 6.1.7. With baseline pain as stratification factor, treatments will be compared to placebo using a stratified log-rank test or a stratified Wilcoxon test. The summary tables will provide the number of subjects analyzed, the number of subjects censored, estimates for the 25th, 75th percentiles and median (including 95% CI), and associated p-value for comparisons versus placebo.

A measure of the treatment effect comparing each of the active arms with placebo will be obtained by calculating a hazard ratio and 95% CI by fitting a Cox proportional hazards model with a factor for treatment group and baseline pain as a continuous covariate. The assumption of proportional hazards will first be evaluated.

8.2.10. Proportion of Responders

For the proportion of subjects who are responders, a logistic regression model that adjusts for baseline pain (as a continuous covariate) and treatment arm will be used to evaluate the treatment effect. As a measure of treatment effect for each of the PR and IR groups versus placebo, odds ratios together with a 95% CI and p-values will be presented.

8.2.11. Numeric rating scale (NRS) pain intensity difference (PID)

PID at each time point will be calculated using the formula specified in Section 6.1.7. PID at each timepoint will be analyzed in a mixed model for repeated measures (MMRM) ANCOVA analysis. The model will include treatment, timepoint, treatment by timepoint, baseline and baseline by timepoint as fixed effects, and subject as a random effect. An unstructured covariance matrix will be used to model the within-subject correlations by timepoint. If the model fails to converge, alternative covariance structures, such as compound symmetry, will be tried instead. The model will be used to show estimated treatment effects at each timepoint. The LS mean and SE for each treatment group will be estimated and the difference in LS means and 95% CI for the comparison of placebo with the IR and PR treatment regimens will be estimated. P-values will be reported but no formal statistical inferences will be made on the basis of these

tests. Descriptive summaries (including mean, SD, median, minimum and maximum) will be presented by treatment group. Pain intensity score at each scheduled time point

Pain intensity is measured using NRS at planned assessment time points. Descriptive summaries (including mean, SD, median, minimum and maximum) will also be presented by treatment group.

8.2.12. Pain relief at each scheduled time point

Pain relief scores at each scheduled time point will be summarized using descriptive statistics (including mean, SD, median, minimum and maximum) as well as counts (and percentages) for each pain relief score by treatment group. Treatment comparison will be done in the following way:

- Pain relief category at each timepoint will also be analyzed using a repeated measures proportional odds model (an extension of the logistic regression). This method allows for an ordinal response variable with more than two categories. Here the categories none = 0, a little = 1, some = 2, a lot = 3, and complete = 4.This model will include the following covariate terms- treatment and baseline pain intensity (as a continuous covariate) timepoint, baseline by timepoint and treatment by timepoint. Subject will be the repeated measure in this model. For each of the PR and IR treatment regimens, the odds of being in a higher (better) pain relief category compared to placebo (odds ratio) will be presented with a 95% CI and associated p-value.

8.2.13. Proportion of Subjects Rescue Medication

The definition of rescue medication use is presented in Section 6.1.7. The proportion of subjects using rescue medication for pain will be analyzed using logistic regression. The logistic regression model will include treatment arm and baseline pain (as a continuous covariate) as covariates. As a measure of treatment effect for each of the PR and IR groups versus placebo, odds ratios together with a 95% CI and p-values will be presented.

8.3. Exploratory Efficacy Analysis

8.3.1. 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 a factor for treatment group and baseline pain intensity as a continuous covariate. For each of the PR and IR treatment regimens, the odds of being in a higher (better) evaluation category compared to placebo (odds ratio) will be presented with a 95% CI and associated p-value.

9. Safety and Tolerability Analysis

Safety will be evaluated from reported AEs, and changes in vital signs.

All safety analyses will be performed on the Safety population.

9.1. Adverse Events

The number and percent of subjects reporting treatment emergent AEs, grouped by MedDRA system organ class and preferred term (coded using MedDRA v21.1), will be tabulated by severity and treatment group. In the case of multiple occurrences of the same TEAE within the same subject, each subject will only be counted once for each preferred term.

The frequency and percentage of subjects reporting TEAEs, grouped by MedDRA SOC and PT, will be tabulated by treatment group for the SAF. Such summaries will be displayed for the following:

- TEAEs by SOC and PT
- TEAEs by SOC, PT, and severity
- TEAEs by SOC, PT, and relationship to the study medication
- TEAEs leading to death by SOC, and PT
- Serious TEAEs other than deaths by SOC, and PT
- TEAEs leading to premature discontinuation by SOC, and PT
- Listing of non-TEAEs

In the case of multiple occurrences of the same AE within the same subject, each subject will only be counted once for each preferred term. In summaries of AE by SOC and PT, along with the number (%) of subjects with at least 1 AE in the category, the number of events will be displayed. In the summaries showing severity and relationship to study medication the event with the maximum severity or strongest relationship will be reported. If a particular event is missing the severity and/or relationship, then the strongest possible severity or relationship will be assumed for analysis (severity = severe, relationship = certain).

Missing and partially missing AE start and/or stop dates will be imputed for the purpose of statistical analysis, according to the specifications described in Section 6.1.7.

In the AE data listings, all AEs will be displayed. AEs that are not treatment-emergent will be flagged.

9.1.1. Adverse Events Leading to Withdrawal

A summary of incidence rates (frequencies and percentages) of TEAEs leading to withdrawal of study drug, by treatment group, SOC, and preferred term will be prepared for the Safety Population. No inferential statistical tests will be performed.

A data listing of AEs leading to withdrawal of study drug will also be provided, displaying details of the event(s) captured on the CRF.

9.1.2. Deaths and Serious Adverse Events

Any deaths that occur during the study will be listed.

Serious adverse events will be listed and also tabulated by system organ class and preferred term and presented by treatment.

9.2. Clinical Safety Laboratory Data

Descriptive statistics for clinical safety laboratory data (laboratory data) recorded at screening will be presented overall and by treatment regimen. Summary tables by treatment regimen will be presented for each category of data separately. Routine clinical laboratory data will include hematology, serum chemistry, and urinalysis. Quantitative laboratory test result summaries will include N (population count for each regimen), n (number of subjects with non-missing values), mean, SD, median, and range. Qualitative tests (e.g., some urinalysis assessments) will be categorized accordingly. The set of laboratory parameters included in each table will correspond to those requested in the study protocol. Urine drug screen, alcohol breath analyzer and urine pregnancy test results will be presented in listings.

9.3. Vital Signs

Descriptive summaries of actual values and changes from baseline will be calculated for supine systolic blood pressure, supine diastolic blood pressure, heart rate, respiratory rate, and oral body temperature, and will be presented by treatment regimen. Summary statistics for 12-lead ECG parameters and counts for ECG interpretations at screening will be presented.

9.4. Concomitant Medication

Prior and concomitant medications will be summarized descriptively by treatment using counts and percentages.

Prior medications will be presented separately from concomitant medications. Medications that started prior to the first dose of study drug will be considered prior medications whether or not they were stopped prior to the first dose of study drug. Any medications continuing or starting post the first dose of study drug will be considered to be concomitant. If a medication starts prior to the first dose and continues after the first dose of study drug, it will be considered both prior and concomitant. Medications will be coded using Sept 2018 version of World Health Organization Drug Coding ASDFK Dictionary (WHODD).

10. Changes to analysis planned in the protocol

For the time to event endpoints an additional measure of the treatment effect comparing each of the active arms with placebo will be obtained by calculating a hazard ratio and 95% CI by fitting a Cox proportional hazards model with a factor for treatment group and baseline pain as a continuous covariate. The assumption of proportional hazards will first be evaluated.

There has been a clarification to the definition of the ITT population to that stated in the

protocol. The ITT population is defined as all subjects who are treated with study drug and who have at least 1 pain assessment after Time 0. In the protocol the ITT population was defined as subjects who have at least 1 pain relief assessment.

11. References

1. ASA. (2016) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April 2016. http://www.amstat.org/about/ethicalguidelines.cfm
2. RSS. (2014) The Royal Statistical Society: Code of Conduct, 2014. http://www.rss.org.uk/Images/PDF/join-us/RSS-Code-of-Conduct-2014.pdf.
3. US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.
4. Ratitich, B. and O'Kelly, M.J. (2011). Implementation of Pattern-Mixture Models Using Standard SAS / STAT Procedures.

12. Tables, Listings, and Figures

All listings, tables, and graphs will have a header showing the sponsor company name and protocol and a footer showing the version of SAS, the file name and path, and the source of the data (CRF page or listing number).

12.1. Planned Table Descriptions

The following are planned summary tables for protocol number 5003601. The table numbers and page numbers are place holders only and will be determined when the tables are produced.

Table 3: Demographic Data Summary Tables

Table Number	Population	Table Title/Summary
14.1 Displays of Demographics and Disposition Data		
Table 14.1.1	All Subjects	Subject Disposition
Table 14.1.2	Safety Population	Demographics and Baseline Characteristics
Table 14.1.2.1	ITT Population	Demographics and Baseline Characteristics
Table 14.1.3	Safety Population	Medical History
Table 14.1.4	Safety Population	Prior Medications
Table 14.1.5	Safety Population	Concomitant Medications
Table 14.1.6	All Enrolled Subjects	Summary of Protocol Deviations
Table 14.1.7	Safety Population	Summary of Study Drug Exposure

12.2. Efficacy Data

Table 4: Efficacy Tables

Table Number	Population	Table Title/Summary
14.2.1	ITT Population	Analysis of SPID-12 Scores
14.2.1.1	PP Population	Analysis of SPID-12 Scores
14.2.1.2	ITT Population	Analysis of SPID-12 Scores- Sensitivity Analysis-WOCF
14.2.1.3	ITT Population	Analysis of SPID-12 Scores- Sensitivity Analysis-No Rescue Adjustment
14.2.1.4	ITT Population	Analysis of SPID-12 Scores- Sensitivity Analysis-Rescue WOCF
14.2.1.5	ITT Population	Analysis of SPID-12 Scores- Sensitivity Analysis-Rescue LOCF
14.2.1.6	ITT Population	Analysis of SPID-12 Scores- Sensitivity Analysis-Multiple Imputation
14.2.1.7	ITT Population	Summary of SPID-12 Scores by Baseline Pain
14.2.2	ITT Population	Analysis of Summed Pain Intensity Difference Scores
14.2.3	ITT Population	Analysis of Total Pain Relief Scores
14.2.4	ITT Population	Analysis of Summed Pain Relief and Intensity Difference Scores
14.2.5	ITT Population	Comparison of SPID-24 in Ibuprofen PR and IR arms
14.2.6	ITT Population	Summary of Peak Pain Relief
14.2.7	ITT Population	Time to First Perceptible Pain Relief
14.2.8	ITT Population	Time to Meaningful Pain Relief
14.2.9	ITT Population	Time to Onset of Analgesia
14.2.10	ITT Population	Time to Peak Pain Relief
14.2.11	ITT Population	Time to First use of Rescue Medication
14.2.12	ITT Population	Proportion of Subjects Using Rescue Medication
14.2.13	ITT Population	Proportion of Responders
14.2.14	ITT Population	Summary of NRS Pain Intensity Difference Score
14.2.15	ITT Population	Summary of Pain Intensity Score at each Scheduled Time Point
14.2.16	ITT Population	Summary of Pain Relief at each Scheduled Time Point
14.2.17	ITT Population	Analysis of Patient Global Evaluation of Study Drug

12.3. Safety Data

Table 5: Safety Tables

Table Number	Population	Table Title/Summary
14.3.1 Summary of Treatment Emergent Adverse Events		
Table 14.3.1.1	Safety Population	Overall Summary of Treatment-Emergent Adverse Events
Table 14.3.1.2	Safety Population	Summary of Treatment-Emergent Adverse Events
Table 14.3.1.3	Safety Population	Summary of Treatment-Emergent Adverse Events by Maximum Severity
Table 14.3.1.4	Safety Population	Summary of Treatment-Emergent Adverse Events by Relationship to Study Drug
Table 14.3.1.5	Safety Population	Summary of Non-Serious Treatment-Emergent Adverse Events
14.3.2 Summary of Deaths, Other Serious and Significant Adverse Events		
Table 14.3.2.1	Safety Population	Summary of Serious Adverse Events
Table 14.3.2.2	Safety Population	Summary of Treatment Emergent Adverse Events Leading to Discontinuation
14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events		
Table 14.3.3.1	Safety Population	Listing of Serious Adverse Events
Table 14.3.3.2	Safety Population	Listing of Treatment Emergent Adverse Events Leading to Study Drug Discontinuation
14.3.4 Abnormal Laboratory Value		
Table 14.3.4.1	Safety Population	Listing of Potentially Clinically Significant Abnormal Laboratory Values
14.3.5 Laboratory Data Summary Tables		
Table 14.3.5.1	Safety Population	Summary of Serum Chemistry Laboratory Results
14.3.6 Other Safety Data Summary Tables		
Table 14.3.6.1	Safety Population	Summary of Vital Signs
Table 14.3.6.2	Safety Population	Summary of Electrocardiogram (ECG) Interpretations
Table 14.3.6.3	Safety Population	Summary of 12-Lead Electrocardiogram (ECG) Parameters
Table 14.3.6.4	Safety Population	Summary of Physical Examination Findings

12.4. Planned Listing Descriptions

The following are planned data and patient/subject data listings for protocol number 5003601.

In general, one listing will be produced per CRF domain. All listings will be sorted by treatment, site, and subject number. All calculated variables will be included in the listings.

In all listings a blank line will be placed between each subject. Within a data listing, if an item appears line after line (e.g., repetition of subject number), then only the first occurrence will be displayed.

In data listings, the information for one subject will be kept on one page if at all possible, rather than splitting a subject's information across pages.

Table 6: Planned Listings

Data Listing Number	Population	Data Listing Title / Summary
16.2.1 Subject Discontinuations/Completions		
Listing 16.2.1	All Subjects	Subject Disposition
16.2.2 Protocol Deviations		
Listing 16.2.2.1	All Subjects	Eligibility Criteria Not Met
Listing 16.2.2.2	All Subjects	Screen Failures
Listing 16.2.2.3	All Subjects	Protocol Deviations
16.2.3 Subjects in Analysis Populations		
Listing 16.2.3	All Subjects	Analysis Populations
16.2.4 Demographic Data and Other Baseline Characteristics		
Listing 16.2.4.1	Safety Population	Demographics and Baseline Characteristics
Listing 16.2.4.2	Safety Population	Medical History
Listing 16.2.4.3	All Randomized Subjects	Listing of Subject Randomization
Listing 16.2.4.4	Safety Population	Study Drug Administration
16.2.7 Adverse Event Listings (by Subject)		
Listing 16.2.7.1	Safety Population	Adverse Events
Listing 16.2.7.2	Safety Population	Serious Adverse Events
Listing 16.2.7.3	Safety Population	Treatment emergent Adverse Events Related to Study Drug
Listing 16.2.7.4	Safety Population	Deaths
16.2.8 Laboratory Values by Subject		
Listing 16.2.8.1	Safety Population	Clinical Laboratory Data: Serum Chemistry
Listing 16.2.8.2	Safety Population	Clinical Laboratory Data: Hematology
Listing 16.2.8.3	Safety Population	Clinical Laboratory Data: Urine
Listing 16.2.8.4	Safety Population	Clinical Laboratory Data: Coagulation
Listing 16.2.8.5	Safety Population	Serum and Urine Pregnancy Test
16.2.9 Other Clinical Observations and Measurements (by Subject)		
Listing 16.2.9.1	Safety Population	Prior and Concomitant Medications
Listing 16.2.9.1.1	Safety Population	Rescue Medications
Listing 16.2.9.2	Safety Population	Vital Signs Measurements
Listing 16.2.9.2.1	Safety Population	Physical Examination Findings
Listing 16.2.9.3	Safety Population	12-lead Electrocardiogram Measurements
Listing 16.2.9.3.1	Safety Population	Alcohol Breathalyzer Test
Listing 16.2.9.4	Safety Population	NRS Pain Intensity Assessment

Data Listing Number	Population	Data Listing Title / Summary
Listing 16.2.9.5	Safety Population	Pain Relief Scores
Listing 16.2.9.6	Safety Population	Time to Pain Relief (Stopwatches)
Listing 16.2.9.7	Safety Population	Subjects Global Evaluation of Study Drug

12.5. Planned Figure Descriptions

The following are planned summary figures for protocol number 5003601. The figure numbers and page numbers are place holders only and will be determined when the figures are produced.

