Study title: A Randomised, 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

ClinicalTrials.gov ID: NCT03785756

Protocol and Protocol Amendments

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File Note, dated 18-Dec-2018

Final Protocol, Version 1.0, dated 20-Nov-2018

RECKITT BENCKISER

STUDY TITLE

A Randomised, 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

Short Study Title

Efficacy Study of 300mg Ibuprofen Prolonged-Release Tablets for the Treatment of Pain After Surgical Removal of Impacted Third Molars

IND (Investigational New Drug) Number:	141948
RB Study Number:	5003601
CRO Study Number:	RECK.177369
Protocol Version and Date:	FINAL V4.0 / 12-May-2020
Previous Versions / Date(s):	FINAL V3.0 / 19-Nov-2019
Confidentiality Statement:	The information contained in this document is privileged and confidential. Do not copy, circulate or otherwise distribute without written authority from Reckitt Benckiser

KEY CONTACTS

Name and title	Address	Phone	e-mail
Sponsor: RB Healthcare UK	Dansom Lane, Hull, HU8 7DS United Kingdom	+44 (0)1482 326151	5003601@rb.com
Sponsor's Medical Expert: Neil Fawkes	Dansom Lane, Hull, HU8 7DS United Kingdom	+44 (0)1482 5833242	neil.fawkes@rb.com
Principal / Chief / Coordinating Investigator(s): Dr Todd Bertoch	JBR Clinical Research 650 East 4500 South Suite 100 Salt Lake City Utah, 84107 USA	+ 1 928 8307354	tbertoch@jbrutah.com
Sponsors Statistician: Darren Targett	Dansom Lane, Hull, HU8 7DS United Kingdom	N/A	darren.targett@primoriscs.co.uk
Contract Research Organisation: Premier Research	One Park Drive, Suite 150 Durham, NC 27709 USA	+ 1 919 627 9100	N/A
CRO Project Manager: Paul Brittain	One Park Drive, Suite 150 Durham, NC 27709 USA	+ 1 617 934 2233	paul.brittain@premier-research.com
Clinical Laboratory: Quest Diagnostics, Inc.	3489 W 2100 S, Suite 200, West Valley City, Utah 84119 USA	N/A	N/A

SIGNATURE PAGE

Protocol Final Author

DocuSigned by:
Steve Fincham
Signer Name: Steve Fincham
Signing Reason: I am the author of this document
Signing Time: 12-05-2020 | 08:06 BST
BE7614371B734BEE96BB73959AA3DE4C

Mr Stephen Fincham Date
BSc, MSc
Associate Clinical Study Manager
RB

Protocol Statistician
(Statistics and DM sections reviewed and approved):

DocuSigned by:
Darren Targett
Signer Name: Darren Targett
Signing Reason: I approve this document
Signing Time: 12-05-2020 | 09:16 BST
AFBA8AD99F4542DDA7D194D987EF1679

Darren Targett Date
Consultant Statistician
RB Representative

Sponsor's Medical Expert
(Reviewed and approved):

DocuSigned by:
Neil Fawkes
Signer Name: Neil Fawkes
Signing Reason: I approve this document
Signing Time: 12-05-2020 | 10:55 BST
FBE2F9E6498A42529274F2FA9073AD21

Dr. Neil Fawkes, MBChB Date
Clinical Research Physician
RB

Sponsor's Medical Director
(Approved to Proceed):

DocuSigned by:
Bruce Charlesworth
Signer Name: Bruce Charlesworth
Signing Reason: I have reviewed this document
Signing Time: 13-05-2020 | 14:26 BST
BD51A4AE69EE4498B7C482A182264320

Bruce Charlesworth, MBChB Date
Chief Medical Officer – Health Relief, Hygiene and Wellness
RB

INVESTIGATOR STATEMENT

I have read and understood this Clinical Study Protocol and agree:

- to conduct this clinical study in accordance with the protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). Amendments to the protocol are acceptable only upon mutual agreement with the exception of urgent safety measures that need to be taken to protect study subjects from any immediate hazard to their health and safety.
- to conduct this clinical study in accordance with the principles as set out in the Declaration of Helsinki and with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.
- to conduct this study only after a favourable opinion is obtained from the Independent Review Board and Regulatory Authority
- to report all information or data in accordance with the protocol.
- to report any serious adverse events as defined in the "Safety Reporting" section of this protocol.
- to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol.

I understand:

- that information that identifies me will be used and disclosed as described in the protocol and that such information may be transferred to countries that do not have laws protecting such information.
- that since the information in the protocol and the references in the Investigator's brochure (if applicable) are confidential, its disclosure to any third parties, other than those involved in approval, supervision or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

Principal Investigator
(Reviewed and Accepted):

13 MAY 2020

Todd Bertoch, MD
Chief Scientific Officer
JBR Clinical Research

Date

TABLE OF CONTENTS

List of Tables Contained in the Body of the Protocol

List of Figures Contained in the Body of the Protocol

LIST OF ABBREVIATIONS

Abbreviation	Abbreviation in Full
AE	Adverse Event
ANCOVA	Analysis of Covariance
AUC	Area Under the Plasma Concentration Curve
BID	Twice Daily
BMI	Body Mass Index
Cmax	Maximum Observed Plasma Concentration
CRF	Case Report Form
CRO	Contract Research Organisation
eCRF	Electronic Case Report Form
FDA	(US) Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GVG	Global Vigilance Group
HDL	High Density Lipoprotein
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IR	Immediate Release
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
IUS	Intrauterine System
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numeric Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
OTC	Over the Counter
PID	Pain Intensity Difference
PP	Per Protocol
PR	Prolonged Release
RB	Reckitt Benckiser
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SNRI	Serotonin and Noradrenaline Reuptake Inhibitor
SPID	Summed Pain Intensity Difference
SPRID	Summed Pain Relief and Intensity Difference
SSRI	Selective Serotonin Reuptake Inhibitor

Abbreviation	Abbreviation in Full
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent Adverse Event
TID	Three Times a Day
Tmax	Time to Maximum Plasma Concentration
TOTPAR	Sum of Total Pain Relief
WOCF	Worst Observation Carried Forward

