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STATISTICAL ANALYSIS PLAN

Protocol Number:	Bayer 21069
Study Title:	A Randomized, Double-Blind, Single-Dose, Parallel, Placebo-Controlled Trial to Determine the Dose of Caffeine in a Fixed Dose Combination Tablet of Naproxen Sodium and Caffeine to Effectively Alleviate Postsurgical Dental Pain
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CCI [redacted]

Statistical Analysis Plan
Bayer 21069
Version: v1
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SAP Approval

Authored by:

SIGNATURE: PPD [redacted] DATE: 14 MAY 2020

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SIGNATURE: PPD [redacted] DATE: 14 May 2020

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CCI [redacted]

Approved by:

SIGNATURE: PPD [redacted] DATE: 5/13/2020

PPD [redacted]

Bayer Consumer Health

Revisions to the Statistical Analysis Plan described herein must be approved through a formal written amendment with the exception of minor editorial changes to tables, figures, or listing shells, and any necessary textual clarifications for programmers that do not affect the stated analysis variables, study endpoints, or statistical methods.

SAP Change History

Version	Date	Summary of Changes	Author
v1	13MAY2020	Original document	PPD

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE(s)	adverse event(s)
CCI [redacted]	[redacted]
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
BMI	body mass index
CI(s)	confidence interval(s)
cm	centimeters
CMH	Cochran-Mantel-Haenszel
ECG	electrocardiogram
FDA	Food and Drug Administration
FDC	Fixed dose combination
HR	heart rate
hr(s)	hour(s)
ITT	intent-to-treat
kg	kilograms
LOCF	last observation carried forward
LSMean	least square mean
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minimum
n	number of observations
N	number of subjects (sample size)
OTC	over-the-counter
PP	per-protocol
PT	preferred term
SAE(s)	serious adverse event(s)
SAS®	Statistical Analysis System (SAS® Institute Inc., Cary, NC)
SD	standard deviation
SOC	system organ class
SPID	Sum of pain intensity difference
TEAE(s)	treatment-emergent adverse event(s)

TOTPAR	Total pain relief
US	United States
WHO-DDE	World Health Organization Drug Dictionary

2. INTRODUCTION

2.1 Background

In the United States, naproxen has been marketed as a prescription medication since 1976 under the brand name Naprosyn®. Its sodium salt, naproxen sodium, was first sold under the trade name Anaprox® in 1980. In 1994, the US Food and Drug Administration (FDA) approved naproxen sodium tablets (using the brand name Aleve®), 220 mg for over-the-counter (OTC) use. Aleve is indicated for the temporary relief of minor aches and pains due to: minor pain of arthritis, muscular aches, backaches, menstrual cramps, headaches, toothaches, and the common cold. It also temporarily reduces fever. As an OTC medication, Aleve should not be taken for longer than 10 days for pain or 3 days for fever unless otherwise directed by a physician.

This dose ranging study is intended to find the minimum effective dose of caffeine to potentiate the analgesic effect of naproxen sodium.

Participants who need to have third molar extraction will be solicited to participate in this study. Participants who consent to participate may benefit by receiving a medical exam, dental radiographs and no-cost surgical procedures for teeth extraction. Furthermore, post-surgical participants will be provided continuous nursing care for approximately 12 hours after surgery. Potential risks of the surgical procedure include pain, dry socket, infection, swelling, bleeding, trismus, and lip or tongue numbness. Potential risks related to local anesthesia and mild sedation include paresthesia and drowsiness. Participants who experience a treatment failure can have the option of taking a standard rescue medication commonly used for post-operative pain relief. Potential study medication benefit will be relief of postsurgical pain, which is highly prevalent following extraction of wisdom teeth. Potential risks of a single dose of OTC study medication are low and described in the Drug Facts Label.

During the study, participants will be closely monitored for evidence of adverse events. Weighing between the potential risks associated with the study and given the ability to mitigate risks through close monitoring and routine peri-operative care, this study is considered clinically and ethically acceptable.