Table 7: Planned Figures

Figure Number	Population	Figure Title / Summary
Figure 14.4.1.1	ITT Population	Kaplan-Meier Plot of Time to First Perceptible Pain Relief
Figure 14.4.1.2	ITT Population	Kaplan-Meier Plot of Time to Meaningful Pain Relief
Figure 14.4.1.3	ITT Population	Kaplan-Meier Plot of Time to Onset Of Analgesia
Figure 14.4.1.4	ITT Population	Kaplan-Meier Plot of Time to Peak Pain Relief
Figure 14.4.1.5	ITT Population	Kaplan-Meier Plot of Time to First Use Of Rescue Medication
Figure 14.4.1.6	ITT Population	Mean Pid Scores versus Time
Figure 14.4.1.7	ITT Population	Mean Pain Relief Scores versus Time

Appendix 1: Premier Research Library of Abbreviations

Abbreviation	Definition
aCRF	annotated case report form
AE	adverse event
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
BMI	body mass index
BSL	biostatistician lead
CCGs	CRF completion guidelines
CDISC	clinical data interchange standards consortium
CEC	central ethics committee
CFR	code of federal regulations
CI	confidence intervals
CM	clinical manager
CMP	clinical monitoring plan
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CS	clinically significant
CSR	clinical study report

Abbreviation	Definition
CTA	clinical trial administrator
CTM	clinical trial manager
CTMS	clinical trial management system
DB	database
DBL	database lock
DM	data management
DMB	data monitoring board
DMC	data monitoring committee
DMP	data management plan
DSMB	data safety monitoring board
DSP	data safety plan
DSUR	development safety update report
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
eTMF	electronic trial master file
EU	European Union
FDA	food and drug administration
FPI	first patient in
GCP	good clinical practice
HR	heart rate

Abbreviation	Definition
IB	investigator's brochure
IC or ICF	informed consent or informed consent form
ICH	international council for harmonization
IP	investigational product
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
LLOQ	lower limit of quantification
LPI	last patient in
LPLV	last patient last visit
LPO	last patient out
MedDRA	medical dictionary for regulatory activities
MHRA	medicines and healthcare products regulatory agency
MM	medical monitor
MMP	medical monitoring plan
MMRM	mixed effect model repeat measurement
N	number
NA	not applicable
NCS	non-clinically significant
NF	non-functional
PD	protocol deviation

Abbreviation	Definition
PDGP	protocol deviation guidance plan
PE	physical examination
PI	principal investigator
PK	pharmacokinetic
PKAP	pharmacokinetic analysis plan
PM	project manager
PMP	project management plan
PP	per-protocol
PS	project specialist
PV	pharmacovigilance
PVG	pharmacovigilance group
QA	quality assurance
QARC	quality assurance, risk and compliance
QC	quality control
QOL	quality of life
SAE	serious adverse event
SAF	Safety Population
SAP	statistical analysis plan
SAS®	a software system used for data analysis
SBP	systolic blood pressure
SD	standard deviation

Abbreviation	Definition
SDS	study design specifications
SDTM	study data tabulation model
SF	screen failure
SFT or SFTP	secure file transfer or secure file transfer plan
SIV	site initiation visit
SMP	safety management plan
SOC	system organ class
TEAE	treatment-emergent adverse event
TMF	trial master file
UAT	user acceptance testing
WHO	world health organization
WHO-DD	world health organization drug dictionary

Sponsor	Reckitt Benckiser
Protocol Title:	A Randomized, Double-Blind, Double-Dummy, Parallel-Group, Multiple-Dose, Active and Placebo-Controlled Efficacy Study of Ibuprofen Prolonged-Release Tablets for the Treatment of Pain after Surgical Removal of Impacted Third Molars
Protocol Number:	5003601
Premier Research PCN:	RECK.177035
Document Version:	Amendment 1.0
Document Date:	28-Feb-2020

Approvals

Role	Signatures	Date (dd-Mmm-yyyy)
Biostatistician Premier Research	Print Name: Raghu Vishnubhotla	28-Feb-2020 | 10:03:19 EST
	Sign Name: DocuSigned by: Raghu Srinivas Vishnubhotla Signer Name: Raghu Srinivas Vishnubhotla Signing Reason: I am the author of this document Signing Time: 28-Feb-2020 | 10:03:09 EST 46FE4E466250408E961764121635BB48	
Reckitt Benckiser Representative	Print Name: Darren Targett	
	Sign Name:	

1.1. Planned Table Shells

Table 14.1.1
Subject Disposition
All Randomized Subjects

Disposition	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Study Populations [1]				
Screened				XXX
Safety Population	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
ITT Population	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Per-Protocol Population	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Completion Status [2]				
Completed Study	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Prematurely Discontinued Study Medication	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Prematurely Discontinued Study	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Reasons for discontinuation from Study				
Lost to Follow-up	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Protocol Violation	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Adverse Event	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Non-Compliance with Study Drug	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Death	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Withdrawal	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Pregnancy	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Physician Decision	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Study Terminated by Sponsor	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Other	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

[1] Percentages are based on the number of randomized subjects.
[2] Percentages are based on the number of subjects in the Safety Population.
Source: Listing 16.2.1

Table 14.1.2
Demographics and Baseline Characteristics
Safety Population

Variable Statistic or Category	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Age (years)				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
Gender				
Male	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Female	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Ethnicity				
Hispanic or Latino	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Not Hispanic or Latino	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Race				
Asian	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Black or African-American	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Native Hawaiian or Other Pacific Islander	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
White	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Baseline Pain [1]				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
Baseline Pain Category [2]				
Moderate	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Severe	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Height (cm)				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
Weight (kg)				

n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
BMI (kg/m2)				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
Surgery Duration (min)				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX

Note: Percentage are based on the number of subjects in the Safety Population.
[1] Subjects rate their pain using a numeric rating scale (NRS) from 0 (no pain) to 10 (worst pain ever).
[2] NRS pain scores at baseline are categorized as moderate (5-7), and severe (8-10).

Source: Listing 16.2.4.1

Table 14.1.2.1
Demographics and Baseline Characteristics
ITT Population
Use Same Shell as Table 14.1.2

Table 14.1.3
Medical History
Safety Population

System Organ Class Preferred Term	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with at least One Recorded Medical History	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 1				
Preferred Term 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Note: Percentages are based on number of subjects in the Safety Population.
Medical conditions were coded using MedDRA version 21.1 or later. Subjects were counted once for each system organ class (SOC) and once for each preferred term (PT). Medical history terms are displayed by descending frequency of SOC, then PT within SOC, and then alphabetically by PT.
SOURCE: Listing 16.2.4.2

Table 14.1.4
Prior Medications
Safety Population

ATC Class Level 4 Preferred Term (ATC Class Level 5)	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with at least one Prior Medication	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
ATC Class 1				
Preferred Term 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
ATC Class 2				
Preferred Term 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Note: Percentages are on number of subjects in the Safety Population.
Medications coded using WHO-DD B2E version September 2018.
Prior medications are all medications taken before the date of the first dose of study drug.
Medications are displayed by descending frequency of Anatomic Therapeutic Chemical (ATC) Level 4 classification, by Preferred Term (PT) within ATC and then alphabetically.
Subjects were counted only once for each ATC and PT.
SOURCE: Listing 16.2.9.1

Table 14.1.5
Concomitant Medications
Safety Population
Use same shell as Table 14.1.4

Table 14.1.6
Summary of Protocol Deviations
All Enrolled Subjects

Deviations	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
XXXXXXXXXXXXXXXXXXXXXX	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
XXXXXXXXXXXXXXXXXXXXXXXXXX	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
XXXXXXXXXXXXXXXXXXXXXXX	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
XXXXXXXXXXXXXXXXXXXXXXXXXXX	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Note: Percentages are based on number of all enrolled subjects.
SOURCE: Listing 16.2.2.3

Table 14.1.7
Summary of Study Drug Exposure
Safety Population

Drug Exposure	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
Number of Tables Taken			
n	XX	XX	XX
Mean	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX
Number of Active Doses Taken [1]			
n	XX	XX	
Mean	XX.X	XX.X	
Std Dev	XX.XX	XX.XX	
Median	XX.X	XX.X	
Min, Max	XX, XX	XX, XX	
Quantity of Active Drug Taken (mg)			
n			
Mean	XX.X	XX.X	
Std Dev	XX.XX	XX.XX	
Median	XX.X	XX.X	
Min, Max	XX, XX	XX, XX	
Treatment Duration (Hours) [2]			
n	XX	XX	XX
Mean	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX

Note: Percentages are based on number of all enrolled subjects.
[1] Active dose is a dose where the tablet taken has an active ingredient
[2] Duration = date/time of last dose administered – date/time of first dose administered
SOURCE: Listing 16.2.4.4.1

Table 14.3.1.1
Overall Summary of Treatment-Emergent Adverse Events
Safety Population

Subjects with at least one	Ibuprofen PR (N=XX)	Ibuprofen PR (N=XX)	Placebo (N=XX)	Overall (N=XX)
TEAE	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
TEAE by Maximum Severity				
Mild	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Moderate	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Severe	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
TEAE by Strongest Relationship				
Unassessable/Unclassifiable	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Conditional/Unclassified	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unrelated	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unrelated	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unlikely	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Possible	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Probable	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Certain	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
AE leading to Discontinuation	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
SAE	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
AE leading to Death	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Abbreviations: TEAE = Treatment emergent adverse event; SAE = Serious adverse event.
Note: Percentages are 100*n/N.
TEAEs are defined as AEs occurring or worsening with an onset at the time of or following the start of treatment with study medication.

SOURCE: Listing 16.2.7.1

Table 14.3.1.2
Summary of Treatment Emergent Adverse Events
Safety Population

System Organ Class Preferred Term	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with at least One TEAE	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]
System Organ Class 1				
Preferred Term 1	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]
Preferred Term 2	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]
Preferred Term 3	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]
System Organ Class 2				
Preferred Term 1	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]
Preferred Term 2	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]
Preferred Term 3	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]	X (XX.X%) [X]

Abbreviations: TEAE = Treatment emergent adverse event.
Note: The first number (n) corresponds to the count of unique subjects and percentage, while the second is the count of the number of events.

Percentages are 100*n/N. Subjects were counted only once for each System Organ Class (SOC) or Preferred Term.
TEAEs are defined as AEs occurring or worsening with an onset at the time of or following the start of treatment with study medication.
AEs were coded using MedDRA version 21.1.

SOURCE: Listing 16.2.7.1
Programmers Note- Ensure there is some space between the Number of subject (%) count and the number of events in the table

Table 14.3.1.3
Summary of Treatment Emergent Adverse Events by Maximum Severity
Safety Population

System Organ Class Preferred Term Maximum Severity [1]	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with at least One TEAE				
Mild	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Moderate	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Severe	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 1				
Mild	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Moderate	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Severe	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 1				
Mild	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Moderate	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Severe	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Abbreviations: TEAE = Treatment emergent adverse event; SAE = Serious adverse event.
[1] The severity shown is the greatest severity reported for a particular subject (Severe > Moderate > Mild). AEs with missing severity have been classified as Severe.
Note: Percentages are 100*n/N. Subjects were counted only once for each System Organ Class (SOC) or Preferred Term. TEAEs are defined as AEs occurring or worsening with an onset at the time of or following the start of treatment with study medication. AEs were coded using MedDRA version 21.1.
SOURCE: Listing 16.2.7.1

Table 14.3.1.4
Summary of Treatment-Emergent Adverse Events by Relationship to Study Drug
Safety Population

System Organ Class Preferred Term Greatest Relationship [1]	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with at least One TEAE	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unassessable/Unclassifiable	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Conditional/Unclassified	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unrelated	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unlikely	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Possible	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Probable	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Certain	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unassessable/Unclassifiable	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Conditional/Unclassified	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unrelated	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unrelated	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unlikely	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Possible	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Probable	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Certain	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unassessable/Unclassifiable	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Conditional/Unclassified	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unrelated	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unrelated	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Unlikely	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Possible	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Probable	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Certain	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

[1] AE relation is marked in the CRF. The relationship shown is the strongest relationship reported for a particular subject. AEs with missing relationship have been classified as Certain.
Abbreviations: TEAE = Treatment emergent adverse event.
Note: Percentages are 100*n/N. Subjects were counted only once for each System Organ Class (SOC) or Preferred Term. TEAEs are defined as AEs occurring or worsening with an onset at the time of or following the start of treatment with study medication. AEs were coded using MedDRA version 21.1.
SOURCE: Listing 16.2.7.1

Table 14.3.1.5
Summary of Non-Serious Treatment Emergent Adverse Events
Safety Population

System Organ Class Preferred Term	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with at least one non-serious TEAE	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
System Organ Class 1				
Preferred Term 1	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 2	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 3	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
System Organ Class 2				
Preferred Term 1	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 2	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 3	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X

Abbreviations: TEAE = Treatment emergent adverse event.

Note: The first number (n) corresponds to the count of unique subjects and percentage, while the second is the count of the number of events. Percentages are 100*n/N. Subjects were counted only once for each System Organ Class (SOC) or Preferred Term. TEAEs are defined as AEs occurring or worsening with an onset at the time of or following the start of treatment with study medication. AEs were coded using MedDRA version 21.1.

SOURCE: Listing 16.2.7.1
Programmers Note- Ensure there is some space between the Number of subject (%) count and the number of events in the table

Table 14.3.2.1
Summary of Serious Adverse Events
Safety Population

System Organ Class Preferred Term	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with at least one SAE	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
System Organ Class 1				
Preferred Term 1	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 2	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 3	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
System Organ Class 2				
Preferred Term 1	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 2	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 3	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X

Abbreviations: SAE = Serious adverse event. TEAE = Treatment emergent adverse event.
Note: The first number (n) corresponds to the count of unique subjects and percentage, while the second is the count of the number of events.
Percentages are 100*n/N. Subjects were counted only once for each System Organ Class (SOC) or Preferred Term.
TEAEs are defined as AEs occurring or worsening with an onset at the time of or following the start of treatment with study medication.
AEs were coded using MedDRA version 21.1.
SOURCE: Listing 16.2.7.1

Programmers Note- Ensure there is some space between the Number of subject (%) count and the number of events in the table

Table 14.3.2.2
Summary of Treatment Emergent Adverse Events Leading to Study Drug Discontinuation
Safety Population

System Organ Class Preferred Term	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Subjects with at least one TEAE that led to study drug discontinuation	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
System Organ Class 1				
Preferred Term 1	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 2	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 3	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
System Organ Class 2				
Preferred Term 1	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 2	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X
Preferred Term 3	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X	X (XX.X%) X

Abbreviations: TEAE = Treatment emergent adverse event.