STUDY SYNOPSIS

Study Title:	A randomised, 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
RB Study Number:	5003601
Background and Rationale:	Reckitt Benckiser (RB) is co-developing a new 300 mg ibuprofen prolonged release (PR) tablet with Strides Shasun Ltd. The product has been developed to meet consumer and patient needs to have access to longer acting over-the-counter analgesics. This PR formulation will reduce fluctuations in drug plasma concentrations and allow for a lower frequency of administration which is desirable in situations where pain duration is expected to be prolonged and require multiple doses of immediate release formulations. As a result, the product would be more consumer friendly, require less dosing and improve compliance with treatment. The proposed therapeutic indications of the PR product are for the short-term symptomatic treatment of mild to moderate pain such as dysmenorrhea, rheumatic pain, muscular pain, pain of non-serious arthritic conditions and backache. The proposed posology in adults over the age of 18 is: Ibuprofen 300 mg PR tablets. Two tablets to be taken every 12 hours when required for pain relief. No more than 2 doses in 24 hours. The maximum daily dose is 1200 mg and there is no proposed indication in the paediatric population. Therefore, the purpose of the proposed study is to provide supporting pivotal efficacy evidence for registration applications in Europe, Australia and Russia. The decision to progress to an efficacy clinical trial was determined on the basis of successful outcomes of the 2 phase 1 clinical trials (BE/17/279 and BE/17/281) in terms of bioavailability (BA) versus a reference ibuprofen immediate release (IR) product and bioequivalence (BE) versus comparator 600 mg ibuprofen PR.
Objectives:	**Primary Objective:** • To evaluate the superiority of 2×300 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. **Key Secondary Objectives:** • 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 2×300 mg ibuprofen PR tablets. **Additional Secondary Objectives:** • To evaluate the total analgesic effect, peak analgesic effect, onset and duration of action and the subject's overall assessment of the study medications.
Design:	This is a single centre, randomised, double-blind, double-dummy, parallel group, multiple-dose, active and placebo-controlled efficacy study to evaluate the efficacy and safety of 2×300 mg ibuprofen PR tablets in subjects with post-surgical dental pain.
Primary Endpoint:	The Summed Pain Intensity Difference (SPID) over 0 to 12 hours (SPID12) will be used to compare the test product (2×300 mg ibuprofen PR tablets) against the placebo product.
Confirmatory Evaluation:	Clinically relevant difference between placebo and PR ibuprofen over 12 hours after initial dose (for the purposes of this study, a difference of 30 % in PID scores over 12 hours after initial dose will be considered clinically relevant).[(1)]
Secondary Endpoints:	**Key secondary efficacy endpoint:** • The summed pain intensity difference (SPID) over 0 to 24 hours (SPID24) will be used to compare the test product (2×300 mg ibuprofen PR tablets twice daily [BID]) and active comparator product (2×200 mg ibuprofen IR tablets three times a day [TID]). **Efficacy endpoints:** • Summed pain intensity difference (SPID) over 0 to 4 hours (SPID4), over 0 to 8 hours (SPID8), and over 0 to 12 hours (SPID12) after Time 0 • 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 (a responder will be defined as a subject with ≥30 % improvement in pain intensity without rescue medication during the first 8 hours) • Numeric rating scale (NRS) pain intensity difference (PID) at each scheduled time point after Time 0 • Pain intensity score at each scheduled time point • Pain relief score at each scheduled time point after Time 0 • Peak pain relief • Time to onset of analgesia (measured as time to perceptible pain relief confirmed by time to meaningful pain relief) using double stopwatch • 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 **Exploratory endpoint:** • Patient's global evaluation of study drug
Safety Endpoints:	• Incidence of treatment-emergent adverse events (TEAEs) • Incidence of clinically relevant changes in vital sign measurements
Subjects:	**Inclusion Criteria** A subject will be eligible for study entry if all the following inclusion criteria are met: 1) Is male or female ≥ 18 and ≤ 50 years of age. 2) Requires extraction of 2 or more third molars. At least 1 of the third molars must be a fully or partially bone impacted mandibular molar. If only 2 molars are removed, then they must be ipsilateral. 3) Experiences moderate to severe pain intensity within 6 hours after surgery, as measured by a numeric rating scale (NRS) score of ≥ 5 on a 0-10 scale. 4) Has a body weight ≥ 45 kg and a body mass index (BMI) ≤ 35 kg/m^2. 5) Female subjects of child-bearing potential must have been using an acceptable method of contraception for at least 30 days prior to randomization and be willing to continue use until at least 48 hours post discharge from the clinic (see Section 4.4). To be considered not of child-bearing potential, females must be surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or post-menopausal (defined as no menses for 12 months without an alternative medical cause).

	6) Free of clinically significant abnormal findings as determined by medical history, physical examination, vital signs, laboratory tests and ECG. 7) Is able to provide written informed consent. 8) Is willing and able to comply with study requirements (including diet and smoking restrictions), complete the pain evaluations, remain at the study site overnight, and return for follow-up 7 (± 2) days after surgery, (Day 8 ± 2 days). **Exclusion Criteria** A subject will not be eligible for study entry if any of the following exclusion criteria are met: 1) Known hypersensitivity reactions or allergy (e.g. asthma, rhinitis, angioedema or urticaria) in response to nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen), acetylsalicylic acid (aspirin), ingredients of the study drug, or any other drugs used in the study, including anaesthetics and antibiotics that may be required on the day of surgery. 2) A history of active or previous peptic ulceration/ haemorrhage, gastrointestinal bleeding or perforation, heart failure, renal or hepatic failure, uncontrolled hypertension, asthma, nasal polyps, or chronic rhinitis. 3) Has complications from the tooth extraction or any other clinically significant medical history that, in the opinion of the investigator, would affect the subject's ability to comply or otherwise contraindicate study participation, including but not limited to the following: cardiac, respiratory, gastroenterological, neurological, psychological, immunological, haematological, oncological, or renal disease. 4) Has undergone another dental surgery within 60 days prior to the day of surgery. 5) A positive urine drugs of abuse screen or alcohol breathalyser test at screening and during the study (with the exception of a positive drugs of abuse screen that is a consequence of permitted prescription medicines). 6) If female, has a positive pregnancy test at screening (serum) or on the day of surgery prior to surgery (urine), or is lactating. 7) Has known or suspected, (in the opinion of the investigator), history of alcoholism or drug abuse within 2 years of screening or evidence of tolerance or physical dependence before dosing with study drug. 8) Taking any concomitant medications that might confound assessments of pain relief, such as psychotropic drugs, antidepressants, sedative-hypnotics (other than those permitted for

	conscious sedation), or other analgesics taken within five times of their elimination half-lives. Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) are permitted if the subject has been on a stable dose for at least four weeks prior to Visit 1 (screening). 9) Is considered by the investigator, for any reason (including, but not limited to the risks described as precautions, warnings and contraindications in the current version of the investigator's brochure for 300 mg ibuprofen PR tablets), to be an unsuitable candidate to receive the study drug. 10) Has a history of chronic use (defined as daily use for > 2 weeks) of nonsteroidal anti-inflammatory (NSAIDs), opiates, or glucocorticoids (except inhaled nasal steroids and topical corticosteroids), for any condition within 6 months before dosing with study drug. 11) Has significant difficulties swallowing capsules or tablets or is unable to tolerate oral medication. 12) Subject has received an investigational product or participated in another trial involving a marketed or investigational drug in the 30 days (or for investigational agents with a long half-life, a washout of 5 half-lives) prior to first drug administration (washout period between studies is defined as the period of time elapsed between the last dose of the previous study and first dose for this study). Or if the investigator believes that any previous participation in an investigational study would be to the detriment of the safety of the participant or the conduct of the study. 13) Enrolment of the Investigator, his / her family members, employees and other dependent persons. 14) Failure to satisfy the investigator of fitness to participate for any other reason.
Products to be Evaluated and Treatment Regimen:	**Test product:** • 300 mg ibuprofen PR tablets for oral administration **Reference products:** • 200 mg ibuprofen IR tablets for oral administration • Placebo (for blinding purposes, two types of placebo tablets will be made; one to look like the test product and one to look like the reference product) **Treatment regimens:** Eligible subjects meeting all study entry criteria will be randomised to receive 1 of the following treatments:

	• Treatment A: test product; 2×300 mg ibuprofen PR tablets, BID (total daily dose 1200 mg) • Treatment B: reference product; 2×200 mg ibuprofen IR tablets, TID (total daily dose 1200 mg) • Treatment C: matching placebo tablets
Methodology:	This is a single centre, randomised, double blind, double-dummy, parallel group-, multiple-dose, active and placebo controlled efficacy study to evaluate the efficacy and safety of ibuprofen 2×300 mg ibuprofen PR tablets in subjects with post-surgical dental pain. Eligible subjects will complete all screening procedures within 28 days before the surgery and randomisation. At Screening, subjects will provide written informed consent to participate in the study before any protocol specified procedures or assessments are completed. On Day 1, subjects who continue to be eligible for study participation after completing screening procedures and assessments will undergo extraction of 2 or more third molars. At least 1 of the third molars must be a fully or partially bone impacted mandibular molar. If only 2 molars are removed, then they must be ipsilateral. All subjects will receive local anaesthesia (2% lidocaine with 1:100,000 epinephrine). Nitrous oxide will be allowed at the discretion of the investigator. Subjects who experience moderate to severe pain intensity (a score of ≥ 5 on a numeric rating scale [NRS] from 0-10 where 0 = no pain, 10 = worst pain ever) within 6 hours after surgery and who continue to meet all study entry criteria will be randomised in a 3:3:1 ratio to receive 2×300 mg ibuprofen PR tablets every 12 hours (Q12h), 2×200 mg ibuprofen IR tablets every 8 hours (Q8h), or placebo. The randomisation 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). Subjects will re-assess their baseline pain intensity using the NRS immediately before receiving study drug (pre-dose, Time 0) and their pain intensity (NRS) and pain relief (5-point categorical scale) at the following time points (pre-dose, if at one of the dosing timepoints of 0, 8, 12 and/or 16 hours): 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, if any. 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. The double stopwatch method will be used to record the time to perceptible pain relief and time to meaningful pain relief during the 8 hours following the first dose or until subject takes rescue