2.2 Study Rationale

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This study is intended to find the optimal dose for caffeine to be added to CCI naproxen sodium in a single tablet. This study will also compare the analgesic efficacy of CCI CCI

3. STUDY OBJECTIVES

The primary objective of this study will be to compare a single oral dose of the FDC relative to naproxen sodium CCI Caffeine CCI and placebo.

The secondary objectives of this study will be to:

- To compare a single oral dose of the FDC relative to naproxen sodium CCI Caffeine CCI and placebo. The assessments are made in terms of:
  - Pain intensity differences Measures of pain relief
  - Duration of analgesic efficacy
  - CCI
  - CCI
  - Overall relief from pain based on measures of pain intensity and pain relief
  - Global assessment of the investigational product
- CCI
- To assess the safety and tolerability of the investigational product in terms of adverse events (AEs) and clinical parameters

4. STUDY DESIGN

4.1 Overall Study Design

This is a single center, randomized, double-blind, parallel, placebo-controlled study in participants experiencing moderate to severe postoperative dental pain. The study will consist of a Prescreening telephone call, a Screening Visit, a one-day Treatment Period and a Post-Operative phone call or visit. Eligible participants who have undergone surgical extraction of three or four third molars, 2 of which were mandibular partial or full bony impacted third molars will be kept in-house and evaluated for efficacy and safety at the study site through completion of all trial procedures.

Qualified participants will then be randomized into one of seven treatments. Approximately 300 participants will be screened prior to surgery. Approximately 190 will have surgery and approximately 180 will be randomized to a specific treatment.

The duration of each participant's participation will be approximately 37 days. For an overview on the study design and study procedures see Figure 1.

	Screening Phase	**Treatment Phase**				**Follow up Phase**
Trial Days	**Day -28 to -1**	**Day 1 Pre-surgery**	**Day 1 Surgery**	**Day 1 Post-surgery**	**Day 1**	**2-5 days after discharge**
		Check-in to study site	Surgical teeth extraction	Categorical pain ✸ NRS pain	Stopwatch method NRS pain relief Global assessment	Phone call or visit

✸ = randomized study intervention of: naproxen sodium/caffeine CCI
naproxen sodium/caffeine CCI
naproxen sodium/caffeine CCI
naproxen sodium/caffeine CCI
naproxen sodium CCI
caffeine CCI
or placebo.

4.1.1 Schedule of Visits and Assessments

The schedule of assessments can be found in Section 1.3 of the protocol.

4.1.2 Method of Assigning Subjects to Treatment Groups

On Day 1, participants will be assigned a unique number (randomization number) in ascending numerical order at the study site. The randomization number encodes the participant's assignment to one of the seven (7) arms of the study, according to the randomization schedule generated prior to the study by the Sponsor. Each participant will be dispensed blinded study intervention, labeled with his/her unique randomization number, throughout the study.

4.1.3 Blinding

Participants enrolled in the trial, investigators and their staff involved in protocol procedures or who are involved in data collection, data entry and data analysis will be blinded to the identity of the treatments until the database is locked. The study monitor will conduct product accountability after database lock. To preserve blinding, participants will be blindfolded during administration of study medication. Study drug will be dispensed by an unblinded study team member based on the randomization schedule. That team member may have no other role in the study conduct and may not reveal the study drug's identity to any members of the blinded study team.

Sponsor will supply study medication in bulk containers. Selection of the proper dose for an individual participant will be performed by an unblinded study team member using the provided randomization schedule. The unblinded study team member will withdraw the appropriate study medication from the bulk container and transfer it to a dispensing cup. All study interventions must be administered as 2 tablets per participant. Some study interventions require the addition of a placebo tablet. The unblinded study team member will then bring the study medication to the treatment room where it will be dispensed to the participant by the study team member. The unblinded study team member should have no other responsibilities in the study.