Note: The first number (n) corresponds to the count of unique subjects and percentage, while the second is the count of the number of events.
Percentages are 100*n/N. Subjects were counted only once for each System Organ Class (SOC) or Preferred Term.
TEAEs are defined as AEs occurring or worsening with an onset at the time of or following the start of treatment with study medication.
AEs were coded using MedDRA version 21.1.

SOURCE: Listing 16.2.7.1

Programmers Note- Ensure there is some space between the Number of subject (%) count and the number of events in the table

Table 14.3.3.1
Listing of Serious Adverse Events
Safety Population

Subject ID	Treatment Group	Gender	Age (Units)	SAE	System Organ Class/ Preferred Term/ Verbatim Term	Start Date/ End Date (Study Day)	Severity/ Causality	Outcome/ Action Taken
XXXX		M	XX	XXXX	XXXX/XXX/XXX	DDMMMYYYY/ DDMMMYYYY ()	MILD/Related	XXX/XXX
				XXXX				

Abbreviations: SAE = Serious adverse event.
AEs were coded using MedDRA version 21.1.
Study day is calculated relative to the date of first dose of study drug.
Source- Listing 16.2.7.2

Table 14.3.3.2
Listing of Treatment Emergent Adverse Events Leading to Study Drug Discontinuation
Safety Population

Subject ID	Treatment Group	Gender	Age (Units)	TEAE	System Organ Class/ Preferred Term/ Verbatim Term	Start Date/ End Date (Study Day)	Severity/ Causality	Outcome/ Action Taken
XXXX	XX	F	XX	XXXX	XXXX/XXX/XXX	DDMMMYYYY/ DDMMMYYYY ()	MILD/Related	XXX/XXX
XXXX	XX	M		XXXX	XXXX/XXX/XXX	DDMMMYYYY/ DDMMMYYYY ()	MILD/Related	XXX/XXX

Abbreviations: TEAE = Treatment Emergent Adverse Event.
AEs were coded using MedDRA version 21.1.
TEAE= AEs that started or changed in the intensity or relationship to treatment on or after the first dose of study drug.
Study day is calculated relative to the date of first dose of study drug.

Source- Listing 16.2.7.3

Table 14.3.4.1
Listing of Potentially Clinically Significant Abnormal Laboratory Values
Safety Population

Subject Number	Treatment Group	Gender	Age (Units)	Lab Parameter	Parameter Value	Reference Range	Test Result Assessment	Date/Time of Collection (Study Day)
XXXX	XX	M	XX	Hemoglobin	XXXXX	XX-XX	High/Low	XXXXX(XX)
				Haematocrit	XXXX			

Study day is calculated relative to the date of first dose of study drug.
Source: Listing 16.2.8.2

Table 14.3.5.1
Summary of Clinical Laboratory Results
Safety Population

Hematology/Chemistry/Urinalysis Lab Parameter:XXXXXX

Visit/ Statistic	Iburprofen PR (N=XX)	Iburprofen PR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Screening				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX

Note- Clinical laboratory tests (hematology, chemistry, urinalysis) tests are only done at Screening.

SOURCE: Listing 16.2.8.1

Table 14.3.6.1
Summary of Vital Signs
Safety Population

Parameter:XXXXX

Visit/ Statistic	Iburprofen PR (N=XX)	Iburprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Baseline				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
12 hours				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
Change from Baseline to 12 hours				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
…….				

Note- Baseline is defined as the last observation recorded prior to the first dose.
Programming Note- Calculate summary stats and change from baseline for 12 hours, 24 hours and Day 8/ET visit.
Source-Listing 16.2.9.2

Table 14.3.6.2
Summary of Electrocardiogram (ECG) Interpretations
Safety Population

Visit/ Categories	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Screening				
Normal	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Abnormal - CS	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Abnormal - NCS	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Abbreviations: CS = clinically significant; NCS = not clinically significant

SOURCE: Listing 16.2.9.3

Table 14.3.6.3
Summary of 12-Lead Electrocardiogram (ECG) Parameters
Safety Population

Parameter: XXXXXX

Visit/ Stat	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Screening				
n	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX

SOURCE: Listing 16.2.9.3.

Table 14.3.6.4
Summary of Physical Examination Findings
Safety Population

Visit- Screening/Day 8/ET

Body System/ Categories	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)	Overall (N=XX)
Body System-XXXX				
Normal	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Abnormal - CS	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Abnormal - NCS	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
…..				

Abbreviations: CS = clinically significant; NCS = not clinically significant ET: end of treatment

SOURCE: Listing 16.2.9.3

Table 14.2.1
Analysis of SPID-12 Scores
ITT Population

Statistics	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
n	XX	XX	XX
Mean	XX.XX	XX.XX	XX.XX
Std Dev	XX.XXX	XX.XXX	XX.XXX
Median	XX.XX	XX.XX	XX.XX
Min, Max	XX.X,XX.X	XX.X,XX.X	XX.X,XX.X
ANCOVA Statistics [1]			
LS Mean (SE)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)
LS Mean Difference from Placebo (95% CI)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	
p-value	0.XXXX	0.XXXX	
.....			

Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error.
[1] Estimates are from an analysis of covariance model with SPID-12 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.
Note: SPID-12 is summed pain intensity difference (SPID) over 0 to 12 hours. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Baseline pain is also recorded using the NRS scale. For subjects who use rescue medication, windowed worst observation carried forward (WOCF) is used.

Source: Listing 16.x.xx

Table 14.2.1.1
Analysis of SPID-12 Scores
PP Population

(Same Shell as Table 14.2.1)

Table 14.2.1.2
Analysis of SPID-12 Scores- Sensitivity Analysis-WOCF
ITT Population
(Same Shell as Table 14.2.1)

(Programming Note-This is sensitivity analysis # 2 in section 6.1.6 of the SAP.)

Table 14.2.1.3
Analysis of SPID-12 Scores- Sensitivity Analysis-No Rescue Adjustment
ITT Population
(Same Shell as Table 14.2.1)

(Programming Note-This is sensitivity analysis # 3 in section 6.1.6 of the SAP.)

Table 14.2.1.4
Analysis of SPID-12 Scores- Sensitivity Analysis-Rescue WOCF
ITT Population
(Same Shell as Table 14.2.1)

(Programming Note-This is sensitivity analysis # 4a in section 6.1.6 of the SAP.)

Table 14.2.1.5
Analysis of SPID-12 Scores- Sensitivity Analysis-Rescue LOCF
ITT Population
(Same Shell as Table 14.2.1)

(Programming Note-This is sensitivity analysis # 4b in section 6.1.6 of the SAP.)

Table 14.2.1.6
Analysis of SPID-12 Scores- Sensitivity Analysis-Multiple Imputation
ITT Population
(Same Shell as Table 14.2.1)

(Programming Note-This is sensitivity analysis # 5 in section 6.1.6 of the SAP.)

Table 14.2.1.7

Summary of SPID-12 Scores by Baseline Pain
ITT Population

Category/Statistic	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
Baseline Pain Category-Moderate			
n	XX	XX	XX
Mean	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX
Median	XX	XX	XX
Min, Max	XX,XX	XX,XX	XX,XX
…….			

Note- SPID-12 is summed pain intensity difference (SPID) over 0 to 12 hours. Subjects will rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Baseline pain using a categorical scale that includes moderate (5-7), and severe (8-10).
Programming Note- Please complete table for all baseline pain categories.

Table 14.2.2
Analysis of Summed Pain Intensity Difference Scores
ITT Population

Category/Statistics	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
SPID-4			
n	XX	XX	XX
Mean	XX.XX	XX.XX	XX.XX
Std Dev	XX.XXX	XX.XXX	XX.XXX
Median	XX.XX	XX.XX	XX.XX
Min, Max	XX.X,XX.X	XX.X,XX.X	XX.X,XX.X
ANCOVA Statistics [1]			
LS Mean (SE)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)
LS Mean Difference from Placebo (95% CI)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	
p-value	0.XXXX	0.XXXX	
…..			

Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error.
[1] Estimates are from an analysis of covariance model with SPID score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.
Note: SPID-4/8/12 is summed pain intensity difference (SPID) over 0 to 4/8/12 hours. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Baseline pain is also recorded using the NRS scale.

Programming Note- Please program for SPID-4 SPID-8 and SPID-24.

Source: Listing 16.x.xx

Table 14.2.3
Analysis of Total Pain Relief Scores
ITT Population

(Programming Note- Use same shell as Table 14.2.2. Please add the following footnote defining sum of total pain relief (TOTPAR) Note- Total pain relief (TOTPAR) is summed total pain relief under the Pain Relief Scale (0 – 4) from 15 min through 4/8/12/24 hours)

Table 14.2.4
Analysis of Summed Pain Relief and Intensity Difference Scores
ITT Population
(Use same shell as Table 14.2.2)

Table 14.2.5
Comparison of SPID-24 in Ibuprofen PR and IR arms
ITT Population

Category/Statistics	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)
SPID-24		
ANCOVA Statistics [1]		
LS Mean (SE)	XX.XX (XX.XX)	XX.XX (XX.XX)
LS Mean Difference (95% CI)	XX.XX (XX.XX, XX.XX)	
p-value	0.XXXX	
…..		

Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval; LS = least-squares, SE = standard error, SPID=summed pain intensity difference.
[1] Estimates are from an analysis of covariance model with SPID-24/TOTPAR-24/SPRID-24 score as the dependent variable. Terms for treatment and baseline pain score were included as covariates.
Note-SPID-24 is summed pain intensity difference (SPID) over 0 to 24 hours. Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever

Table 14.2.6
Summary of Peak Pain Relief
ITT Population

Category/Statistics	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
None	X (XX.X%)	X (XX.X%)	X (XX.X%)
A Little Relief	X (XX.X%)	X (XX.X%)	X (XX.X%)
Some Relief	X (XX.X%)	X (XX.X%)	X (XX.X%)
A lot of Relief	X (XX.X%)	X (XX.X%)	X (XX.X%)
Complete Relief	X (XX.X%)	X (XX.X%)	X (XX.X%)
Odds Ratio (vs placebo) [1]	XX.XX	XX.XX	
95% CI	(XX.XX,XX.XX)	XX.XX,XX.XX)	
p-value	0.XXXX	0.XXXX	

Abbreviations: CI=Confidence Interval
[1] From a proportional odds model treatment group and baseline pain as covariates. An odds ratio > 1 means that patients experienced higher pain relief than the placebo.
Note- Subjects rate their pain relief relative to Time 0 using a 5-point categorical scale, none = 0, a little = 1, some = 2, a lot = 3, and complete = 4.

SOURCE: Listing 16.x.xx

Table 14.2.7
Time to First Perceptible Pain Relief
ITT Population

Category/Statistic	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
Number of Subjects with First Perceptible Pain Relief	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of Subjects Censored	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Time to first perceptible pain relief (hours) [1]			
Median (95% CI)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)
Q1	XX.XX	XX.XX	XX.XX
Q3	XX.XX	XX.XX	XX.XX
Range (Min-Max)	XX.X-XX.X	XX.X-XX.X	XX-XX
p-value (vs placebo) [2]	0.XXXX	0.XXXX	
Hazard Ratio (vs placebo) [3]	XX.XX	XX.XX	
95% CI	(XX.XX,XX.XX)	(XX.XX,XX.XX)	

Abbreviation- Q1- 25th Percentile, Q3- 75th Percentile
[1] From Kaplan-Meier Estimates
[2] From Log-rank/Wilcoxon test stratified by baseline pain
[3] Hazard Ratio calculated from Cox proportional hazards model with treatment group as a categorical factor and baseline pain as a continuous covariate. A hazard ratio of <1 means that patients in the Ibuprofen groups achieved pain relief faster than the placebo.
Note- Time of first perceptible pain relief is the time of first reported pain relief as assessed by the subject (i.e. subject stops the first stopwatch (irrespective of the second stopwatch)). Pain scores at baseline are categorized as moderate (5-7), and severe (8-10).

Table 14.2.8
Time to Meaningful Pain Relief
ITT Population

Use same shell as Table 14.2.4
(Programmers Note- Please add the following footnote- Abbreviation- Q1- 25th Percentile, Q3- 75th Percentile
[1] From Kaplan-Meier Estimates.
[2] From Log-rank/Wilcoxon test stratified by baseline pain.
[3] Hazard Ratio calculated from Cox proportional hazards model with treatment group as a categorical factor and baseline pain as a continuous covariate. A hazard ratio of <1 means that patients in the Ibuprofen groups achieved pain relief faster than the placebo.
Note- Time of meaningful pain relief is the time of the first reported meaningful (subjective) pain relief assessed by stopping the second stopwatch. Pain scores at baseline pain) are categorized as moderate (5-7), and severe (8-10

Table 14.2.9
Time to Onset of Analgesia
ITT Population

Category/Statistic	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
Number of Subjects with First Perceptible Pain Relief and Meaningful Pain Relief	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of Subjects Censored	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Time to onset of analgesia (hours) [1]			
Median (95% CI)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)
Q1	XX.XX	XX.XX	XX.XX
Q3	XX.XX	XX.XX	XX.XX
p-value (vs placebo) [2]	0.XXXX	0.XXXX	
p-value (PR vs IR) [2]	0.XXXX		
Range (Min-Max)	XX.X-XX.X	XX.X-XX.X	XX.X-XX.X
Hazard Ratio (95% CI) (vs placebo) [3]	XX.XX (XX.XX,XX.XX)	XX.XX (XX.XX,XX.XX)	
Hazard Ratio (95% CI) (PR vs IR) [4]	XX.XX (XX.XX,XX.XX)		

(Programmers Note- Please add the following footnote- Abbreviation- Q1- 25th Percentile, Q3- 75th Percentile
[1] From Kaplan-Meier Estimates
[2] From Log-rank/Wilcoxon test stratified by baseline pain.
[3] Hazard Ratio calculated from Cox proportional hazards model with treatment group as a categorical factor and baseline pain as a continuous covariate. If hazard ratio <1 means that patients in the Ibuprofen groups achieved pain relief faster than the placebo
[4] Hazard Ratio calculated from Cox proportional hazards model with treatment group as a categorical factor and baseline pain as a continuous covariate. If hazard ratio <1 means that patients in the PR group achieved pain relief faster than the IR.
Note- If the subject has had meaningful pain relief (i.e., presses both stopwatches) then time to onset of analgesia is date/time when the first stopwatch is stopped. Pain scores at baseline are categorized as moderate (5-7), and severe (8-10).