	medication. Subjects will complete a global evaluation of study drug 24 hours (+/- 5 minutes) after Time 0 or immediately before the first dose of rescue medication (whichever occurs first). Vital signs will be recorded after the subject has been in a sitting position for 3 minutes at the following times: before surgery, within 30 minutes before Time 0, 12 and 24 hours after Time 0, and/or immediately before the first dose of rescue medication. Adverse events (AEs) will be monitored and recorded from the time of signing of the informed consent form (ICF) until the Follow up- Visit (or Early Termination Visit). During the 24 hours following Time 0, subjects will complete efficacy and safety assessments. Subjects will remain at the study site overnight and will be discharged on Day 2. Paracetamol / acetaminophen (1000 mg) will be permitted as the initial rescue medication. Subjects will be encouraged to wait at least 60 minutes after receiving study drug before taking rescue medication. If acetaminophen rescue medication is not effective in relieving the subject's pain, 5 mg oxycodone rescue medication may be administered at the discretion of the investigator. Subjects are not permitted to take any concomitant medications that might confound assessments of pain relief, such as psychotropic drugs, antidepressants, sedative-hypnotics (other than those permitted for conscious sedation), or other analgesics taken within five times of their elimination half-lives (other than those used at the surgery). Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) are permitted if the subject has been on a stable dose for at least four weeks prior to Visit 1 (screening). Other restrictions include the following: alcohol use is prohibited from 24 hours before surgery until discharge on Day 2; nothing by mouth from midnight before surgery until 1 hour after surgery; clear liquids only are allowed starting 1 hour after surgery until 1 hour after dosing; 1 hour after dosing, the subject's diet may be advanced according to standard practice. Upon discharge from the study site, subjects may be prescribed pain medication for use at home according to the standard practice of the study site. On Day 8 (± 2 days), subjects will return to the study site for an abbreviated confirmatory physical assessment and AE assessments.
Statistical Evaluation:	**Analysis Populations** The analysis populations include the following:

	• The intent-to-treat (ITT) population will consist of all subjects who are treated with study drug and who have at least 1 pain relief assessment after Time 0. The ITT population is the primary population for the efficacy analysis. • The per protocol- (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 utilized to evaluate the sensitivity of the primary efficacy analysis. • The safety population will include all subjects who are treated with study drug. The safety population is the population for all safety assessments. **Subject Characteristics** Demographic and baseline characteristics (including date of birth, sex, race, weight, height, BMI and medical history) will be summarized for each treatment group and for the overall population using descriptive statistics. No formal statistical analyses will be performed. **Efficacy Analyses** The primary efficacy null hypothesis is that SPID12 for placebo is equal to SPID12 for ibuprofen 2×300 mg PR tablets. The primary analysis will be an ANCOVA (Analysis of Covariance) model that includes the main effect of treatment and the baseline pain score as a covariate 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. All other comparisons between the treatment regimens, including ibuprofen 2×200 mg IR tablets versus placebo, will be considered secondary. No P value adjustment will be made for multiple endpoints or multiple comparisons. Each efficacy endpoint will be summarized descriptively by treatment group. For continuous secondary endpoints such as pain intensity score, SPID at each scheduled time point, peak pain intensity, TOTPAR4, TOTPAR8, TOTPAR12, TOTPAR24, SPID4, SPID8, SPID24, SPRID4, SPRID8, SPRID12, and SPRID24, descriptive statistics (such as mean, standard deviation, median, minimum, and maximum) will be provided for each treatment regimen. Nominal P values from ANCOVA models comparing the placebo group with other treatment groups, including terms for treatment and baseline pain will be provided for SPID, SPRID, and TOTPAR variables, but no formal statistical inferences will be drawn on the basis of these tests. For ordinal secondary endpoints, such as pain intensity difference at each scheduled time point, pain relief at each scheduled time point,

	peak pain relief, response to study drug, and global evaluation of study drug, descriptive summaries will be provided and will include the number and percentage of subjects within each category for each treatment group. Nominal P values from Fisher's exact tests (or chi-square- tests, as appropriate) comparing the placebo group with other treatment groups will be provided for peak pain relief and global evaluation of study drug, but no formal statistical inferences will be drawn on the basis of these tests. For each time to- event endpoint, Kaplan Meier methodology will be used to evaluate the treatment effect. Time to onset of analgesia (measured as time to perceptible pain relief confirmed by meaningful pain relief) will be based on data collected using the double stopwatch method. Time to onset of analgesia will be -right censored- at 8 hours for subjects who do not experience both perceptible pain relief and meaningful pain relief during the 8-hour interval after Time 0. For time to onset of analgesia, the comparison of interest will be the ibuprofen 2×300 mg PR group versus the ibuprofen 2×200 mg IR group. The summary tables will provide the number of subjects analysed, the number of subjects censored, estimates for the quartiles, and 95% confidence intervals (CIs) for the estimated median and the restricted mean estimate. P values from the Wilcoxon or log rank- tests (as appropriate) will also be used to compare placebo to the active treatments. For the responder analysis and the proportion of subjects using rescue medication, logistic regression models that adjust for baseline intensity and/or significant demographic variables, if appropriate, will be used to evaluate the treatment effect. Baseline values are defined as the last measurements taken before dosing with a study drug. 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. The primary analysis will use windowed worst observation carried forward (WOCF) methodology for subjects who use rescue medication. Any pain measurements taken during a period of time in which rescue

	medication (any intervention used by the participant intended to alleviate pain) is active (4 hours) will be replaced by the worst pain measurement from time 0 up until when the first dose of rescue medication was taken. 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 the pain relief scores. Any pain assessments impacted by the use of prohibited medications/therapies and thus needing to implement windowed WOCF will be identified during the blinded Data Review Meeting (DRM) prior to database lock and study unblinding. A sensitivity analysis will also be performed, in which all pain assessments recorded after the first dose of rescue medication has been taken will be disregarded and the rules outlined above will be used for missing data. All data for assessments other than pain assessments will be analysed as collected; missing data due to premature termination or any other reason will be left as missing. Additional sensitivity analyses including use of rescue medication will be detailed in the Statistical Analysis Plan. **Safety Analysis** Data listings will be provided for protocol-specified safety data. The Medical Dictionary for Regulatory Activities (MedDRA) (Version 19.0 or higher) will be used to classify all AEs with respect to system organ class and preferred term. Adverse event summaries will include only TEAEs, which will be summarized for each treatment group. For vital sign measurements, descriptive statistics will be provided at each scheduled time point for each treatment group. Changes from Baseline for vital signs will be calculated for each subject, and descriptive statistics will be provided on changes in vital signs from Baseline for each treatment group at each scheduled time point after Baseline. No formal statistical tests will be performed.

1 BACKGROUND AND RATIONALE

1.1 Background for the Study and Rationale

Reckitt Benckiser (RB) is co-developing a new 300 mg ibuprofen prolonged release (PR) tablet with Strides Shasun Ltd. The product has been developed to meet consumer and patient needs to have access to longer acting over-the-counter analgesics. This PR formulation will reduce fluctuations in drug plasma concentrations and allow for a lower frequency of administration which is desirable in situations where pain duration is expected to be prolonged and require multiple doses of immediate release formulations. As a result, the product would be more consumer friendly, require less dosing and improve compliance with treatment.