5. EFFICACY AND SAFETY ENDPOINTS

5.1 Efficacy Endpoints

5.1.1 Primary Efficacy Endpoints

The primary efficacy endpoint is the Sum of Pain Intensity Difference over 8 hours (SPID0-8).

5.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Total Pain Relief over 8 hours (TOTPAR0-8)
- Time to first use of rescue medication.
- SPID0-2, SPID0-4, SPID0-12
- TOTPAR0-2, TOTPAR 0-4, TOTPAR0-12, TOTPAR8-12
- Pain Intensity Difference (PID) at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours post-dose
- Pain Relief Scores at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours post-dose
- CCI [redacted]
- [redacted]
- CCI [redacted]
- CCI [redacted]
- Cumulative proportion taking rescue medication by timepoint
- Peak PID
- Peak Pain Relief
- CCI [redacted]
- Global Assessment of the investigational product

5.2 Safety Endpoints

Safety will be assessed by reports of adverse events (AEs), urine laboratory results, and absolute and change from baseline in vital signs.

6. STATISTICAL AND ANALYTICAL PLANS

6.1 General Methodology

CCI [redacted]

CCI [redacted]

CCI [redacted]

Reported AEs, medical history terms, and prior and concomitant procedures and therapies will be classified on the basis of Medical Dictionary for Regulatory Activities (MedDRA) terminology version 22.1 or later. Prior and concomitant medications as well as rescue medication will be classified on the basis of World Health Organization Drug Dictionary Enhanced (WHO-DDE) terminology version March 2019 or later.

6.1.1 Statistical Analysis

CCI [redacted]

6.1.2 Baseline Definition

Baseline is from the last measurement prior to study treatment.

6.1.3 Visit Windowing

Visits will not be windowed. Visits will be summarized and listed by their nominal value.

6.1.4 Adjustments for Covariates

Baseline pain intensity will be used as a covariate for the efficacy analysis where appropriate.

6.1.5 Handling of Dropouts or Missing Data

CCI [redacted]

If a partial date is reported where the day is missing, then the day will be imputed as the first day of the month unless the month is the same month as the first dose then the day will be that of first dose with the month and year remaining the same. If a partial date is reported where the month is

missing, then the month will be imputed to January unless the year is the same year as the first dose then the month will be that of first dose with the year remaining the same. If a partial date where both the day and month is missing, follow details as stated previously.

Missing AE start dates will be imputed using partial date imputation rules as previously described in this Section. Missing data for other parameters will not be imputed for analysis unless otherwise defined.

6.1.6 Interim Analyses and Data Monitoring

No interim analysis or data monitoring is planned for this study.

6.1.7 Multicenter Studies

Not applicable to this study.

6.1.8 Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons or multiplicity will be made.

6.1.9 Use of an Efficacy Subset of Subjects

The PP population will be used for the primary analysis.

6.1.10 Active-Control Studies Intended to Show Equivalence

Not applicable to this study.

6.1.11 Examination of Subgroups

Not applicable to this study.

6.2 Disposition of Subjects

The number of subjects enrolled, randomized, completed, and discontinued (including the reasons for discontinuation) will be summarized for each treatment group.

6.3 Protocol Deviations

Protocol deviations will not be entered into the database. Deviations leading to exclusion from analysis populations will be identified and summarized. All deviations will be provided to CCI via an Excel file prior to database lock and will be presented in a by-subject listing.

6.4 [redacted]

[redacted]

6.5 Demographic and Other Baseline Characteristics

All baseline summaries will be done on the ITT, PP, and Safety populations.

Sex, race, and ethnicity will be summarized by counts and percentages. Age, height (cm), weight (kg), and body mass index (BMI) will be summarized with descriptive statistics by treatment group and overall.

Oral surgery site will be presented by frequency counts and percentages for each treatment group and overall. Number of teeth extracted, impaction scores, and duration of surgery (first incision to last suture) will be summarized with descriptive statistics by treatment group and overall. All dental surgery information and oral examination data will be presented in by-subject listings.