Table 14.2.10
Time to Peak Pain Relief
ITT Population
Use same shell as Table 14.2.7

(Programmers Note- Please add the following footnote- Abbreviation- Q1- 25th Percentile, Q3- 75th Percentile
[1] From Kaplan-Meier Estimates
[2] From Log-rank/Wilcoxon test stratified by baseline pain.
[3] Hazard Ratio calculated from Cox proportional hazards model with treatment group as a categorical factor and baseline pain as a continuous covariate. A hazard ratio of <1 means

that patients in the Ibuprofen groups achieved pain relief faster than the placebo.
Note- Time of peak pain relief is the time when pain relief, which is measured on a scale from 0 (none)-4 (complete), is maximum. Subjects who do not experience any pain relief are censored at the time of their last pain assessment.

Table 14.2.11
Time to First use of Rescue Medication
ITT Population

Use same shell as Table 14.2.7

(Programmers Note- Please add the following footnote- Abbreviation- Q1- 25th Percentile, Q3- 75th Percentile
[1] From Kaplan-Meier Estimates
[2] From Log-rank/Wilcoxon test stratified by baseline pain.
[3] Hazard Ratio calculated from Cox proportional hazards model with treatment group as a categorical factor and baseline pain as a continuous covariate. A hazard ratio of >1 means that patients in the Ibuprofen groups refrained from taking rescue medication for longer than the placebo.

Note- Subjects who do not take rescue medication are censored at the time of their last pain assessment.

Table 14.2.12
Proportion of Subjects Using Rescue Medication
ITT Population

Category/Statistic	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
Number of subjects using Rescue Medication	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Odds Ratio for Rescue Medication (Active/Placebo) [1]	XX.XX	XX.XX	
(95% CI)	(XX.XX,XX.XX)	(XX.XX,XX.XX)	
p-value	0.XXXX	0.XXXX	

Abbreviation: CI= Confidence Interval
[1] Odds ratio, CI, and p-value are from a logistic regression model estimating the probability of using rescue medication with baseline pain and treatment arm as covariates in the model. An odds ratio < 1 means patients in the Ibuprofen groups are less likely to have used rescue medication compared to those in placebo.

Table 14.2.13
Proportion of Responders
ITT Population

(Use same shell as 14.2.12. Please use footnote below.)

Abbreviation: CI=Confidence Interval
Note- A subject with ≥ 30% improvement in NRS pain intensity from T0 (predose) without rescue medication during the first 8 hours is considered a responder.
[1] Odds ratio, CI, and p-value are from a logistic regression model estimating the probability of being a responder with baseline pain and treatment arm as covariates in the model. An odds ratio > 1 means patients in the Ibuprofen groups are more likely to be responders compared to those in placebo.

Table 14.2.14
Summary of NRS Pain Intensity Difference Score
ITT Population

	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
PID 15 mins after Time 0			
n	XX	XX	XX
Mean	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX
Median	XX	XX	XX
Min, Max	XX,XX	XX,XX	XX,XX
LS Mean Difference from Placebo (95% CI)[1]	XX.XX (XX.XX, XX.XX)	XX.XX (XX.XX, XX.XX)	
p-value (vs Placebo)	0.XXXX	0.XXXX	

Abbreviations: PID= Pain Intensity Difference NRS- Numeric Rating Scale.
Note- Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. Pain intensity difference score at a time point is the difference in NRS pain intensity from baseline to that time point.
[1] From a repeated measures mixed model with treatment, timepoint, treatment by timepoint, baseline and baseline by timepoint as fixed effects, and subject as a random effect.

Programming Note- Please complete table for all scheduled time assessments.

Table 14.2.15
Summary of Pain Intensity Score at each Scheduled Time Point
ITT Population
Use same shell as Table 14.2.14

(Programmers please add the following footnote-
Note- Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever.
Programming Note- Please complete table for all scheduled time assessments. No need for LS mean difference 95%CI and p value from 14.2.14 shell)

Table 14.2.16
Summary of Pain Relief at each Scheduled Time Point
ITT Population

	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
Pain Relief 5 mins after Time 0			
n	XX	XX	XX
Mean	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX
Median	XX	XX	XX
Min, Max	XX,XX	XX,XX	XX,XX
None	X (XX.X%)	X (XX.X%)	X (XX.X%)
A Little Relief	X (XX.X%)	X (XX.X%)	X (XX.X%)
Some Relief	X (XX.X%)	X (XX.X%)	X (XX.X%)
A lot of Relief	X (XX.X%)	X (XX.X%)	X (XX.X%)
Complete Relief	X (XX.X%)	X (XX.X%)	X (XX.X%)
Odds Ratio (vs placebo) [1]	XX.XX	XX.XX	
95% CI	(XX.XX,XX.XX)	XX.XX,XX.XX)	
p-value	0.XXXX	0.XXXX	

(Programmers please add the following footnote-
1] From a repeated measures proportional odds model with treatment, timepoint, treatment by timepoint, baseline and baseline by timepoint as fixed effects, and subject as a random effect. An odds ratio > 1 means that patients experienced higher pain relief than the placebo.
Note- Subjects rate their pain relief relative to Time 0 using a 5-point categorical scale, none = 0, a little = 1, some = 2, a lot = 3, and complete = 4.
Programming Note- Please complete table for all scheduled time assessments.)

Table 14.2.17
Analysis of Patient Global Evaluation of Study Drug
ITT Population

Category/Statistics	Ibuprofen PR (N=XX)	Ibuprofen IR (N=XX)	Placebo (N=XX)
Poor	X (XX.X%)	X (XX.X%)	X (XX.X%)
Fair	X (XX.X%)	X (XX.X%)	X (XX.X%)
Good	X (XX.X%)	X (XX.X%)	X (XX.X%)
Very Good	X (XX.X%)	X (XX.X%)	X (XX.X%)
Excellent	X (XX.X%)	X (XX.X%)	X (XX.X%)
Odds Ratio (vs placebo) [1]	XX.XX	XX.XX	
95% CI	(XX.XX,XX.XX)	XX.XX,XX.XX)	
p-value	0.XXXX	0.XXXX	

Note- Patient's global evaluation of study drug is measured on a scale of 0=poor, 1=fair, 2=good, 3=very good, 4=excellent.
[1] From a proportional odds model treatment group and baseline pain as covariates. An odds ratio > 1 means that patients rated active arm more highly than placebo

1.2. Planned Listing Shells

Listing 16.2.1
Subject Disposition
All Subjects

Subject Number	Randomized?	Patient Status	Date of Last Dose (Study Day)	Date of Completion/ Discontinuation (Study Day)	Reason for Discontinuation	Was blind broken?
XXXXXX		Yes	DDMMMYYYY (XX)	DDMMMYYYY (XX)		XX
XXXXXX		Yes	DDMMMYYYY (XX)	DDMMMYYYY (XX)		XX
XXXXXX		Yes	DDMMMYYYY (XX)	DDMMMYYYY (XX)		XX
XXXXXX		No	DDMMMYYYY (X)	DDMMMYYYY (X)	XXXXXXXXXX: XXXXXXXXX	XX
XXXXXX		No	DDMMMYYYY (XX)	DDMMMYYYY (XX)	XXXXXXXXXXXXXXXXXXXXX	XX

Note: Study day is calculated relative to the date of first dose of study drug
Programming Note: If reason for early termination is other, concatenate the specify text as follows: “Other: XXXXXXXXX”. If additional details about reason for discontinuation are present in DSREASSP, then concatenate reason for discontinuation with “DSREASSP”.
If reason for early termination is lost to follow-up, concatenate with date of last contact as follows: “Lost to follow-up; date of last contact: DDMMMYYYY”.
If reason for discontinuation is a PI decision, concatenate PI decision reason as follows: “PI Decision: XXXXXXXXXX

Listing 16.2.2.1
Eligibility Criteria Not Met
All Subjects

Subject Number	Gender	Date (Study Day)		All Inclusion Criteria Met?	Any Exclusion Criteria Met?
		Screening	Informed Consent		
XXXXXX	XXXX	DDMMMYYYY (-X)	DDMMMYYYY (-X)	Yes	No
XXXXXX	XXXXXX	DDMMMYYYY (-X)	DDMMMYYYY (-X)	No: 02, 09	No
XXXXXX	XXXXXX	DDMMMYYYY (-X)	DDMMMYYYY (-X)	No: 06	No
XXXXXX	XXXX	DDMMMYYYY (-X)	DDMMMYYYY (-X)	Yes	Yes: 06
XXXXXX	XXXXXX	DDMMMYYYY (-X)	DDMMMYYYY (-X)	Yes	No
XXXXXX	XXXX	DDMMMYYYY (-X)	DDMMMYYYY (-X)	Yes	No

Note: Study day is calculated relative to the date of first dose of study drug
Programming note: If more than 1 inclusion or exclusion criterion number exists, concatenate with a comma. Decode any relevant criteria in the footnotes.

Listing 16.2.2.2
Screen Failures

Subject Number	Gender	Date of Birth	Age	Screen Fail Date	Screen Fail Reason
XXXXXX	XXXXXX	DDMMMYYYY	XX	DDMMMYYYY	Inclusion #2
XXXXXX	XXXXXX	DDMMMYYYY	XX	DDMMMYYYY	Inclusion #6
XXXXXX	XXXXXX	DDMMMYYYY	XX	DDMMMYYYY	Inclusion #4, Exclusion #6
XXXXXX	XXXXXX	DDMMMYYYY	XX	DDMMMYYYY	Other: XXXXXXXXXXXXX

Programming note: If more than 1 inclusion or exclusion criterion number exists, concatenate with a comma

Programming note: If additional details about reason for screen failure are present in, then concatenate reason for screen failure reason with “DSSFOTRN”.

Listing 16.2.2.3
Protocol Deviations
All Subjects

Subject Number	Treatment Group	Event Date (Study day)	Event Type	Violation Level	Description
XXXXXX	XXXX	XXXX(XXX)	XXXXXXXXXX XXXXXXXXXXXXX	MAJOR MINOR	XXXXXXX XXXXXXXXXXXXXX
XXXXXX	XXXX	XXXX(XXX)	XXXXXXXXXXX XXXXXXXXXXXXXXX	MINOR MINOR	XXXXXXXXXXXXXXXXXX XXXXXXXXXX
XXXXXX	XXXX	XXXX(XXX)	XXXXXXXXXXX	MAJOR	XXXXXXXXXXXXXXXXXXX

Note: Study day is calculated relative to the date of first dose of study drug.

Listing 16.2.3
Analysis Populations
All Subjects

Subject Number	Treatment Group	SAF	PP	ITT	Primary Reason(s) for Exclusion
XXXXXX	XXX	Yes	No		XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX.
XXXXXX	XXX	Yes	Yes		
XXXXXX	XXXX	No	No		

Abbreviations: PP = Per Protocol Population; SAF= Safety Population; ITT= Intent-to-treat population

Listing 16.2.4.1
Demographics and Baseline Characteristics
Safety Population

Subject Number	Gender	If Female, is she of childbearing potential?	Treatment Group	Age (years)	Ethnicity	Race	Weight (kg)	Height (cm)	BMI (kg/m2)	Duration of Surgery (hours)
XXXXXX	XX	XX	XX	XX	XXXXXXX	XXXXXXX	XX.X	XX.X	XX.XX	XX.XX
XXXXXX	XX	XX	XX	XX	XXXXXXX	XXXXXX	XX.X	XX.X	XX.XX	XX.XX
XXXXXX	XX	XX	XX	XX	XXXXXXX	XXXXXX	XX.X	XX.X	XX.XX	XX.XX
XXXXXX	XX	XX	XX	XX	XXXXXXX	XXXXX	XX.X	XX.X	XX.XX	XX.XX
XXXXXX	XX	XX	XX	XX	XXXXXXX	XXXXXX	XX.X	XX.X	XX.XX	XX.XX
XXXXXX	XX	XX	XX	XX	XXXXXX	XXXXXX	XX.X	XX.X	XX.XX	XX.XX

Abbreviation: BMI = Body mass index
Note: Height, weight, and BMI are the values at Screening.

Listing 16.2.4.2
Medical History
Safety Population

Subject Number	Treatment Group	Any Medical History	SOC/PT/VT	Start date(Study Day) / End Date(Study Day)	Ongoing?
XXX	XX	XX	XXXX/XXX/XXX	DDMMMYYYY/DDMMMYYYY(XXX)	
XXX	XX	XX	XXXX/XXX/XXX	DDMMMYYYY/DDMMMYYYY(XXX)	
XXX	XX	XX	XXXX/XXX/XXX	DDMMMYYYY/DDMMMYYYY(XXX)	
XXX	XX	XX	XXXX/XXX/XXX	DDMMMYYYY/DDMMMYYYY(XXX)	
XXX	XX	XX	XXXX/XXX/XXX	DDMMMYYYY/DDMMMYYYY(XXX)	
XXX	XX	XX	XXXX/XXX/XXX	DDMMMYYYY/DDMMMYYYY(XXX)	

SOC = System Organ Class; PT = Preferred Term; VT = Verbatim Term.
Note: All medical history terms are coded using MedDRA dictionary version 21.1. Study day is calculated relative to the date of first dose of study drug

Listing 16.2.4.3
Listing of Subject Randomization
All Randomized Subjects

Subject Number	Randomization Date	Randomization Time	Randomization Number	Kit Number Assigned	Randomized Arm
XXX	DDMMMYYYY	hh:mm	XXX	XXX	XX
XXX	DDMMMYYYY	hh:mm	XXX	XXX	XX
XXX	DDMMMYYYY	hh:mm	XXX	XXX	XX
XXX	DDMMMYYYY	hh:mm	XXX	XXX	XX
XXX	DDMMMYYYY	hh:mm	XXX	XXX	XX

Listing 16.2.4.4
Study Drug Administration
Safety Population

Subject Number	Treatment Group	Timepoint	Was Study Drug Administered?	Reason Not Administered	Date of Administration	Time of Administration
XXX	XXX	0 hours	Yes/no	XXXXXXXXXXXXX	DDMMMYYYY	hh:mm
XXX	XXX	8 hours	Yes/no	XXXXXXXXXXXXX	DDMMMYYYY	hh:mm
XXX	XXX	12 hours	Yes/no	XXXXXXXXXXXXX	DDMMMYYYY	hh:mm
XXX	XXX	16 hours	Yes/no	XXXXXXXXXXXXX	DDMMMYYYY	hh:mm

Listing 16.2.7.1
Adverse Events
Safety Population

Subject Number	Gender	Treatment Group	Any AEs reported?	TEAE?	SOC/PT/VT	Start date time(Study Day) / End Date time(Study Day)	Severity/ Relationship	Medical Treatment Received?	Outcome/ Action Taken	Other Action Taken	Serious?	Relationship to study drug
XXX	XXX	XX	XX	NO	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XX	XXXX/ XXXX		No	XX
XXX	XXX	XX	XX	YES	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XX	XXXX/ XXXX		YES	XX
XXX	XXX	XX	XX	NO	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XX	XXXX/ XXXX		No	XX
XXX	XXX	XX	XX	YES	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XX	XXXX/ XXXX		No	XX
XXX	XXX	XX	XX	YES	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XX	XXXX/ XXXX		YES	XX
XXX	XXX	XX	XX	NO	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XX	XXXX/ XXXX		NO	XX

SOC = System Organ Class; PT = Preferred Term; VT = Verbatim Term.
Abbreviation: TEAE-Treatment Emergent Adverse Event.
Note: AEs are coded using MedDRA dictionary version 21.1. TEAE is defined as any AE that occurs or worsens in severity or frequency on or after the initiation of treatment. Study day is calculated relative to the date of first dose of study drug
Programming note= Fatal/hospitalization/life threatening/persistent/congenital/important medical event

Listing 16.2.7.2
Serious Adverse Events
Safety Population

(Same shell as Listing 16.2.7.1)

Listing 16.2.7.3
Treatment emergent Adverse Events Related to Study Drug
Safety Population

(Same shell as Listing 16.2.7.1)

Listing 16.2.7.4
Deaths
Safety Population

Subject Number	Gender	Treatment Group	Date of Death(Study Day)	Cause of Death (Specify if Other)
001-003			DDMMMYYYY(XX)	XXXXXXXXXX

Note-Study day is calculated relative to the date of first dose of study drug.