The proposed therapeutic indications of the PR product are for the short-term symptomatic treatment of mild to moderate pain such as dysmenorrhea, rheumatic pain, muscular pain, pain of non-serious arthritic conditions and backache.

The proposed posology in adults over the age of 18 is:

Ibuprofen 300 mg PR tablets. Two tablets to be taken every 12 hours when required for pain relief. No more than 2 doses in 24 hours. The maximum daily dose is 1200 mg and there is no proposed indication in the paediatric population.

Therefore, the purpose of the proposed study is to provide supporting pivotal efficacy evidence for European, Russian, and Australian applications and not to support any application in the USA. This efficacy study will provide further evidence on the safety and efficacy of the product in addition to the data obtained in two bioequivalence studies BE/17/279 and BE/17/281.

1.2 Investigational Product

Ibuprofen [2-(4-isobutylphenyl) propionic acid] is a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and anti-pyretic properties [(2)]. It was initially available in 1969 as a prescription only medicine, indicated for rheumatoid arthritis, osteoarthritis and other chronic painful conditions such as ankylosing spondylitis. Following further research and the establishment of a reassuring safety profile, it was launched in 1983 as an over-the-counter (OTC) medication, marketed as Nurofen®.

Absorption of ibuprofen after oral administration is fairly rapid with peak serum concentrations occurring within 1 to 2 hours after administration. Ibuprofen is extensively bound to plasma proteins (99%) when administered at therapeutic levels and has a plasma half-life of about 2 hours. Excretion by the kidney is both rapid and complete, but only a small proportion of drug is excreted unchanged in urine, the majority being extensively metabolised in the liver to 2 major inactive metabolites. The pharmacokinetics of ibuprofen has been extensively reviewed by Davies [(3)].

1.3 Treatment Rationale

The treatment of the test product is in line with the proposed posology of the final product and the treatment of the active comparator is in line with the posology provided in the label of the product. The treatments will be administered orally, as this is the standard route of administration for these products.

The following are the treatment regimens of each product in the study:

- Treatment A: test product, 2x300 mg PR ibuprofen tablet, twice daily [total daily dose 1200 mg]
- Treatment B: reference product, 2x200 mg IR ibuprofen tablet, three times a day [total daily dose 1200 mg]
- Treatment C: matching placebo tablets for both the test and reference regimens

The active comparator (Treatment B) currently marketed in a number of geographies including a number of different European countries. It has therefore been chosen to fulfil requirements that when it is included in a marketing authorisation dossier as a comparator that it is licenced within the EU.

1.4 Study Population and Indication

The following study population will be invited to participate in this clinical trial:

Adult participants aged 18 to 50 requiring extraction of 2 or more third molars, at least 1 of which must be a fully or partially bone-impacted mandibular molar, (if only 2 molars are removed, then they must be ipsilateral), and who experience moderate to severe pain following surgery.

Such population is expected to present pain levels that will allow for assessing the magnitude of treatment effect in a low variability setting.

1.5 Non-Clinical Evidence

No non-clinical evidence is available for the PR tablet.

1.6 Clinical Evidence to Date

A total of 5 single and multiple-dose pharmacokinetic studies (139-15, BE-16-081, BE-16-295, BE-17-279, BE-17-281) have been performed with the test product. These studies demonstrated the oral bioavailability (BA) of the ibuprofen PR tablets (dosed at 2x300 mg) is comparable to Brufen® (Ibuprofen) IR Tablets (dosed at 3x200 mg) after a single dose and at steady state conditions. In terms of the release profile and absorption, C_{max} tends to be slightly higher in the IR formulation when compared with the PR formulation [21.96 ±3.87 µg/mL vs 14.51 ±3.1 µg/mL]. However the C_{max}, (Maximum Observed Plasma Concentration), T_{max}, (Time to Maximum Plasma Concentration) and $AUC_{0\text{-}Tmax}$ (Area Under the Plasma Concentration Curve) of the PR formulation suggest that's the onset of action should not be any slower than the IR reference when considering the minimum effective concentration of ibuprofen [(4)]. In terms of total exposure ($AUC_{0\text{-}\infty}$) the concentration profile is bioequivalent between the PR test product and the IR reference product [163.41 ±43.0 µg.h/mL vs 168.59 ±37.7 µg.h/mL]. A food effect is demonstrated when the test product is taken in the fed state, with an expected increase in the absorption rate.

In the 5 PK studies performed (over 200 subjects) only a limited number of mild, transient adverse events were reported.

Summary Outcomes:

- The Clinical data available for this reformulation (Ibuprofen 300 mg PR) suggests an adequate pharmacokinetic profile to achieve a sufficient therapeutic effect in the proposed study
- There are no safety concerns with the test product
- Ibuprofen 300 mg PR had an increased rate of absorption when administered with food.
- Ibuprofen 300 mg PR tablets had a comparable concentration profile to the comparator IR product and was bioequivalent based on $AUC_{0\text{-}\infty}$

1.7 Risks / Benefits

This study has been designed to confirm the therapeutic efficacy of ibuprofen 300 mg PR. Participants in this study are subjects aged 18-50 who require the extraction of 2 or more third molars, at least 1 of which must be a fully or partially bone impacted mandibular molar. Subjects will undergo dental surgery that is equivalent to that of the standard-of-care that would be expected for the above condition. They should be otherwise healthy and each subject will undergo a full health check as part of the enrolment into the study to confirm that they are healthy as defined in this protocol (see Section 4).

Participants randomised into the placebo arm would not be expected to derive any therapeutic benefit from the administration of the placebo tablets. The placebo arm is essential to the study

design as it ensures that any conclusion of non-inferiority from the trial is a reflection of the true properties of the treatments; that is, it demonstrates the assay sensitivity of the study. However, this obviously leaves the participants without adequate analgesia in the post-surgery procedure and from an ethical perspective this is mitigated in the study design by the use of rescue medication that would be in line with standards of treatment. Although it is hypothesised that the investigational medicinal product (IMP) will provide adequate analgesia in the study, this cannot be guaranteed, and therefore the use of rescue medication also addresses the potential of reduced or lack of efficacy.

Ibuprofen is an established pharmaceutical ingredient and the adverse reactions associated with administration of 1200 mg/24 hour (OTC doses) are well known and documented [(2)(5)]. The adverse reactions most frequently occurring with a single dose being nausea, gastrointestinal upset, vomiting, diarrhoea, light headedness, dizziness and headache. Rarely, more serious reactions have been reported including GI bleeding, ulceration and perforations, hypertension and renal failure. When OTC doses of ibuprofen (200-400 mg/dose; 1200 mg/day) are taken for acute episodes of pain there is an extremely low risk of causing serious gastrointestinal events [(5)].

The specific 200mg Ibuprofen tablet to be used in this study as the active comparator (Treatment B) is marketed in the EU under the Nurofen brand and has an excellent safety profile.

It is not anticipated that the safety profile of ibuprofen will be altered after administration of multiple single doses of ibuprofen 300 mg PR in the context of this study. There are not expected to be any drug-drug interactions with the non-investigational medicinal products included within the study design. A washout period of at least 6 days is deemed to be sufficient prior to the Follow-up/Early Termination Visit to ensure adequate safety monitoring of the IMP.

The investigation site will have adequate set up, experience and safety measures that would be expected of a centre able to perform regular molar extractions. They will also have adequate experience in the safety monitoring of participants post dose that would be expected in a clinical trial setting. Therefore, it is considered that the risk related to study procedures are low and limited to common adverse events (AEs) related to the dental procedure, administration of routine anaesthetics, and discomfort from vital sign measurements. Any subject that experiences immediate complications during the surgery will be excluded from the study.

Therefore, the overall benefit-risk profile for the use of the investigational product as defined in this protocol is considered favourable.

1.8 Ethical Conduct of the Study

This study will be conducted in accordance with this protocol and the principles set out in the Declaration of Helsinki. It will comply with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

2 STUDY OBJECTIVES

Primary Objective:

- To evaluate the superiority of 2×300 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.