Baseline pain score will be summarized with frequency counts and percentages as well as with descriptive statistics by treatment group and overall.

Social history (drug, alcohol, tobacco, and caffeine use) will be summarized with frequency counts and percentages by treatment group and overall. Social history will also be presented in a by-subject listing.

Medical histories / surgeries will be coded using the MedDRA dictionary and presented in a by-subject listing. Inclusion / exclusion criteria will also be presented in by-subject listings.

6.6 Prior and Concomitant Medications

Concomitant medications will be coded to preferred name and Anatomical Therapeutic Chemical (ATC) classification of ingredients using the WHO-DDE.

Medications which start prior to first dose will be considered prior medications. Ongoing medications and medications ending after the date of first dose will be considered concomitant medications. Incomplete start and end dates which could be either prior to first dose or after first dose will be considered prior to first dose.

A by-subject listing of all prior and concomitant medications will be presented. Concomitant medications will summarize drug class and preferred name by treatment group and overall for each population.

6.7 Rescue Medications

Rescue medications will be coded to preferred name and ATC classification of ingredients using the WHO-DDE.

Rescue medications will be summarized by drug class and preferred name by treatment group and overall for each population.

A by-subject listing of all rescue medications will be presented.

6.8 Analysis of Efficacy

CCI [redacted]

CCI [redacted]

For the purposes of analysis, dates of the subject assessments for efficacy will be populated programmatically when the time indicates a date change, i.e., the collection time of the time point went past midnight.

6.8.1 Primary Efficacy Analysis

CCI [redacted]

The primary efficacy endpoint is the Sum of Pain Intensity Difference over 8 hours (SPID0-8).

For each post-dose time point, PIDs will be derived by subtracting the pain intensity at the post-dose time point from the baseline intensity score (baseline score – post-baseline score). A positive difference is indicative of improvement. The time-weighted sum of pain intensity differences over 8 hours (SPID0-8) will be calculated by multiplying the PID score at each post-dose time point by the duration (in hours) since the preceding time point and then summing these values over 8 hours.

CCI [redacted]

6.8.2 Secondary Efficacy Analysis

6.8.2.1 Total Pain Relief over 8 hours

Total Pain Relief over 8 hours (TOTPAR0-8) will be calculated by multiplying the pain relief score at each post-dose time point by the duration (in hours) since the preceding time point and then summing these values over 8 hours. Nominal times as recorded by the site will be used for time points mentioned above.

TOTPAR0-8 will be analyzed in an analogous manner to the primary endpoint, SPID0-8.

6.8.2.2 Time to First Use of Rescue Medication

Time to first use of rescue medication during the treatment period will be analyzed. CCI [redacted]

CCI

[redacted]

Time to first use of rescue medication will also be presented in a by-subject listing.

6.8.2.3 Sum of Pain Intensity Differences, SPID0-2, SPID0-4, SPID0-12

SPID0-2, SPID0-4 and SPID0-12 will be calculated for 2, 4, and 12 hours by multiplying the PID score at each post-dose time point by the duration (in hours) since the preceding time point and then summing these values over 2, 4, and 12 hours, respectively.

The SPID 0-2, 0-4, and 0-12 will be analyzed similarly as to the primary endpoint.

6.8.2.4 Total Pain Relief, TOTPAR0-2, TOTPAR0-4, TOTPAR0-12, TOTPAR8-12

Total pain relief from 0 to 2, 4, and 12 hours, and 8-12 hours (TOTPAR0-2, TOTPAR0-4, TOTPAR0-12, TOTPAR8-12) will be calculated by multiplying the pain relief score at each post-dose time point by the duration (in hours) since the preceding time point and then summing these values. Nominal times as recorded by the site will be used for time points mentioned above.