Listing 16.2.8.1
Clinical Laboratory Data: Serum Chemistry
Safety Population

Subject Number	Gender	Treatment Group	Was Sample Collected?	Date/Time of Assessment	Test Name	Standard Results	Units	Abnormal? / If Yes, H or L	Comments/Reason not Done
XXX	XXX	XX		DDMMMYYYY(XX)		XX	XX	NO	
XXX	XXX	XX		DDMMMYYYY(XX)		XX	XX	NO	
XXX	XXX	XX		DDMMMYYYY(XX)		XX	XX	YES/ NO	
XXX	XXX	XX		DDMMMYYYY(XX)		XX	XX	YES/ YES	
XXX	XXX	XX		DDMMMYYYY(XX)		XX	XX	NO	

Abbreviation:H=High, L=Low
Note: Study day is calculated relative to the date of first dose of study drug.

Listing 16.2.8.2
Clinical Laboratory Data: Hematology
Safety Population

(Same shell as Listing 16.2.8.1)

Listing 16.2.8.3
Clinical Laboratory Data: Urine
Safety Population

(Same shell as Listing 16.2.8.1)

Listing 16.2.8.4
Clinical Laboratory Data: Coagulation
Safety Population

(Same shell as Listing 16.2.8.1)

Listing 16.2.8.5
Serum and Urine Pregnancy Test
Safety Population

Subject Number	Treatment Group	Visit	Was Sample Collected?	Reason not collected	Date of Assessment	Time of Assessment	Serum or Urine Test ?	Result of Pregnancy Test
001-003					DDMMMYYYY		XXXXXXXXXX	

Listing 16.2.9.1
Prior and Concomitant Medications
Safety Population

Subject Number	Treatment Group	Prior, Concomitant or Both?	ATC Class (Level 4)/ /PT /VT	Start date (Study Day)/ End Date (Study Day)	Dose Unit	Frequency	Route	Ongoing ?
XXX	XX	Prior	XXXX/XXX/XXX	DDMMMYYYY(XX) / DDMMMYYYY(XX)	XXX	XXX		
XXX		Both	XXXX/XXX/XXX	DDMMMYYYY(XX) / DDMMMYYYY (XX)	XXX	XXX		
XXX		Conmed	XXXX/XXX/XXX	DDMMMYYYY(XX) / DDMMMYYYY(XX)	XXX	XXX		
XXX			XXXX/XXX/XXX	DDMMMYYYY(XX) / DDMMMYYYY (XX)	XXX	XXX		
XXX			XXXX/XXX/XXX	DDMMMYYYY (XX) / DDMMMYYYY(XX)	XXX	XXX		
XXX			XXXX/XXX/XXX	DDMMMYYYY(XX) / DDMMMYYYY (XX)	XXX	XXX		

ATC = Anatomic Therapeutic Chemical; PT = Preferred Term; VT = Verbatim Term.
Note: Study day is calculated relative to the date of first dose of study drug. Medications are coded using WHO-DD Enhanced version MMM YYYY. Prior medications are defined as medications with start date/time before the administration of study drug. Concomitant medications are defined as any medication starting on or after the first dose of the study drug or starting before the first dose of the study drug and continuing after the first dose.

Listing 16.2.9.1.1
Rescue Medications
Safety Population

Subject Number	Treatment Group	Were any rescue medications reported ?	Medication	Date for pain relief/pain intensity	NRS Pain intensity assessment	Pain Relief Assessment	ATC Class (Level 4)/ /PT /VT	Start datetime	Dose Unit	Frequency	Route	Ongoing ?
XXX	XX	XX					XXXX/XXX/ XXX	XXXX	XXX	XXX		
XXX		XX					XXXX/XXX/ XXX	XXXX	XXX	XXX		
XXX		XX					XXXX/XXX/ XXX	XXXX	XXX	XXX		
XXX							XXXX/XXX/ XXX	XXXX	XXX	XXX		
XXX							XXXX/XXX/ XXX	XXXX	XXX	XXX		
XXX							XXXX/XXX/ XXX	XXXX	XXX	XXX		

ATC = Anatomic Therapeutic Chemical; PT = Preferred Term; VT = Verbatim Term.
Note: Medications are coded using WHO-DD Enhanced version MMM YYYY.

Listing 16.2.9.2
Vital Signs Measurements
Safety Population

Subject Number	Treatment Group	Were Vital Signs Collected?	Temperature (Units)	Heart Rate (Units)	Respiration Rate (Units)	Systolic Blood Pressure (Units)	Diastolic Blood Pressure (units)
XXX	XX		XXX	XXX	XXX	XXX	XXX
XXX			XXX	XXX	XXX	XXX	XXX
XXX			XXX	XXX	XXX	XXX	XXX
XXX				XXX	XXX	XXX	XXX
XXX				XXX	XXX	XXX	XXX
XXX				XXX	XXX	XXX	XXX

Note: Study day is calculated relative to the date of first dose of study drug.

Listing 16.2.9.2.1
Physical Examination Findings
Safety Population

Subject Number	Treatment Group	Was Sample Collected?	Date/Time of Assessment	Were mouth and neck examined ?	If no, reason	Body System	Standard Results	Abnormal? / If Yes, CS	Comments/Reason not Done
XXX	XX		DDMMMYYYYThh:mm(XX)				XX	NO	
XXX	XX		DDMMMYYYYThh:mm (XX)				XX	NO	
XXX	XX		DDMMMYYYYThh:mm(XX)				XX	YES/ NO	
XXX	XX		DDMMMYYYYThh:mm(XX)				XX	YES/ YES	
XXX	XX		DDMMMYYYYThh:mm(XX)				XX	NO	

Note: Study day is calculated relative to the date of first dose of study drug.

Listing 16.2.9.3
12-Lead Electrocardiogram Measurements
Safety Population

Subject Number	Treatment Group	Was ECG Performed?	Date of Assessment (Study Day)	Time of Assessment	Heart Rate (Unit)	RR Interval (Unit)	PR Interval (Units)	QRS (Unit)	QT (Unit)	QTc Interval (Unit)	Investigator Interpretation
XXX	XXX	XXX	DDMMMYYYY(XX)	HH:MM	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	Normal
XXX	XXX	XXX	DDMMMYYYY (XX)	HH:MM	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	Abnormal-NCS
XXX	XXX	XXX	DDMMMYYYY (XX)	HH:MM	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	Abnormal-CS
XXX	XXX	XXX	DDMMMYYYY(XX)	HH:MM	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	Normal

Abbreviation: CS=Clinically Significant, NCS=Not Clinically Significant

Note: Study day is calculated relative to the date of first dose of study drug

Listing 16.2.9.3.1
Alcohol Breathalyzer Test
Safety Population

Subject Number	Treatment	Was Alcohol Breathalyzer Test performed?	Test Date/Time (Study Day)	Alcohol Breathalyzer Test Result
XXXX	XX	Yes	DDMMMYYYYThh:mm(XX)	XXXXXXX

Note: Study day is calculated relative to the date of first dose of study drug.

Listing 16.2.9.4
NRS Pain Intensity Assessment
Safety Population

Subject Number	Treatment Group	Was NRS Pain Assessment collected?	Reason not collected	Timepoint	Was Rescue Medication Taken? (Y/N)	Date time post dose	NRS Pain Intensity Score	NRS Pain Intensity Score when rescue medication was taken	Responder (Y/N)
XXXX	XX	Yes	XXXXXXXX	XXX		XXXX	XXX	XXX	

Note- Subjects rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever. A subject with ≥ 30% improvement in NRS pain intensity from T0 (predose) without rescue medication during the first 8 hours is considered a responder.

Programing Note- For those cases where “Was rescue medication taken?” is ‘Yes’, the datetime needs to be presented in the “Date time post dose” column.

Listing 16.2.9.5
Pain Relief Scores
Safety Population

Subject Number	Treatment Group	Was assessment completed?	Reason not collected	Date of Assessment	Date time pain relief collected	Timepoint	Was Rescue Medication Taken? (Y/N)	Date time post dose	How much relief have you had since your starting pain?
XXXX	XX	Yes	XXXXXXXX			XXX		XXXX	XXX

Note: Subjects rate their pain relief relative to Time 0 using a 5-point categorical scale, none = 0, a little = 1, some = 2, a lot = 3, and complete = 4.

Programing Note- For those cases where “Was rescue medication taken?” is ‘Yes’, the datetime needs to be presented in the “Date time post dose” column

Listing 16.2.9.6
Time to Pain Relief (Stopwatches)
Safety Population

Subject Number	Treatment Group	Which stopwatch pressed, perceptible or meaningful	Hours on Stopwatch	Minutes on stopwatch	Seconds on stopwatch
XXXX	XX	Perceptible/meaningful	XX	XXX	XXX

Note: Perceptible pain relief stopwatch refers to the first stop watch and meaningful pain relief, the second stopwatch.

Listing 16.2.9.7
Subjects Global Evaluation of Study Drug
Safety Population

Subject Number	Treatment Group	Was Subject Global Evaluation of study drug completed	Date/Time of evaluation	Global evaluation score
XXXX	XX		XXXX	XX

Note: Patient's global evaluation of study drug is measured on a scale of 0=poor, 1=fair, 2=good, 3=very good, 4=excellent

Figure 14.4.1.1
Kaplan-Meier plot of time to first perceptible pain relief

ITT Population

X-Axis- Time (hours)

Y-Axis- Proportion of patients experiencing first perceptible pain relief

Figure 14.4.1.2
Kaplan-Meier plot of time to Meaningful Pain Relief

ITT Population

X-Axis- Time (hours)

Y-Axis- Proportion of patients experiencing meaningful pain relief

Figure 14.4.1.3
Kaplan-Meier plot of time to onset of analgesia

ITT Population

X-Axis- Time (hours)

Y-Axis- Proportion of patients experiencing analgesia

Figure 14.4.1.4
Kaplan-Meier plot of time to peak pain relief

ITT Population

X-Axis- Time (hours)

Y-Axis- Proportion of patients experiencing peak pain relief

Figure 14.4.1.5
Kaplan-Meier plot of time to first use of rescue medication

ITT Population

X-Axis- Time (hours)

Y-Axis- Proportion of patients using rescue medication

Figure 14.4.1.6

Mean PID Scores versus Time

ITT Population

x-axis Time (hours)

y-axis- Mean PID score

Present with error bars of +/- 1 standard error.

Figure 14.4.1.7

Mean Pain Relief Scores versus Time

ITT Population

x-axis Time (hours)

y-axis- Mean pain relief score

Present with error bars of +/- 1 standard error.

Statistical Analysis Plan

Sponsor	Reckitt Benckiser
Protocol Title:	A Randomized, Double-Blind, Double-Dummy, Parallel-Group, Multiple-Dose, Active and Placebo-Controlled Efficacy Study of Ibuprofen Prolonged-Release Tablets for the Treatment of Pain after Surgical Removal of Impacted Third Molars
Protocol Number:	5003601
Premier Research PCN:	RECK.177035
Document Version:	Final v1.0
Document Date:	7-Oct-2019

Approvals

Role	Signatures	Date (dd-Mmm-yyyy)
Biostatistician Premier Research	Print Name: Raghu Vishnubhotla Sign Name: DocuSigned by: Signer Name: Raghu Srinivas Vishnubhotla Signing Reason: I am the author of this document Signing Time: 16-Oct-2019 | 12:35:55 EDT 46FE4E466250408E961764121635BB48	16-Oct-2019 | 12:35:58 EDT
Reckitt Benckiser Representative	Print Name: Darren Targett Sign Name:	16-OCT-2019

Document History

Not applicable.

Table of Contents

List of Tables

List of Figures

No table of figures entries found.

1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Reckitt Benckiser protocol number 5003601 (A Randomized, Double-Blind, Double-Dummy, Parallel-Group, Multiple-Dose, Active and Placebo-Controlled Efficacy Study of Ibuprofen Prolonged-Release Tablets for the Treatment of Pain after Surgical Removal of Impacted Third Molars), dated 20-Nov-2018, version 1.0. Reference materials for this statistical plan include the protocol and the accompanying sample data collection documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association[2] and the Royal Statistical Society[3], for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The statistical plan described hereafter is an *a priori* plan. It will be submitted to file prior to any unblinded inferential or descriptive analysis of data pertaining to Reckitt Benckiser's study 5003601.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective is:

- To evaluate the superiority of 2 x 300 mg ibuprofen PR tablets compared with placebo in subjects experiencing acute moderate to severe pain after third molar extraction over 12 hours post initial dose.

2.1.2. Secondary Objectives

The key secondary objectives are:

- To evaluate the analgesic performance of a total daily dose of 1200 mg of ibuprofen PR formulation compared to ibuprofen immediate release (IR) formulation over 24 hours post initial dose.
- To evaluate the safety and tolerability of 2 x 300 mg ibuprofen PR tablets.

Additional secondary objectives include:

- To evaluate the total analgesic effect, peak analgesic effect, onset and duration of action and the subject's overall assessment of the study medications.

2.2. Study Endpoints

2.2.1. Safety Endpoints

The safety endpoints of this study include the following:

- Incidence of treatment-emergent adverse events (TEAEs)
- Incidence of changes in vital sign measurements

2.2.2. Efficacy Endpoints

2.2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint of this study is the summed pain intensity difference (SPID) over 0 to 12 hours (SPID12).