Key Secondary Objectives:

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

Additional Secondary Objectives:

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

3 STUDY DESIGN AND RATIONALE FOR DESIGN

This is a single centre randomised, double-blind, double dummy, parallel group, multiple-dose, active and placebo-controlled efficacy study to evaluate the efficacy and safety of 2×300 mg ibuprofen PR tablets in subjects with post-surgical dental pain.

The dental pain model used in this study is a robust and well established post-surgical pain model that produces pain that is predictable in its character, duration, and intensity[(6)]. The model is widely accepted and has a proven record of assay sensitivity (i.e. separating active drugs from each other, as well as from placebo). The model is frequently used to evaluate NSAID type analgesics. Results from dental pain studies are accepted by the US Food and Drug Administration (FDA) and European authorities and have been widely extrapolated to other general pain conditions.

The decision to conduct the study in the United States was taken as suitably qualified and experienced test sites could not be found in Europe. The specific test site has been chosen to conduct the study as they have a proven history of quality and safety when conducting studies of this type.

The placebo products have two purposes:

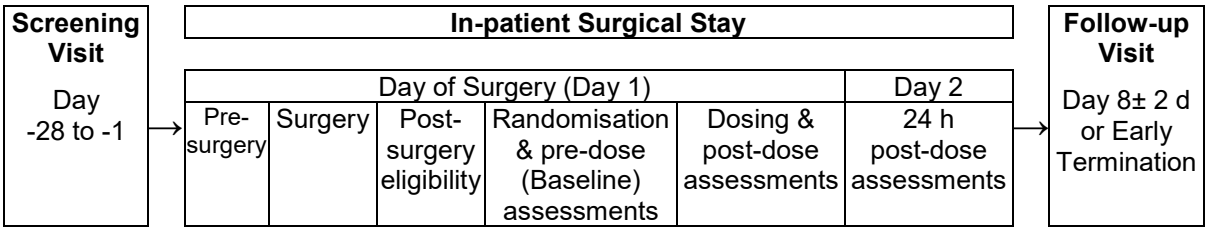
1. To mask the treatment identify for PR and IR arms
2. Act as a control arm

The dose of the test product is the proposed posology of the final product and the dose of the active comparator is the posology provided in the label of the product.

Eligible subjects will be randomised in a 3:3:1 ratio to receive 2×300 mg ibuprofen PR tablets Q12h, 2×200 mg ibuprofen IR tablets Q8h, or placebo. The randomisation 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 randomisation schedule will be prepared by a statistician not otherwise involved in the study. Randomisation will be performed using an interactive web response system (IWRS). 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.

Figure 3.1 Study Design Schematic



Note: Un-scheduled visits may occur at any point throughout the study

Table 3-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary Objective: To evaluate the superiority of 2×300 mg ibuprofen PR tablets compared with placebo in subjects experiencing acute dental pain after third molar extraction over 12 hours post initial dose.	**Primary Endpoint:** The primary efficacy endpoint is the summed pain intensity difference (SPID) over the 0 to 12 hours (SPID12) after Time 0 and will be used to compare the test product (2x300 mg PR ibuprofen) and the placebo product. The clinical relevance of the difference between placebo and PR ibuprofen over 12 hours after initial dose will be evaluated as confirmatory evidence (for the purposes of this study, a difference of 30% in PID scores over 12 hours after initial dose will be considered clinically relevant).
Secondary Efficacy Objectives: • To evaluate the analgesic performance of a total daily dose of 1200 mg of ibuprofen PR formulation compared to ibuprofen IR formulation over 24 hours post initial dose. • To evaluate the total analgesic effect, peak analgesic effect, onset and duration	**Key Secondary Efficacy Endpoints:** • The summed pain intensity difference (SPID) over 0 to 24 hours (SPID24) will be used to compare the test product (2×300 mg ibuprofen PR tablets twice daily [BID]) and comparator product (2×200 mg ibuprofen IR tablets three times a day [TID]).

of action and the subject's overall assessment of the study medications.	**Efficacy Endpoints:** • Summed pain intensity difference (SPID) over 0 to 4 hours (SPID4), over 0 to 8 hours (SPID8), over 0 to 12 hours (SPID12), and over 0 to 24 hours (SPID24) after Time 0 • 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 (a responder will be defined as a subject with ≥30% improvement in pain intensity without rescue medication during the first 8 hours) • NRS pain intensity difference (PID) at each scheduled time point after Time 0 • Pain intensity score at each scheduled time point • Pain relief score at each scheduled time point after Time 0 • Peak pain relief • Time to onset of analgesia (measured as time to perceptible pain relief confirmed by time to meaningful pain relief) using double stopwatch • 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

	Exploratory Endpoint: • Patient's global evaluation of study drug
Safety Objective: To evaluate the safety and tolerability of 2×300 mg ibuprofen PR tablets.	**Safety Endpoints:** • Incidence of treatment-emergent adverse events (TEAEs) • Incidence of clinically relevant changes in vital sign measurements

Subjects in the PR group will take 2×300 mg ibuprofen PR tablets at Hours 0 and 12. Subjects in the IR group will take 2×200 mg ibuprofen IR tablets at Hours 0, 8, and 16. To maintain double-blinding, at each dosing timepoint (Hours 0, 8, 12, and 16) all subjects will take a total of 4 tablets (placebo-only or active plus placebo, depending on randomised treatment group).

Table 3-2 Treatment Regimens

	PR Group	IR Group	Placebo Group
Hour 0	2 PR, 2 placebo for IR	2 placebo for PR, 2 IR	2 placebo for PR, 2 placebo for IR
Hour 8	2 placebo for PR, 2 placebo for IR	2 placebo for PR, 2 IR	2 placebo for PR, 2 placebo for IR
Hour 12	2 PR, 2 placebo for IR	2 placebo for PR, 2 placebo for IR	2 placebo for PR, 2 placebo for IR
Hour 16	2 placebo for PR, 2 placebo for IR	2 placebo for PR, 2 IR	2 placebo for PR, 2 placebo for IR
Hour 24	final assessments	final assessments	final assessments

The study will enrol approximately 280 male and female subjects 18-50 years of age who experience moderate to severe pain intensity within 6 hours after dental surgery to remove 2 or more third molars. At least 1 of the third molars must be a fully or partially bone impacted mandibular molar. If only 2 molars are removed, they must be ipsilateral. Subjects must satisfy all eligibility criteria including providing informed consent and willingness to remain at the clinic overnight.

The study will be conducted in 1 study site in the United States.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Study Population

The study will enrol approximately 280 male and female subjects.

4.2 Inclusion Criteria

Only subjects to whom all of the following conditions apply will be included:

1. Is male or female ≥ 18 and ≤ 50 years of age.
2. Requires extraction of 2 or more third molars. At least 1 of the third molars must be a fully or partially bone-impacted mandibular molar. If only 2 molars are removed, then they must be ipsilateral.
3. Experiences moderate to severe pain intensity within 6 hours after surgery, as measured by a numeric rating scale (NRS) score of ≥ 5 on a 0-10 scale.
4. Has a body weight ≥ 45 kg and a body mass index (BMI) ≤ 35 kg/m^2.
5. Female subjects of child-bearing potential must have been using an acceptable method of contraception for at least 30 days prior to randomization and be willing to continue use until at least 48 hours post discharge from the clinic (see Section 4.4). To be considered not of child-bearing potential, females must be surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or post-menopausal (defined as no menses for 12 months without an alternative medical cause).
6. Free of clinically significant abnormal findings as determined by medical history, physical examination, vital signs, laboratory tests and ECG.
7. Is able to provide written informed consent.
8. Is willing and able to comply with study requirements (including diet and smoking restrictions), complete the pain evaluations, remain at the study site overnight, and return for follow-up 7 (± 2) days after surgery, (Day 8 ± 2 days).