TOTPAR0-2, TOTPAR0-4, TOTPAR0-12, and TOTPAR8-12 will be analyzed in an analogous manner to the primary endpoint, SPID0-8.

6.8.2.5 Pain Intensity Difference (PID) and Pain Relief

PIDs will be derived by subtracting the pain intensity at the post-dose time point from the baseline intensity score (baseline score – post-baseline score). A positive difference is indicative of improvement. Pain intensity scores and PIDs at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours post-dose will be summarized using descriptive statistics for each treatment group. In addition, line graphs showing the time effect curves will be presented by treatment group.

6.8.2.6 Peak PID and Peak Pain Relief

Peak PID and peak pain relief will be summarized using descriptive statistics for each treatment group.

6.8.2.7 [redacted]

[redacted]

6.8.2.9 Cumulative Proportion of Subjects Taking a Rescue Medication

The cumulative proportion of subjects taking rescue medication by each time point will be summarized[redacted]. In addition, the cumulative proportion of subjects taking rescue medication will be plotted at every time point for each treatment group to show the time-effect. The number of times a subject took a rescue medication over the 12-hour period will be summarized using frequency counts and percentages by treatment group.

6.8.2.10 [redacted]

[redacted]

CCI [redacted]

6.8.2.11 Global Assessment Scores

The global assessment score will be summarized using frequency counts and percentages as well as with descriptive statistics. CCI [redacted]

6.9 Safety Evaluation

Only descriptive analyses will be presented for the Safety population. No imputation will be made for missing safety data. Quantitative data for safety variables will be described by summary statistics for the original data as well as for the differences to baseline when it is appropriate. Frequency tables will be provided for qualitative data.

6.9.1 Extent of Exposure

Study treatment administration data will be presented with a by-subject listing.

6.9.2 Adverse Events

All AEs that occur during the study will be recorded and classified on the basis of Medical Dictionary for Regulatory Activities (MedDRA) terminology. Treatment-emergent AEs (TEAEs) are defined as AEs with an onset on or after the date of the first study drug administration. AEs noted prior to the first study drug administration that worsen after baseline will also be reported as AEs and included in the summaries.

TEAEs will be summarized by treatment group, the number of subjects reporting a TEAE, system organ class, preferred name, severity, relationship to study treatment (causality), and seriousness. When summarizing TEAEs by severity and relationship, each subject will be counted once within a system organ class or a preferred term by using the event with the highest severity and greatest relationship within each classification.

Serious AEs (SAEs) will be summarized.

The number and percent of subjects who experience any event, by System Organ Class (SOC), and by Preferred Term (PT) will be displayed by treatment group for the Safety population.

All adverse events and all serious adverse events will be presented in individual listings. In addition, a list of subjects who prematurely discontinue from the study due to an AE will be provided.

6.9.3 Clinical Laboratory Evaluation

Urine pregnancy tests will be presented in a by-subject listing.

Urine drug screens taken during screening and pre-surgery will be presented in a by-subject listing.

6.9.4 Other Observations Related to Safety

6.9.4.1 Vital Signs

Vital signs data for blood pressure, pulse rate, and respiratory rate will be summarized using descriptive statistics by treatment group for both the observed values and change from baseline values.

Blood pressure measurements are collected in triplicate at each timepoint. Prior to computing summary statistics, the mean of each measurement will be calculated for each subject at each timepoint. Summary statistics will be computed from each subject's mean blood pressure values at each timepoint. Individual vital sign data, as well as means of blood pressure triplicates, will be presented in a by-subject listing.

6.9.4.2 Physical Examination

Physical examination data will be presented in a by-subject listing.

6.9.4.3 Electrocardiogram (ECG) Measurements

Not applicable to this study.

7. DETERMINATION OF SAMPLE SIZE

CCI [redacted]

8. CHANGES IN THE PLANNED ANALYSES

CCI [redacted] Also, TOTPAR8-12 is included and analyzed similarly to other TOTPARs.