2.2.2.2. Secondary Efficacy Endpoint(s)

The secondary efficacy endpoints of this study include the following:

- Summed pain intensity difference (SPID) over 0 to 24 hours (SPID24) after Time 0.
- SPID4, SPID8 and SPID12
- Sum of total pain relief (TOTPAR) over 0 to 4 hours (TOTPAR4), over 0 to 8 hours (TOTPAR8), over 0 to 12 hours (TOTPAR12) and over 0 to 24 hours (TOTPAR24) after Time 0.
- Summed pain relief and intensity difference (sum of TOTPAR and SPID [SPRID]) over 0 to 4 hours (SPRID4), over 0 to 8 hours (SPRID8), over 0 to 12 hours (SPRID12) and over 0 to 24 hours (SPRID24) after Time 0.
- Response to study drug
- Numeric rating scale (NRS) pain intensity difference (PID) at each scheduled timepoint after Time 0. NRS ranges from 0=no pain to 10=worst pain ever and pain relief is a 5 point categorical scale 0=none, 1=a little, 2=some, 3=a lot, 4=complete. PID is the difference in NRS pain intensity between each time point and Time 0.
- Pain intensity score at each scheduled time point after Time 0.
- Peak pain relief
- Time to onset of analgesia
- Time to first perceptible pain relief
- Time to peak pain relief
- Proportion of subjects using rescue medication
- Time to first use of rescue medication

2.2.2.3. Exploratory Endpoint

- Patient's global evaluation of study drug. It is measured on a scale of 0=poor, 1=fair, 2=good, 3=very good, 4=excellent

3. Overall Study Design and Plan

3.1. Overall Design

3.2. Sample Size and Power

The sample size determination is based on the primary efficacy variable, SPID12. According to Farrar 2001, a clinically important improvement in pain is represented by a 2 point reduction on an 11-point NRS. Based on a baseline pain score of 7 this corresponds to an approximate 30% reduction in pain. An average 2 point difference in pain scores between ibuprofen PR and placebo across all 14 assessments up to 12 hours will correspond to a difference in SPID12 of 24 points. In a previous study, the pooled standard deviation (SD) for SPID12 was 31.65. Assuming the same variability in this study, a sample size of 40 subjects per group will have >90% power to detect a difference of 24 points in SPID12, between ibuprofen 2x300-mg PR tablets and placebo using a 2-sided test with an alpha level of 0.05. In order to provide a robust estimate of treatment effect differences between PR and IR, and to obtain a more precise estimate for this comparison, a 3:3:1 allocation ratio will be used, so that 120 subjects are randomized into each of the PR and IR groups. Thus 280 subjects will be enrolled in the study.

3.3. Study Population

Subjects with moderate to severe pain after extraction of 2 or more third molars will participate in this study.

3.4. Treatments Administered

Treatment A (test product): 2x300 mg ibuprofen PR tablets, BID (total daily dose 1200 mg)

Treatment B (reference product): 2x200 mg ibuprofen IR tablets, TID (total daily dose 1200 mg)

Treatment C: matching placebo tablets

3.5. Method of Assigning Subjects to Treatment Groups

Eligible subjects will be randomized in a 3:3:1 ratio to receive 2x300 mg ibuprofen PR tablets Q12h, 2x200 mg ibuprofen IR Q8h, or placebo using permuted blocks of fixed size. The randomization will be stratified by baseline pain category (moderate or severe) using a categorical scale that includes the categories of none (0), mild (1-4), moderate (5-7), and severe (8-10). The randomization schedule will be prepared by a statistician not otherwise involved in the study. Randomization will be performed using an interactive response system (IRT).

3.6. Blinding and Unblinding

This is a double-blind, double-dummy study. There will be two placebo tablets designed to be comparable to each of the active products (PR and IR) in both shape, size, color and weight.

All subjects will receive 4 tablets at each dosing timepoint. All subject packs will be designed and labelled to ensure blinding is maintained.

Access to the unblinding codes will be restricted to personnel not otherwise involved in the study

and will be available to the investigator only in the case of a subject requiring unblinding prior to database lock.

Unblinding will only occur after database lock or in the case of emergency unblinding.

3.7. Schedule of Events

A detailed schedule of events for the study is provided in Table 1.

Table 1: Schedule of Events

	Screening (Day -28 to Day -1)	Surgery (Day 1)						Day 2		Follow-up (Day 8 ±2 days) or ET[k]
			Post-op							
		Pre-Surgery	Pre-dose	0 h	15, 30, 45 min	1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 h	12 h	16 h	24h	
Written informed consent	X									
Assign a screening number	X									
Inclusion/exclusion criteria	X	X								
Demographics	X									
Medical history	X	X[b]								
Physical examination[c]	X									X
Vital signs[d]	X	X	X				X		X	X
Height, weight, and BMI	X									
Clinical laboratory tests (hematology, chemistry, urinalysis)	X									
Electrocardiogram	X									
Pregnancy test for female subjects of childbearing potential[e]	X	X								
Urine drug screen	X	X								
Alcohol breathalyzer test		X								
Oral radiography[f]	X									
Review study restrictions with subject	X									
Pain intensity (NRS)[g]			X		X	X	X	X	X	
Randomisation			X							
Dosing with study drug				0 h		8 h	12 h	16h		
Stopwatch assessment[h]				X						
Pain relief (5-point categorical scale)[g]					X	X	X		X	

	Screening (Day -28 to Day -1)	Surgery (Day 1)						Day 2		Follow-up (Day 8 ±2 days) or ET[k]
			Post-op							
		Pre-Surgery	Pre-dose	0 h	15, 30, 45 min	1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 h	12 h	16 h	24h	
Global evaluation of study drug[i]									X	
Concomitant medications		X[b]	X	X	X	X	X		X	X
Adverse events[j]		X	X	X	X	X	X		X	X
Dispense/prescribe pain medication for use at home, as needed									X	
Collect unused home pain medications, as needed										X
Discharge from study site									X	

Abbreviations: BMI=body mass index; ET=early termination; h=hour; min=minute; NRS=numeric rating scale; pre-op=pre-operative; post-op=post-operative.

a Times listed are relative to dosing with study drug.
b Medical history and concomitant medication use since Screening will be updated on Day 1 before surgery.
c A complete physical examination (excluding the genitourinary examination) will be performed at Screening. An abbreviated confirmatory physical assessment, including an examination of the subject's mouth and neck, will be performed at the Follow-up Visit (or Early Termination Visit).
d Vital signs will be recorded after the subject has been in a sitting position for 3 minutes at the following times: at Screening, before surgery, within 30 minutes before Time 0, 12 hours after Time 0, 24 hours after Time 0, and/or immediately before the first dose of rescue medication, and at the Follow-up Visit (or Early Termination Visit).
e Serum pregnancy test at Screening and urine pregnancy test before surgery on Day 1 (female subjects of childbearing potential only). Test results must be negative for the subject to continue in the study.
f Oral radiographs taken within 1 year before Screening will be acceptable and do not need to be repeated.
g Pain assessments will be conducted (pre-dose, if at one of the dosing timepoints of 0, 8, 12 or 16 hours) at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16 and 24 hours after Time 0 and immediately before each dose of rescue medication. Pain intensity will also be assessed pre-dose. At each assessment time point, the pain intensity assessment will be completed first and the pain relief assessment will be completed second. Subjects will not be able to compare their responses with their previous responses. Note for assessments less than 1 hour apart a window of +/-2 min is allowable whilst for assessments at least 1 hour apart a +/-5 min window is allowable.
h Two stopwatches will be started immediately after the subject has swallowed the first dose of study drug with 8 ounces of water (Time 0). Subjects will record the time to perceptible and meaningful pain relief, respectively, by stopping the stopwatches.

4. Statistical Analysis and Reporting

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher). If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

Continuous (quantitative) variable summaries will include the number of subjects (n) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum.

Categorical (qualitative) variable summaries will include the frequency and percentage of subjects who are in the particular category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population in each of the treatment arms, unless otherwise specified.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and measures of spread (SD) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified.

Unless otherwise indicated, all statistical tests will be conducted at the 0.05 significance level using 2-tailed tests, and P values will be reported. Corresponding 95% confidence intervals (CIs) will be presented for statistical tests. In addition to what is detailed in the SAP, other additional analyses may be conducted on the data which will only serve as exploratory evidence and the unplanned nature of these analyses will be made clear in the Clinical Study Report.

4.2. Interim Analysis

No interim analyses are planned.

5. Analysis Populations

The following analysis populations are planned for this study:

- **Safety Population (SAF):** The Safety Population includes all subjects who receive any amount of planned study medication. Subjects will be assigned to treatment received.
- **Intent-To-Treat Population (ITT):** The ITT population includes all subjects who are treated with study drug and who have at least 1 pain assessment after Time 0. The ITT population is the primary population for the efficacy analysis. Subjects will be assigned to treatment randomized.
- **Per Protocol (PP)**: The PP Population will consist of all ITT subjects who do not incur a major protocol violation that would challenge the validity of their data. This population will be determined at a data review meeting prior to database lock and used to evaluate the sensitivity of the primary efficacy analysis. Subjects will be assigned to treatment received.

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

The last observation recorded prior to the first dose of study drug will be used as the baseline observation for all calculations of change from baseline.

6.1.2. Adjustments for Covariates

For the primary endpoint analysis, the baseline NRS pain score will be included as a covariate.

For the secondary endpoint analyses, baseline pain will be included as a covariate for SPID, SPRID, and TOTPAR variables.

For the proportion of subjects who are responders and the proportion of subjects using rescue medication, logistic regression models will adjust for baseline pain.

For time to event endpoints, baseline pain will be included as a stratification factor.

6.1.3. Multiple Comparisons

No adjustment for multiplicity is required for the primary efficacy analysis – a single comparison of SPID12 for placebo versus SPID12 for ibuprofen PR.

No adjustments will be made for multiple comparisons for other endpoints.

6.1.4. Handling of Dropouts or Missing Data

Missing pain assessments for all efficacy analyses will be handled as follows:

- Missing pain assessments scheduled before the first observed assessment will be imputed with the subject's worst observed pain assessment.
- Missing intermediate pain assessments will be replaced by linear interpolation.
- Missing pain assessments at the end of the observation period due to premature discontinuation of pain assessments will be imputed by carrying forward the last observation prior to that missing.

All data for assessments other than pain assessments will be analyzed as collected; missing data due to premature termination or any other reason will be left as missing. Since this is a short-term study and subjects remain at the study site throughout the 24-hour pain assessment period, the discontinuation rate and the amount of missing data is expected to be minimal.

In the event that more than 10% of subjects in ibuprofen IR or PR arms take rescue medication within the first 12 hours other sensitivity analyses may be performed such as a tipping point analysis. These sensitivity analyses will be applicable to assessments taken within 4 hours after rescue. The missing pain assessments of subjects who take rescue medication will be assumed to be missing at random (MAR). Standard multiple imputation of the pain assessments under the MAR assumption is applied using PROC MI, using treatment group and baseline pain as

covariates. The missing pain assessment values after rescue medication are imputed. The resulting imputed datasets are analyzed using the ANOVA technique described in Section 8.1. The results of these analyses are pooled using PROC MIANALYZE.

The robustness of the MAR assumption and the impact of the missing data is further investigated via a tipping point approach. The tipping points are defined to be the particular setting for the missing pain assessment values that would change the study's conclusions. Multiple imputation under the Missing Not At Random (MNAR) assumption is applied by searching for a tipping point by using "shift" approaches until the MAR inferences change from significance to non-significance, or vice-versa. The shifts are applied to the Least Squares mean (LS means from the ANOVA analysis) for the subjects who take rescue medication in the Ibuprofen PR treatment arm.

6.1.5. Analysis Windows

Subjects are required to record their pain assessment (NRS and pain relief) immediately prior to each dose of rescue medication. The primary analysis will use windowed worst observation carried forward (WOCF) methodology for subjects who use rescue medication. If a subject received rescue medication at time x, for any time point within x + 4 hours, the highest pain score from time 0 up until time x will be used. If the pain score for the windowed observation is higher than the worst observed score, it will not be replaced. The same approach will be used for pain relief scores. The following sensitivity analyses will also be performed for the primary endpoint SPID12:

1. Analysis using windowed WOCF based on the PP population.

2. Pain assessments are used regardless of whether rescue medication has been taken, and no adjustment is made for use of rescue medication. In this analysis, the pain assessment recorded at the time of rescue medication is disregarded (unless it coincides with a planned pain assessment). This analysis will be done on the ITT population.

3. All pain assessments recorded after the first dose of rescue medication has been taken will be disregarded. WOCF and LOCF (Last Observation Carried Forward) imputation methods will then be used to impute the disregarded data.

    a. WOCF- The worst (highest) pain assessment until first dose of rescue medication will be used to impute all subsequent pain assessments. In other words, this method would be treating the subject as if they got no worse than their worst observed value prior to rescue medication. This analysis will be done on the ITT population.

    b. LOCF-Also, this scenario will be analyzed using LOCF method. In this LOCF analysis, the pain assessment taken immediately prior to/at the time of rescue medication will be taken as the last observed score, i.e., this method would be treating the subject as if they got no worse than their last observed value prior to rescue medication. This analysis will be done on the ITT population.

4. If more than 10% of subjects in either Ibuprofen group use rescue medication in first 12

hours, then a tipping point analysis will be implemented for all pain assessments made within 4 hrs after rescue medication. This will be done on the ITT population.

For pain assessments less than 1 hour apart a window of +/- 2 minutes is allowable, while for assessments at least 1 hour apart a +/- 5 minute window is allowable.

6.1.6. Derived Variables

At each assessment time point, subjects will complete the pain intensity NRS assessment first and the pain relief assessment second.

Planned assessment time points are as follows: 0 (predose), 15, 30, and 45 minutes, and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hours after Time 0. Please see Table 2 below.

Table 2: Planned Assessment Times

i	T_i (hours)
0	0 (predose)
1	0.25
2	0.5
3	0.75
4	1
5	1.5
6	2
7	3
8	4
9	5
10	6
11	7
12	8
13	10
14	12

15	16
16	24

- SPID-12 = summed pain intensity difference (change from Time 0) under the numeric rating scale (NRS)-time curve from 15 min through 12 hours calculated using the linear trapezoidal rule and the actual time points, where Time 0 is the time of the first dose of study drug. Scheduled time points in Table 2 will be used when actual time is missing.

$$SPID_{12} = \sum_{i=1}^{14} (T_i - T_{i-1}) * PID_i$$

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

PID is defined as

$$PID_i = PI_i - PI_0$$

Where PI is the pain intensity as measured by the NRS scale.

- SPID-x = summed pain intensity difference (change from Time 0) under the numeric rating scale (NRS)-time curve from 15 min through x hours calculated using the linear trapezoidal rule and the actual time points, where Time 0 is the time of the first dose of study drug. Scheduled time points in Table 2 will be used when actual time is missing. X = 4, 8, and 24.

$$SPID_x = \sum_{i=1}^{y} (T_i - T_{i-1}) * PID_i$$

For x=4 y=8; x=8 y=12; x=24 y=16.

- TOTPAR-x = total pain relief under the Pain Relief Scale (0 – 4) from 15 min through x hours calculated using the linear trapezoidal rule and actual time points, where Time 0 is the time of the first dose of study drug. Scheduled time points in Table 2 will be used when actual time is missing. x = 4, 8, 12, and 24.

$$TOTPAR_x = \sum_{i=1}^{y} (T_i - T_{i-1}) * PAR_i$$

For x=4 y=8; x=8 y=12; x=12 y=14; x=24 y=16. PAR_i is the pain relief score on the Pain Relief Scale (0-4) at time T_i

- SPRID-x = summed pain relief (TOTPAR) and intensity difference (SPID) from 15 min through x hours calculated using the linear trapezoidal rule and actual time points, where Time 0 is the time of the first dose of study drug. Scheduled time points in Table 2 will be used when actual time is missing. X = 4, 8, 12, and 24.

$$SPRID_x = SPID_x + TOTPAR_x$$

- Responder: subject with ≥ 30% improvement in NRS pain intensity from T_0 (predose) without rescue medication during the first 8 hours. If a subject takes rescue medication prior to the 8-hour pain assessment or if the 8-hour assessment is not performed they will be considered a non-responder. i.e.,

$$\frac{(PI_0 - PI_8)}{PI_0} * 100 \geq 30$$

  Where PI_0 and PI_8 are the predose and 8-hour NRS pain intensity measurements respectively.