4.3 Exclusion Criteria

A subject will not be eligible for study entry if any of the following exclusion criteria are met:

1. Known hypersensitivity reactions or allergy (e.g., asthma, rhinitis, angioedema or urticaria) in response to nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen), acetylsalicylic acid (aspirin), ingredients of the study drug, or any other drugs used in the study, including anaesthetics and antibiotics that may be required on the day of surgery.
2. A history of active or previous peptic ulceration/ haemorrhage, gastrointestinal bleeding or perforation, heart failure, renal or hepatic failure, uncontrolled hypertension, asthma, nasal polyps, or chronic rhinitis.
3. Has complications from the tooth extraction or any other clinically significant medical history that, in the opinion of the investigator, would affect the subject's ability to comply or otherwise contraindicate study participation, including but not limited to the

following: cardiac, respiratory, gastroenterological, neurological, psychological, immunological, haematological, oncological, or renal disease.

4. Has undergone another dental surgery within 60 days prior to the day of surgery.
5. A positive urine drugs of abuse screen or alcohol breathalyser test at screening and during the study (with the exception of a positive drugs of abuse screen that is a consequence of permitted prescription medicines).
6. If female, has a positive pregnancy test at screening (serum) or on the day of surgery prior to surgery (urine), or is lactating.
7. Has known or suspected, (in the opinion of the investigator), history of alcoholism or drug abuse within 2 years of screening or evidence of tolerance or physical dependence before dosing with study drug.
8. Taking any concomitant medications that might confound assessments of pain relief, such as psychotropic drugs, antidepressants, sedative-hypnotics (other than those permitted for conscious sedation), or other analgesics taken within five times of their elimination half-lives. Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) are permitted if the subject has been on a stable dose for at least four weeks prior to Visit 1 (screening).
9. Is considered by the investigator, for any reason (including, but not limited to the risks described as precautions, warnings and contraindications in the current version of the investigator's brochure [IB] for 300 mg ibuprofen PR tablets), to be an unsuitable candidate to receive the study drug.
10. Has a history of chronic use (defined as daily use for > 2 weeks) of nonsteroidal anti-inflammatory (NSAIDs), opiates, or glucocorticoids (except inhaled nasal steroids and topical corticosteroids), for any condition within 6 months before dosing with study drug.
11. Has significant difficulties swallowing capsules or tablets or is unable to tolerate oral medication.
12. Subject has received an investigational product or participated in another trial involving a marketed or investigational drug in the 30 days (or for investigational agents with a long half-life, a washout of 5 half-lives) prior to first drug administration (washout period between studies is defined as the period of time elapsed between the last dose of the previous study and first dose for this study). Or if the investigator believes that any previous participation in an investigational study would be to the detriment of the safety of the participant or the conduct of the study.
13. Enrolment of the Investigator, his / her family members, employees and other dependent persons.
14. Failure to satisfy the investigator of fitness to participate for any other reason.

4.4 Subjects of Reproductive Potential

Female subjects of childbearing potential must have been using an acceptable method of contraception for at least 30 days prior to randomization and be willing to continue use until at least 48 hours post discharge from the clinic. An acceptable method of contraception includes:

a. Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action

b. Male or female condom with or without spermicide

c. Cap, diaphragm or sponge with spermicide

Alternatively, highly effective methods of contraception are also considered acceptable, such as:

d. Surgical sterilisation

e. Established use of oral, injected or implanted hormonal methods of contraception

f. Some intrauterine devices (IUDs) or intrauterine systems (IUSs)

g. Male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). [For female subjects on the study, the vasectomised male partner should be the sole partner for that subject]

h. True abstinence which is in line with the preferred and usual lifestyle of the subject. Periodic abstinence such as calendar, ovulation, symptothermal, or post-ovulation methods; declaration of abstinence for the duration of the trial; and withdrawal are not acceptable methods of contraception.

4.5 Discontinuation / Withdrawal and Replacement of Subjects

The Investigator may withdraw the subject from the study at any time. Reasons for removing a subject from the study include, but are not limited to:

- AEs that in the judgement of the Investigator may cause severe or permanent harm (significant clinical deterioration is an AE)
- Violation of the study protocol
- In the Investigator's judgement, it is in the subject's best interest
- Subject declines further study participation
- If applicable, randomisation code is broken

If subjects choose to prematurely stop the study prior to the scheduled discharge at Hour 24, safety and tolerability assessments must be performed prior to discharge, and, if possible, efficacy assessments should be performed.

If subjects choose to prematurely stop the study after clinic discharge but prior to the follow-up visit, at least 2 documented attempts should be made to contact the subjects for follow-up assessments which will include the assessments described for the follow-up visit (Section 7.4).

5 STUDY TREATMENT

5.1 Investigational Products

Active Test Product

Ibuprofen PR tablets 300 mg, single oral dose of 600 mg. A yellow to pale yellow coloured, film coated, caplet shaped tablet, debossed as 'N12' on one side and plain on the other side.

Table 5-1 Active Test Product

Name of Ingredient	Quantity/Tablet(mg)	Function	Reference
Ibuprofen	300.00	Active	Ph.Eur.
Silicon dioxide	3.00	Glidant/Anti-adherent	Ph.Eur.
Hypromellose K4M Premium	62.50	Rate Controlling Polymer	Ph.Eur.
Hypromellose K100 LV	32.50	Rate Controlling Polymer	Ph.Eur.
Silicified Microcrystalline cellulose 50	100.00	Filler/Binder	NF
Silicified Microcrystalline cellulose 90	50.00	Filler/Binder	NF
Croscarmellose sodium	17.50	Disintegrant	Ph.Eur.
Glycine	25.00	Release Modifier	Ph.Eur
Silicon dioxide	3.00	Glidant/Anti-adherent	Ph.Eur.
Stearic acid	6.00	Lubricant	Ph.Eur.
Total weight of core tablet	**599.50 mg**		
Film coating and Polishing			
Opadry Yellow 15B520019	7.50	Coating agent	In House
Purified water[#]	q.s.	Coating vehicle	Ph.Eur.
Carnauba Wax	0.025	Polishing Agent	Ph.Eur
Total weight	**607.025 mg**		

[#] Removed during the process.

Placebo for Test Product

A yellow to pale yellow coloured, film coated, caplet shaped tablet, debossed as 'N12' on one side and plain on the other side.

Table 5-2 Placebo for Test Product

Ingredient	mg/tablet	Function	Reference Standard
Core			
Hypromellose K4M Premium	125.10	Rate Controlling Polymer	Ph. Eur.
Hypromellose K100 Premium LV	65.05	Rate Controlling Polymer	Ph. Eur.
Silicified Microcrystalline Cellulose 50	200.17	Filler/ Binder	NF
Silicified Microcrystalline Cellulose 90	100.08	Filler/ Binder	NF
Croscarmellose Sodium	35.03	Disintegrant	Ph. Eur.
Glycine	50.04	Release Modifier	Ph. Eur.
Silica, Colloidal Hydrated	12.02	Glidant/ Anti-adherent	Ph. Eur.
Stearic Acid	12.01	Lubricant	Ph. Eur.
Coating and Polishing			
Opadry Yellow 15B520019	7.50	Coating Agent	In house
Carnauba Wax	0.025	Polishing Agent	Ph. Eur.
Processing agent			
Purified Water	q.s.*	Coating Vehicle	Ph. Eur.
Total	**607.025**		

* Does not remain in final product except traces. Removed during the coating process.

Comparator Product

Nurofen Ibuprofen acid tablets 200 mg, single oral dose of 400 mg. A white to off white, biconvex, round, sugar coated tablet.

Table 5-3 Comparator Product

Name of Ingredient	Unit Formula (mg/tablet)	Function	Reference to Standards
Active Ingredient			
Ibuprofen	200.0	Active ingredient	Ph.Eur.
Other Ingredients			
Croscarmellose Sodium	30.0	Disintegrating agent	Ph.Eur.
Sodium Lauryl Sulphate	0.5	Tablet lubricant	Ph.Eur.
Sodium Citrate	43.5	Bulk filler	Ph.Eur.
Stearic Acid	2.0	Tablet lubricant	Ph.Eur.
Colloidal Anhydrous Silica	1.0	Granule flow aid	Ph.Eur.
Tablet Core Weight	277.0		
Sugar Coat Ingredients			
Carmellose Sodium	0.7	Sugar coat binder	Ph.Eur.
Talc	33.0	Sugar coat bulking agent	Ph.Eur.
Acacia Spray Dried	0.6	Sugar coat binder	Ph.Eur.
Sucrose	116.1	Sugar coat	Ph.Eur.
Titanium Dioxide	1.4	Colour	Ph.Eur.
Macrogol 6000	0.2	Tablet polish	Ph.Eur.
Purified Water	ND	Sugar syrup solvent	Ph.Eur.
Coated Tablet Weight	429.0		

Placebo for Comparator Product

A white to off white, biconvex, round, sugar coated tablet.

Table 5-4 Placebo for Comparator Product

Ingredient	Quantity (%w/w)	Function	Reference Standard
Core			
Mannitol	46.81	Filler	Ph. Eur
Microcrystalline Cellulose	16.14	Filler	USP/NF
Magnesium Stearate	1.61	Lubricant	Ph. Eur.
Sugar coating			

Carmellose Sodium	0.16	Sugar coat binder	Ph. Eur
Talc	7.69	Sugar coat bulking agent	Ph. Eur
Acacia Spray Dried	0.14	Sugar coat binder	Ph. Eur
Sucrose	27.06	Sugar coat	Ph. Eur
Titanium Dioxide	0.33	Colour	Ph. Eur
Macrogol 6000	0.05	Tablet polish	Ph. Eur
Purified Water*	ND	Sugar syrup solvent	Ph. Eur

Test Product and Placebo for Test Product will be manufactured and packed (primary pack) to Good Manufacturing Practice (GMP) standards by Strides Shasun Limited, R.S No 32-34 PIMS Road, Periyakalpet, Kalapet, Pondicherry, 605014, India and shipped to Investigational Materials Supplies Unit (IMSU), RB, Dansom Lane, Hull, HU8 7DS.

Nurofen Ibuprofen acid (Comparator) and the Placebo for Comparator tablets will be manufactured to GMP standards by Reckitt Benckiser, Thane Road, Nottingham, NG90 2DB, UK. Both active and placebo tablets will be unprinted for blinding purpose.

Both the products (Comparator and Placebo) will be primary packed at Sharp Clinical Services, Elvicta Business Park, Crichowell, NP8 1DF, UK and shipped to Investigational Materials Supplies Unit (IMSU), RB, Dansom Lane, Hull, HU8 7DS.

The Test Product, Placebo for Test Product, Comparator Product and the Placebo for Comparator product will be assembled to GMP standards by the IMSU, RB, Dansom Lane, Hull HU8 7DS, and bulk certified by RB Research and Development Qualified Person. All the products will be shipped directly from IMSU to the study site.

5.2 Non-Investigational Products

In preparation for the surgery, subjects will receive local anaesthesia (2% lidocaine with 1:100,000 epinephrine). Nitrous oxide will be allowed at the discretion of the investigator.

5.3 Permitted Therapies

After randomisation and administration of study drug, paracetamol / acetaminophen (1000 mg) will be permitted as the initial rescue medication. Subjects will be encouraged to wait at least 60 minutes after receiving study drug before taking rescue medication. If acetaminophen rescue medication is not effective in relieving the subject's pain, 5 mg oxycodone rescue medication may be administered at the discretion of the investigator.

At the investigators discretion repeat doses of rescue medication may also be administered as required.

The Investigator or designees will record all medication taken by the subject at the screening visit in the subject's electronic Case Report Form (eCRF). Any medication taken by the subject

from the time of giving informed consent through to the end of the subject's participation in the study (last assessment) will be recorded on the concomitant medication page in the eCRF.

Upon discharge from the study site, subjects may be prescribed pain medication for use at home according to the standard practice of the study site.

5.4 Treatment Compliance

For the duration of each assessment the subject will remain at the study site under the supervision of the Investigator or designees. The Investigator or designees will provide supervised drug administration along with clear instructions and support to the subject to facilitate the best possible compliance with study requirements. Any non-compliance during the study will be observed and recorded by study site staff as a protocol deviation.

5.5 Packaging and Labelling and Supply / Resupply

For each subject one pack will be provided containing all required tablets for each dosing timepoint. Each tablet will be held in a blister within the pack. The pack will clearly show which tablets are to be taken at which timepoint.

All packs regardless of treatment regimen will be the same except for a kit number and will therefore not identify the treatment.

The IMP will be labelled in accordance with EudraLex Volume 4 Good Manufacturing Practice (GMP) Guidelines, Annex 13 - Manufacture of Investigational Medicinal Products, parts 26 to 33 (Labelling) and in accordance with directive 2003/94/EC as amended and including any other applicable national/state legislation. The IMP will be labelled in English

All IMP will be packed and labelled to GMP by the Investigational Material Supplies Unit (IMSU), Reckitt Benckiser Healthcare (UK) Ltd, Dansom Lane, Hull, HU8 7DS, UK. IMP will be shipped from the IMSU to the study site.

5.6 Storage Conditions

The Investigator or designated individual will keep all IMP(s) in a pharmacy or a secure storage facility, accessible only to those individuals authorised by the Investigator to dispense the medication.

The Investigator or designated individual will maintain an inventory. This will include the description and quantity of IMP(s) received during the course of this study, as well as a record of the materials that are dispensed and returned (how much, to whom and when). This inventory ("Drug Dispensing Log") will be subject to review by the study monitor during monitoring visits.

The Investigator agrees not to supply IMP(s) to any person except study personnel and patients enrolled in this study.

The IMP should be stored between 8-25 °C and is not to be refrigerated or frozen.

Temperatures must be constantly monitored and readings logged in a temperature log on working days.

The temperature in the secure storage facility will be recorded using a minimum/maximum thermometer. If the temperature falls outside the specified range of 8-25 °C, the Sponsor should be notified immediately and appropriate action should be agreed and documented. The temperature log will be reviewed by the study monitor at each monitoring visit.

5.7 Blinding

This study 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, colour and weight.

All subjects will receive 4 tablets at each dosing timepoint. At each timepoint each subject will receive 2 tablets that may be either PR or the placebo made to look like PR and 2 tablets that may be IR or the placebo made to look like IR. See Table 3-2 Treatment Regimens. This includes those in the placebo arm who will receive 2 placebo tablets designed to look like PR and 2 placebo tablets designed to look like IR at all dose timepoints.

All subject packs will be designed and labelled to ensure blinding is maintained.

Subjects, investigators and site staff will all be blind to the treatments.

Unblinding will only occur after database lock or in the case of emergency unblinding, see Section 5.8.

5.8 Emergency Unblinding Procedures

Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment.

For emergency unblinding, study personnel will use the IWRS. If treatment assignment is unblinded for an individual subject, study personnel will be notified of that subject's treatment assignment without unblinding the treatment assignments for the remaining subjects in the study. Thus, the overall study blind will not be compromised. If a subject's treatment assignment is unblinded, he/she may or may not be asked to withdraw from the study. The investigator should make this decision after consultation with the medical monitor.

5.9 Drug Accountability

The Investigator will keep all study medication (including rescue medication) in a pharmacy or a secure storage facility, accessible only to those individuals authorised by the Investigator to dispense the medication.

The Investigator or designated individual will maintain an inventory. This will include the description and quantity of study drug received during the course of the study, as well as a record of the materials that are dispensed and returned (how much, to whom and when). This inventory will be subject to review by the study monitor during monitoring visits.

The Investigator agrees not to supply study drug to any person except study personnel and subjects in this study.