- Time to onset of analgesia = If the subject has had meaningful pain relief (i.e., presses both stopwatches) then time to onset of analgesia is date/time of perceptible pain relief – date/time of the first dose of study drug. If subjects don't experience both perceptible pain relief and meaningful pain relief during the 8-hour interval after Time 0, time to onset to analgesia will be right censored at the time of their last pain assessment in the first 8 hours. For subjects who take rescue medication prior to onset of analgesia during the 8-hour interval after Time 0, time to onset of analgesia will be right censored at the time rescue medication was taken.

- Time to first perceptible pain relief = date/time of the first reported pain relief (any) as assessed by the subject (i.e. subject stops the first stopwatch (irrespective of the second stopwatch)) – date/time of the first dose of study drug. If subjects don't experience perceptible pain relief during the 8-hour interval after Time 0, time to first perceptible pain relief will be right censored at the time of their last pain assessment in the first 8 hours. If the first stopwatch is not stopped but the second stopwatch is stopped, time will be left censored at the time that the second stopwatch is stopped. In other words, it is assumed that the first stopwatch measurement has already occurred but was missed/not recorded. For subjects who take rescue medication prior to first perceptible pain relief during the 8-hour interval after Time 0, time to first perceptible pain relief will be right censored at the time rescue medication was taken.

- Time to meaningful pain relief = date/time of the first reported meaningful (subjective) pain relief as assessed by the subject (i.e. the subject stops the second stopwatch) – date/time of the first dose of study drug. If subjects don't experience meaningful pain relief during the 8-hour interval after Time 0, time to meaningful pain relief will be right censored at the time of their last pain assessment in the first 8 hours. If the subject stops the second stopwatch but doesn't stop the first stopwatch or the first stopwatch assessment is missing, then time to meaningful pain relief will be right censored at the time of their last pain assessment in the first 8 hours. For subjects who take rescue medication prior to achieving meaningful pain relief during the 8-hour interval after Time 0, time to meaningful pain relief will be right censored at the time rescue medication was taken.

- Peak pain relief- Pain relief is measured on a scale from 0 (None) to 4 (Complete). If PR_i is the pain relief measurement at time T_i , peak pain relief PPR is defined as

$$PPR = \max\{PR_1, PR_2, PR_3, \dots, PR_{16}\}$$

- Time to first use of rescue medication = date/time to the first dose of rescue medication – date/time of the first dose of study drug. If subjects don't take rescue medication, subjects will be right censored at the time of their last pain assessment.

- Time to peak pain relief = date/time of peak pain relief– date/time of the first dose of study drug. Time of peak pain relief is the time T_i when peak pain relief (PPR) first occurs. If no pain relief is observed then the time to peak pain relief will be right censored at the time of their last pain assessment.

- Change from baseline = value at current time point – value at baseline.

- TEAE = TEAE is defined as any event that started or worsened in intensity or relationship to treatment on or after the first dose of study drug.

6.1.7. Data Adjustments/Handling/Conventions

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included only in the data listings.

All *P* values will be displayed in four decimals and rounded using standard scientific notation (e.g., 0.XXXX). If a *P* value less than 0.0001 occurs it will be shown in tables as <0.0001.

Adverse events will be coded using the MedDRA version 21.1 thesaurus.

A treatment related AE is any AE with a relationship to the study drug with possible, probable or certain causality to the study drug as determined by the Investigator.

If partial dates occur, the convention for replacing missing dates for the purpose of statistical analysis is as follows: if just day is missing then the day assigned is the first day of the month or the date of first dose (if in the same month), whichever is later; if just month is missing then the month assigned is the month of the first dose, unless that results in a date prior to the first dose in which case the month after the first dose is used; and if both month and day are missing then the month assigned is the month of the first dose and the day assigned is either the first day of the month or the first dose date, whichever is later.

If partial times occur, the convention is as follows: if the missing time occurs on the day of the first dose and both the hour and minute are missing then the time assigned is the time of the first dose, otherwise if both the hour and minute are missing and the date is not the date of first dose the time assigned is 12:00; if the date is the same as the date of the first dose and only hour is missing the hour assigned is 12 or the hour of first dose, whichever is later, and if the date is the same as the date of first dose and only the minute is missing the minute assigned is 30 or the minute of first dose, whichever is later. Otherwise the hour assigned is 12 if the hour is missing and the date is not the same as the date of first dose and the minute assigned is 30 is the the date is not the same as the date of first dose.

These conventions will be applied only to adverse event onset dates and times with the following precaution: if the missing date and time reflect the date and time of onset of an adverse event, the modified date and time will be constructed to match the first documented date/time post drug administration while preserving the order in which the AE was reported in the CRF.

7. Study Patients/Subjects and Demographics

7.1. Disposition of Patients/Subjects and Withdrawals

Disposition will include tabulations of the number of subjects screened, number of subjects randomized into each treatment group, the number of subjects who received treatment, tabulated reasons for discontinuation from the study, and number of subjects in each analysis population.

7.2. Protocol Violations and Deviations

Protocol deviations will be listed.

7.3. Demographics and Other Baseline Characteristics

Summary statistics for age, gender, race, ethnicity, height, weight, BMI, baseline pain category and baseline pain (continuous) will be presented by treatment groups and overall. For the continuous variables, the number of non-missing values and the mean, standard deviation, minimum, median and maximum will be tabulated.

For the categorical variables, the counts and proportions of each value will be tabulated.

These analyses will be conducted for the ITT, PP, and Safety populations.

The number and percent of subjects reporting various medical histories, grouped by MedDRA system organ class and preferred term (coded using MedDRA v21.1), will be tabulated by

treatment group. This analysis will be conducted for the Safety Population. Physical examination findings will also be summarized by body system and examination result- Normal, Abnormal – Clinically Significant, Abnormal-Not Clinically Significant.

7.4. Exposure and Compliance

The number of doses taken and treatment duration will be summarized by descriptive statistics. All study drug will be administered in clinic. The total number of tablets taken, and the number of tablets with active ingredient taken at each time point will be summarized. The dosage (in mg) of active ingredient taken and duration of exposure, from first dose to last dose of the study treatment will be summarized using descriptive statistics. Any deviations from the planned dose should be reported.

8. Efficacy Analysis

8.1. Primary Efficacy Analysis

The primary efficacy endpoint is the summed pain intensity difference (SPID) over 0 to 12 hours (SPID12). The primary endpoint will be used to compare the test product (2x300 mg ibuprofen PR tablets) against placebo.

The primary efficacy hypothesis is that SPID12 for placebo is equal to SPID12 for ibuprofen 2x300 mg PR tablets. The primary analysis will be an ANCOVA model that includes the main effect of treatment and a covariate of the baseline NRS pain score and will use windowed worst observation carried forward (WOCF) imputation for subjects who use rescue medication. The primary analysis will be based on a 2-sided test at the significance level of 0.05. The treatment difference will be presented with a 95% confidence interval.

Normality assumptions will be tested. If the data is considered non-normal, the Wilcoxon rank sum test will be used for the comparison between treatments, and the point estimate and 95% confidence interval will be calculated using the Hodges-Lehmann estimator.

The primary efficacy analysis will be based on the ITT population. These analyses will be repeated for the PP population. SPID-12 scores will also be summarized by baseline pain category (moderate or severe).

8.2. Secondary Efficacy Analysis

8.2.1. SPID

Summed Pain Intensity Difference (SPID) will be calculated for secondary efficacy analysis as described in Section 6.1.6 at 4, 8, and 24 hours. Descriptive statistics by treatment regimen will be produced.

ANCOVA models for comparing placebo with other treatment regimens with SPID as the dependent variable and treatment group and baseline pain as covariates will be generated. These models will be computed for SPID4, SPID8 and SPID12. The least square (LS) mean and standard error (SE) for each treatment group will be estimated and the difference in LS means and 95% confidence interval (CI) for the comparison of placebo with the IR and PR treatment

regimens will be estimated. P-values will be reported but no formal statistical inferences will be made on the basis of these tests. In addition, for the SPID24 endpoint, the difference in LS means and 95% CI for the IR versus PR groups will be presented. In the event that normality assumptions are violated for a parameter, non-parametric analysis methods will be used.

8.2.2. TOTPAR

Total pain relief (TOTPAR) will be calculated as described in Section 6.1.6 at 4, 8, 12 and 24 hours. Descriptive statistics by treatment regimen will be produced.

ANCOVA models for comparing placebo with other treatment regimens with TOTPAR as the dependent variable and treatment group and baseline pain as covariates will be generated. These models will be generated at TOTPAR4, TOTPAR8, TOTPAR12 and TOTPAR24. The LS mean and SE for each treatment group will be estimated and the difference in LS means and 95% CI for the comparison of placebo with the IR and PR treatment regimens will be estimated. P-values will be reported but no formal statistical inferences will be made on the basis of these tests. In the event that normality assumptions are violated for a parameter, non-parametric analysis methods will be used.

8.2.3. SPRID

Summed pain relief and intensity difference is the sum of TOTPAR and SPID and will be calculated at 4, 8, and 12 and 24 hours as described in Section 6.1.6.

Descriptive statistics by treatment regimen will be produced for SPRID at each planned assessment time point.

ANCOVA models for comparing placebo with other treatment regimens with SPRID as the dependent variable and treatment group and baseline pain as covariates will be generated. The LS mean and SE for each treatment group will be estimated and the difference in LS means and 95% CI for the comparison of placebo with the IR and PR treatment regimens will be estimated. P-values will be reported but no formal statistical inferences will be made on the basis of these tests. In the event that normality assumptions are violated for a parameter, non-parametric analysis methods will be used.

8.2.4. Peak Pain Relief

Peak pain relief will be calculated as described in Section 6.1.6 and will be summarized by counts (and percentages) for each pain relief score. It 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 a factor for treatment and baseline pain intensity as a continuous covariate. For each of the PR and IR treatment regimens, the odds of being in a higher (better) pain relief category compared to placebo (odds ratio) will be presented with a 95% CI and associated p-value.

8.2.5. 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 6.1.6. With baseline pain as a stratification factor, treatments will be compared to placebo using a stratified log-rank test or a stratified Wilcoxon test as appropriate. Summary tables will provide the number of subjects analyzed, the number of subjects censored, estimates for the 25th, 75th percentiles and median (including 95% CI), and associated p-value for comparisons versus placebo.

A measure of the treatment effect comparing each of the active arms with placebo will be obtained by calculating a hazard ratio and 95% CI by fitting a Cox proportional hazards model with a factor for treatment group and baseline pain as a continuous covariate. The assumption of proportional hazards will first be evaluated.

8.2.6. Time to Meaningful Pain Relief

Time to first meaningful pain relief will be summarized using Kaplan-Meier methods. The definition and censoring rules are described in Section 6.1.6. With baseline pain as a stratification factor, treatments will be compared to placebo using a stratified log-rank test or a stratified Wilcoxon test. Summary tables will provide the number of subjects analyzed, the number of subjects censored, estimates for the 25th, 75th percentiles and median (including 95% CI), and associated p-value for comparisons versus placebo.

A measure of the treatment effect comparing each of the active arms with placebo will be obtained by calculating a hazard ratio and 95% CI by fitting a Cox proportional hazards model with a factor for treatment group and baseline pain as a continuous covariate. The assumption of proportional hazards will first be evaluated.

8.2.7. Time to onset of Analgesia

Time to onset of analgesia will be summarized using Kaplan-Meier methods. The definition and censoring rules are described in Section 6.1.6. With baseline pain as a stratification factor, treatments will be compared to placebo and with each other (IR vs PR) using a stratified log-rank test or a stratified Wilcoxon test. The summary tables will provide the number of subjects analyzed, the number of subjects censored, estimates for the 25th, 75th percentiles and median (including 95% CI), and associated p-value for treatment comparisons.

A measure of the treatment effect comparing each of the active arms with placebo and with each other (IR vs PR) will be obtained by calculating a hazard ratio and 95% CI by fitting a Cox proportional hazards model with a factor for treatment group and baseline pain as a continuous covariate. The assumption of proportional hazards will first be evaluated.

8.2.8. 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 6.1.6. With baseline pain as a stratification factor, treatments will be compared to placebo using a stratified log-rank test or a stratified Wilcoxon test. The summary tables will provide the number of subjects analyzed, the number of subjects censored, estimates for the 25th, 75th percentiles and median (including 95% CI), and associated p-value for comparisons versus placebo.

A measure of the treatment effect comparing each of the active arms with placebo will be

obtained by calculating a hazard ratio and 95% CI by fitting a Cox proportional hazards model with a factor for treatment group and baseline pain as a continuous covariate. The assumption of proportional hazards will first be evaluated.

8.2.9. Time to first use of Rescue Medication

Time to first use of rescue medication will be summarized using Kaplan-Meier methods. The definition of time to first use of rescue medication and censoring rules for subjects who don't take rescue medication are described in Section 6.1.6. With baseline pain as stratification factor, treatments will be compared to placebo using a stratified log-rank test or a stratified Wilcoxon test. The summary tables will provide the number of subjects analyzed, the number of subjects censored, estimates for the 25^{th}, 75^{th} percentiles and median (including 95% CI), and associated p-value for comparisons versus placebo.

A measure of the treatment effect comparing each of the active arms with placebo will be obtained by calculating a hazard ratio and 95% CI by fitting a Cox proportional hazards model with a factor for treatment group and baseline pain as a continuous covariate. The assumption of proportional hazards will first be evaluated.

8.2.10. Proportion of Responders

For the proportion of subjects who are responders, a logistic regression model that adjusts for baseline pain (as a continuous covariate) and treatment arm will be used to evaluate the treatment effect. As a measure of treatment effect for each of the PR and IR groups versus placebo, odds ratios together with a 95% CI and p-values will be presented.

8.2.11. Numeric rating scale (NRS) pain intensity difference (PID)

PID at each scheduled time point will be calculated using the formula specified in Section 6.1.6. Descriptive summaries (including mean, SD, median, minimum and maximum) will also be presented by treatment group.

8.2.12. Pain intensity score at each scheduled time point

Pain intensity is measured using NRS at planned assessment time points. Descriptive summaries (including mean, SD, median, minimum and maximum) will also be presented by treatment group.

8.2.13. Proportion of Subjects Rescue Medication

The definition of rescue medication use is presented in Section 6.1.6. The proportion of subjects using rescue medication for pain will be analyzed using logistic regression. The logistic regression model will include treatment arm and baseline pain (as a continuous covariate) as covariates. As a measure of treatment effect for each of the PR and IR groups versus placebo, odds ratios together with a 95% CI and p-values will be presented.

8.3. Exploratory Efficacy Analysis

8.3.1. 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 a factor for treatment group and baseline pain intensity as a continuous covariate. For each of the PR and IR treatment regimens, the odds of being in a higher (better) evaluation category compared to placebo (odds ratio) will be presented with a 95% CI and associated p-value.

9. Safety and Tolerability Analysis

Safety will be evaluated from reported AEs, and changes in vital signs.

All safety analyses will be performed on the Safety population.

9.1. Adverse Events

> The number and percent of subjects reporting treatment emergent AEs, grouped by MedDRA system organ class and preferred term (coded using MedDRA v21.1), will be tabulated by severity and treatment group. In the case of multiple occurrences of the same TEAE within the same subject, each subject will only be counted once for each preferred term.

The frequency and percentage of subjects reporting TEAEs, grouped by MedDRA SOC and PT, will be tabulated by treatment group for the SAF. Such summaries will be displayed for the following:

- TEAEs by SOC and PT
- TEAEs by SOC, PT, and severity
- TEAEs by SOC, PT, and relationship to the study medication
- TEAEs leading to death by SOC, and PT
- Serious TEAEs other than deaths by SOC, and PT
- TEAEs leading to premature discontinuation by SOC, and PT
- Listing of non-TEAEs

In the case of multiple occurrences of the same AE within the same subject, each subject will only be counted once for each preferred term. In summaries of AE by SOC and PT, along with the number (%) of subjects with at least 1 AE in the category, the number of events will be displayed. In the summaries showing severity and relationship to study medication the event with the maximum severity or strongest relationship will be reported. If a particular event is missing the severity and/or relationship, then the strongest possible severity or relationship will be assumed for analysis (severity = severe, relationship = certain).

Missing and partially missing AE start and/or stop dates will be imputed for the purpose of statistical analysis, according to the specifications described in Section 6.1.7.

In the AE data listings, all AEs will be displayed. AEs that are not treatment-emergent will be flagged.

9.1.1. Adverse Events Leading to Withdrawal

A summary of incidence rates (frequencies and percentages) of TEAEs leading to withdrawal of study drug, by treatment group, SOC, and preferred term will be prepared for the Safety Population. No inferential statistical tests will be performed.

A data listing of AEs leading to withdrawal of study drug will also be provided, displaying details of the event(s) captured on the CRF.

9.1.2. Deaths and Serious Adverse Events

Any deaths that occur during the study will be listed.

Serious adverse events will be listed and also tabulated by system organ class and preferred term and presented by treatment.

9.2. Clinical Safety Laboratory Data

Descriptive statistics for clinical safety laboratory data (laboratory data) recorded at screening will be presented overall and by treatment regimen. Summary tables by treatment regimen will be presented for each category of data separately. Routine clinical laboratory data will include hematology, serum chemistry, and urinalysis. Quantitative laboratory test result summaries will include N (population count for each regimen), n (number of subjects with non-missing values), mean, SD, median, and range. Qualitative tests (e.g., some urinalysis assessments) will be categorized accordingly. The set of laboratory parameters included in each table will correspond to those requested in the study protocol. Urine drug screen, alcohol breath analyzer and urine pregnancy test results will be presented in listings.

9.3. Vital Signs

Descriptive summaries of actual values and changes from baseline will be calculated for supine systolic blood pressure, supine diastolic blood pressure, heart rate, respiratory rate, and oral body temperature, and will be presented by treatment regimen. Summary statistics for 12-lead ECG parameters and counts for ECG interpretations at screening will be presented.

9.4. Concomitant Medication

Prior and concomitant medications will be summarized descriptively by treatment using counts and percentages.

Prior medications will be presented separately from concomitant medications. Medications that started prior to the first dose of study drug will be considered prior medications whether or not they were stopped prior to the first dose of study drug. Any medications continuing or starting post the first dose of study drug will be considered to be concomitant. If a medication starts prior to the first dose and continues after the first dose of study drug, it will be considered both prior

and concomitant. Medications will be coded using Sept 2018 version of World Health Organization Drug Coding ASDFK Dictionary (WHODD).

10. Changes to analysis planned in the protocol

For the time to event endpoints an additional measure of the treatment effect comparing each of the active arms with placebo will be obtained by calculating a hazard ratio and 95% CI by fitting a Cox proportional hazards model with a factor for treatment group and baseline pain as a continuous covariate. The assumption of proportional hazards will first be evaluated.

There has been a clarification to the definition of the ITT population to that stated in the protocol. The ITT population is defined as all subjects who are treated with study drug and who have at least 1 pain assessment after Time 0. In the protocol the ITT population was defined as subjects who have at least 1 pain **relief** assessment.

11. References

1. ASA. (2016) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April 2016. http://www.amstat.org/about/ethicalguidelines.cfm
2. RSS. (2014) The Royal Statistical Society: Code of Conduct, 2014. http://www.rss.org.uk/Images/PDF/join-us/RSS-Code-of-Conduct-2014.pdf.
3. US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.

12. Tables, Listings, and Figures

All listings, tables, and graphs will have a header showing the sponsor company name and protocol and a footer showing the version of SAS, the file name and path, and the source of the data (CRF page or listing number).

12.1. Planned Table Descriptions

The following are planned summary tables for protocol number 5003601. The table numbers and page numbers are place holders only and will be determined when the tables are produced.

Table 3: Demographic Data Summary Tables

Table Number	Population	Table Title/Summary
14.1 Displays of Demographics and Disposition Data		
Table 14.1.1	All Subjects	Subject Disposition
Table 14.1.2	Safety Population	Demographics and Baseline Characteristics
Table 14.1.2.1	ITT Population	Demographics and Baseline Characteristics
Table 14.1.3	Safety Population	Medical History
Table 14.1.4	Safety Population	Prior Medications
Table 14.1.5	Safety Population	Concomitant Medications
Table 14.1.6	All Enrolled Subjects	Summary of Protocol Deviations
Table 14.1.7	Safety Population	Summary of Study Drug Exposure

12.2. Efficacy Data

Table 4: Efficacy Tables

Table Number	Population	Table Title/Summary
14.2.1	ITT Population	Analysis of SPID-12 Scores
14.2.1.1	PP Population	Analysis of SPID-12 Scores
14.2.1.2	ITT Population	Analysis of Imputed SPID-12 Scores
14.2.1.3	PP Population	Analysis of SPID-12 Scores- Sensitivity Analysis
14.2.1.4	ITT Population	Summary of SPID-12 Scores by Baseline Pain
14.2.2	ITT Population	Analysis of Summed Pain Intensity Difference Scores
14.2.3	ITT Population	Analysis of Total Pain Relief Scores
14.2.4	ITT Population	Analysis of Summed Pain Relief and Intensity Difference Scores
14.2.5	ITT Population	Comparison of SPID-24 in Ibuprofen PR and IR arms
14.2.6	ITT Population	Summary of Peak Pain Relief
14.2.7	ITT Population	Time to First Perceptible Pain Relief
14.2.8	ITT Population	Time to Meaningful Pain Relief
14.2.9	ITT Population	Time to Onset of Analgesia
14.2.10	ITT Population	Time to Peak Pain Relief
14.2.11	ITT Population	Time to First use of Rescue Medication
14.2.12	ITT Population	Proportion of Subjects Using Rescue Medication
14.2.13	ITT Population	Proportion of Responders
14.2.14	ITT Population	Summary of NRS Pain Intensity Difference Score
14.2.15	ITT Population	Summary of Pain Intensity Score at each Scheduled Time Point
14.2.16	ITT Population	Summary of Pain Relief at each Scheduled Time Point
14.2.17	ITT Population	Analysis of Patient Global Evaluation of Study Drug

12.3. Safety Data

Table 5: Safety Tables

Table Number	Population	Table Title/Summary
14.3.1 Summary of Treatment Emergent Adverse Events		
Table 14.3.1.1	Safety Population	Overall Summary of Treatment-Emergent Adverse Events
Table 14.3.1.2	Safety Population	Summary of Treatment-Emergent Adverse Events
Table 14.3.1.3	Safety Population	Summary of Treatment-Emergent Adverse Events by Maximum Severity
Table 14.3.1.4	Safety Population	Summary of Treatment-Emergent Adverse Events by Relationship to Study Drug
Table 14.3.1.5	Safety Population	Summary of Non-Serious Treatment-Emergent Adverse Events
14.3.2 Summary of Deaths, Other Serious and Significant Adverse Events		
Table 14.3.2.1	Safety Population	Summary of Serious Adverse Events
Table 14.3.2.2	Safety Population	Summary of Treatment Emergent Adverse Events Leading to Discontinuation
14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events		
Table 14.3.3.1	Safety Population	Listing of Serious Adverse Events
Table 14.3.3.2	Safety Population	Listing of Treatment Emergent Adverse Events Leading to Study Drug Discontinuation
14.3.4 Abnormal Laboratory Value		
Table 14.3.4.1	Safety Population	Listing of Potentially Clinically Significant Abnormal Laboratory Values
14.3.5 Laboratory Data Summary Tables		
Table 14.3.5.1	Safety Population	Summary of Serum Chemistry Laboratory Results
14.3.6 Other Safety Data Summary Tables		
Table 14.3.6.1	Safety Population	Summary of Vital Signs
Table 14.3.6.2	Safety Population	Summary of Electrocardiogram (ECG) Interpretations
Table 14.3.6.3	Safety Population	Summary of 12-Lead Electrocardiogram (ECG) Parameters
Table 14.3.6.4	Safety Population	Summary of Physical Examination Findings

12.4. Planned Listing Descriptions

The following are planned data and patient/subject data listings for protocol number 5003601.

In general, one listing will be produced per CRF domain. All listings will be sorted by treatment, site, and subject number. All calculated variables will be included in the listings.

In all listings a blank line will be placed between each subject. Within a data listing, if an item appears line after line (e.g., repetition of subject number), then only the first occurrence will be displayed.

In data listings, the information for one subject will be kept on one page if at all possible, rather than splitting a subject's information across pages.

Table 6: Planned Listings

Data Listing Number	Population	Data Listing Title / Summary
16.2.1 Subject Discontinuations/Completions		
Listing 16.2.1	All Subjects	Subject Disposition
16.2.2 Protocol Deviations		
Listing 16.2.2.1	All Subjects	Eligibility Criteria Not Met
Listing 16.2.2.2	All Subjects	Screen Failures
Listing 16.2.2.3	All Subjects	Protocol Deviations
16.2.3 Subjects in Analysis Populations		
Listing 16.2.3	All Subjects	Analysis Populations
16.2.4 Demographic Data and Other Baseline Characteristics		
Listing 16.2.4.1	Safety Population	Demographics and Baseline Characteristics
Listing 16.2.4.2	Safety Population	Medical History
Listing 16.2.4.3	All Randomized Subjects	Listing of Subject Randomization
Listing 16.2.4.4	Safety Population	Study Drug Administration
16.2.7 Adverse Event Listings (by Subject)		
Listing 16.2.7.1	Safety Population	Adverse Events
Listing 16.2.7.2	Safety Population	Serious Adverse Events
Listing 16.2.7.3	Safety Population	Treatment emergent Adverse Events Related to Study Drug
Listing 16.2.7.4	Safety Population	Deaths
16.2.8 Laboratory Values by Subject		
Listing 16.2.8.1	Safety Population	Clinical Laboratory Data: Serum Chemistry
Listing 16.2.8.2	Safety Population	Clinical Laboratory Data: Hematology
Listing 16.2.8.3	Safety Population	Clinical Laboratory Data: Urine
Listing 16.2.8.4	Safety Population	Clinical Laboratory Data: Coagulation
Listing 16.2.8.5	Safety Population	Serum and Urine Pregnancy Test
16.2.9 Other Clinical Observations and Measurements (by Subject)		
Listing 16.2.9.1	Safety Population	Prior and Concomitant Medications
Listing 16.2.9.1.1	Safety Population	Rescue Medications
Listing 16.2.9.2	Safety Population	Vital Signs Measurements
Listing 16.2.9.2.1	Safety Population	Physical Examination Findings
Listing 16.2.9.3	Safety Population	12-lead Electrocardiogram Measurements
Listing 16.2.9.3.1	Safety Population	Alcohol Breathalyzer Test
Listing 16.2.9.4	Safety Population	NRS Pain Intensity Assessment

Data Listing Number	Population	Data Listing Title / Summary
Listing 16.2.9.5	Safety Population	Pain Relief Scores
Listing 16.2.9.6	Safety Population	Time to Pain Relief (Stopwatches)
Listing 16.2.9.7	Safety Population	Subjects Global Evaluation of Study Drug

12.5. Planned Figure Descriptions

The following are planned summary figures for protocol number 5003601. The figure numbers and page numbers are place holders only and will be determined when the figures are produced.

Table 7: Planned Figures

Figure Number	Population	Figure Title / Summary
Figure 14.4.1.1	ITT Population	Kaplan-Meier Plot of Time to First Perceptible Pain Relief
Figure 14.4.1.2	ITT Population	Kaplan-Meier Plot of Time to Meaningful Pain Relief
Figure 14.4.1.3	ITT Population	Kaplan-Meier Plot of Time to Onset Of Analgesia
Figure 14.4.1.4	ITT Population	Kaplan-Meier Plot of Time to Peak Pain Relief
Figure 14.4.1.5	ITT Population	Kaplan-Meier Plot of Time to First Use Of Rescue Medication
Figure 14.4.1.6	ITT Population	Mean Pid Scores versus Time
Figure 14.4.1.7	ITT Population	Mean Pain Relief Scores versus Time

Appendix 1: Premier Research Library of Abbreviations

Abbreviation	Definition
aCRF	annotated case report form
AE	adverse event
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
BMI	body mass index
BSL	biostatistician lead
CCGs	CRF completion guidelines
CDISC	clinical data interchange standards consortium
CEC	central ethics committee
CFR	code of federal regulations
CI	confidence intervals
CM	clinical manager
CMP	clinical monitoring plan
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CS	clinically significant
CSR	clinical study report

Abbreviation	Definition
CTA	clinical trial administrator
CTM	clinical trial manager
CTMS	clinical trial management system
DB	database
DBL	database lock
DM	data management
DMB	data monitoring board
DMC	data monitoring committee
DMP	data management plan
DSMB	data safety monitoring board
DSP	data safety plan
DSUR	development safety update report
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
eTMF	electronic trial master file
EU	European Union
FDA	food and drug administration
FPI	first patient in
GCP	good clinical practice
HR	heart rate

Abbreviation	Definition
IB	investigator's brochure
IC or ICF	informed consent or informed consent form
ICH	international council for harmonization
IP	investigational product
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
LLOQ	lower limit of quantification
LPI	last patient in
LPLV	last patient last visit
LPO	last patient out
MedDRA	medical dictionary for regulatory activities
MHRA	medicines and healthcare products regulatory agency
MM	medical monitor
MMP	medical monitoring plan
MMRM	mixed effect model repeat measurement
N	number
NA	not applicable
NCS	non-clinically significant
NF	non-functional
PD	protocol deviation

Abbreviation	Definition
PDGP	protocol deviation guidance plan
PE	physical examination
PI	principal investigator
PK	pharmacokinetic
PKAP	pharmacokinetic analysis plan
PM	project manager
PMP	project management plan
PP	per-protocol
PS	project specialist
PV	pharmacovigilance
PVG	pharmacovigilance group
QA	quality assurance
QARC	quality assurance, risk and compliance
QC	quality control
QOL	quality of life
SAE	serious adverse event
SAF	Safety Population
SAP	statistical analysis plan
SAS®	a software system used for data analysis
SBP	systolic blood pressure
SD	standard deviation

Abbreviation	Definition
SDS	study design specifications
SDTM	study data tabulation model
SF	screen failure
SFT or SFTP	secure file transfer or secure file transfer plan
SIV	site initiation visit
SMP	safety management plan
SOC	system organ class
TEAE	treatment-emergent adverse event
TMF	trial master file
UAT	user acceptance testing
WHO	world health organization
WHO-DD	world health organization drug dictionary