5.10 Return and Destruction

The Investigator agrees to conduct a drug-supply inventory, to record the results of this inventory ("IMP Removal from Site" form) and to ensure all original IMP containers whether empty or containing IMP are sent to RB's representative at the end of the study.

RBs representative will then arrange for the appropriate and timely destruction of all containers and unused IMP upon confirmation from RB following provision of a full reconciliation by Premier (on finalisation of the study report).

6 STUDY PROCEDURES BY VARIABLE

6.1 Informed Consent

Prior to conducting any study-related activities, written informed consent must be obtained from the subject (Section 12.2).

6.2 Randomisation

Eligible subjects will be randomised in a 3:3:1 ratio to receive 2×300 mg ibuprofen PR tablets Q12h, 2x200 mg ibuprofen IR tablets Q8h, or placebo using permuted blocks of fixed size. The randomisation 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 randomisation schedule will be prepared by a statistician not otherwise involved in the study. Randomisation will be performed using an interactive web response system. 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.

6.3 Drug Administration

Subjects will be dosed under clinic supervision to ensure compliance. Prior to dosing, each subject will be instructed by the Investigator or clinic staff on how to take the medication.

6.4 Demographics

Demographic information will be recorded including gender, date of birth and race.

6.5 Medical History and Concomitant Medication

Relevant medical history, including history of current disease and information regarding underlying diseases will be recorded. The duration of surgery and all concomitant medication taken will be recorded as well as permitted therapies (see Section 5.3).

6.6 Physical Examination

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).

Height, weight, and BMI will be assessed at Screening.

6.7 Laboratory Tests

The following clinical laboratory tests will be performed at Screening.

Hematology:	hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count (or estimate), white blood cell count including differential
Serum Chemistry:	albumin, total bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, glucose, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase, uric acid, urea, inorganic phosphorous, cholesterol (total and High Density Lipoprotein (HDL)), triglycerides, gamma glutamyl transferase
Coagulation:	prothrombin time, partial thromboplastin time, fibrinogen
Urinalysis:	pH, specific gravity, blood, glucose, protein, ketones, leucocyte esterase, nitrites (in the event that the dipstick test is positive, red blood cells, white blood cells, epithelial cells, crystals, bacteria and casts will be examined microscopically)
Virology:	hepatitis B, hepatitis C, HIV

The following laboratory tests will also be performed:

- Alcohol breathalyzer test will be performed before surgery on Day 1.
- Urine drug screen samples will be collected at Screening and before surgery on Day 1 to test for amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine (PCP), and tetrahydrocannabinol (THC).

- For female subjects of childbearing potential, a blood sample for the serum pregnancy test will be collected at Screening and a urine pregnancy test sample will be collected before surgery on Day 1.

Blood and urine samples for hematology, serum chemistry, and urinalysis will be prepared using standard procedures and will be sent to a central laboratory for analyses.

6.8 Electrocardiograms

A 12-lead electrocardiogram will be performed at Screening.

6.9 Vital Signs

Vital signs will be recorded after the subject has been in a sitting position for 3 minutes. Vital sign assessments will include blood pressure, heart rate, respiratory rate, and body temperature. Clinically significant abnormalities in vital signs should be recorded as AEs.

6.10 Blood Sampling

Blood sampling will be performed according to the site's standard practices, as described in the study manual or other site documentation.

6.11 Oral Radiography

Oral radiographs (X-rays) will be taken at Screening (radiographs taken within 1 year before Screening will be acceptable and do not need to be repeated).

6.12 Pain Intensity

Subjects will rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever at the timepoints mentioned on Table 7-1.

6.13 Stopwatch Assessment

Two stopwatches will be started immediately after the subject has swallowed the study drug with 8 ounces of water. Each subject will be instructed, "Stop the first stopwatch when you first feel any pain relief whatsoever. This does not mean you feel completely better, although you might, but when you first feel any relief in the pain you have now" (perceptible pain relief). The subject will also be instructed, "Stop the second stopwatch when you feel the pain relief is meaningful to you" (meaningful pain relief). If the subject does not press the stopwatches within 8 hours after Time 0 the subject will discontinue use of the stopwatches.

6.14 Pain Relief Scale

Subjects will rate their pain relief relative to Time 0 using a 5-point categorical scale. Subjects will be asked "How much relief have you had since your starting pain?" with response choices of none = 0, a little = 1, some = 2, a lot = 3, and complete = 4. At each assessment time point, the pain intensity NRS 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.

6.15 Subject's Global Evaluation of Study Drug

For the global evaluation of study drug, the subject will be asked "How effective do you think the study drug is as a treatment for pain?" with response choices of 0 = poor, 1 = fair, 2 = good, 3 = very good, or 4 = excellent. Subjects will complete the global evaluation of study drug 24 hours after Time 0 or immediately before the first dose of rescue medication (whichever occurs first).

6.16 Adverse Events

During the study the Investigator will ask the subject: "Are you experiencing any symptoms or complaints?" at the baseline visit, and "Have you had any symptoms or complaints since the last time you were asked?" during the study. In addition, spontaneously reported AEs are collected.

The observation period for an individual subject will start after giving informed consent and will finish at the last visit (follow-up visit) for the given individual subject. All AEs that arise during the observation period will be recorded and an assessment of the AE will be performed as per Section 8.2 by a medically qualified Investigator. If a subject has an AE that is still ongoing at the last visit, an attempt will be made by the Investigator to follow this up as per Section 8.4.

If an untoward medical occurrence happens after the subject has signed the consent form but before administration of the IMP, it should be reported as an adverse event, including those associated with study procedures.

Note this does not include any pre-existing medical conditions or findings associated with medical history which are identified during the screening process.

7 STUDY PROCEDURES BY VISIT

7.1 Study Flow Chart / Table of Study Procedures and Assessments

Table 7-1 Schedule of Assessments

	Screening (Day -28 to Day -1)	Surgery (Day 1)						Day 2		Follow-up (Day 8 ±2 days) or ET[k]
			Post-surgery							
		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-surgery							
		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
Provide prescription for pain medication.									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;.

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.

i Subjects will complete a global evaluation of study drug 24 hours after Time 0 or immediately before the first dose of rescue medication (whichever occurs first).

j Adverse events will be monitored and recorded from the time of signing of the informed consent form until the Follow-up Visit (or Early Termination Visit).

k If an unscheduled visit occurs the Investigator should follow the activities detailed in Section 7.5.

7.2 Screening Visit (Day -28 to Day -1)

- Written informed consent
- Assign a screening number
- Inclusion/exclusion criteria
- Demographics
- Medical history
- Complete physical examination (excluding the genitourinary examination)
- Vital signs
- Electrocardiogram
- Height, weight, and BMI
- Clinical laboratory tests (haematology, chemistry, urinalysis)
- Serum pregnancy test for female subjects of childbearing potential
- Urine drug screen
- Oral radiography (oral radiographs taken within 1 year before Screening will be acceptable and do not need to be repeated)
- Review study restrictions with subject
- Schedule surgery

7.3 Day of Surgery (Day 1)

7.3.1 Pre-Surgery

- Inclusion/exclusion criteria review
- Medical history review
- Vital signs
- Urine pregnancy test for female subjects of childbearing potential
- Urine drug screen
- Alcohol breathalyzer test
- Concomitant medications

- Adverse events

7.3.2 Surgery

- Subjects who continue to be eligible for study participation after completing screening procedures and assessments will undergo extraction of 2 or more third molars. At least 1 of the third molars must be a fully or partially bone impacted mandibular molar. If only 2 molars are removed, then they must be ipsilateral.
- All subjects will receive local anesthesia (2% lidocaine with 1:100,000 epinephrine).
- Nitrous oxide will be allowed at the discretion of the investigator.

7.3.3 Post-surgery Eligibility Assessments and Randomisation

- Vital signs
- Concomitant medications
- Adverse events
- Pain intensity NRS
- Subjects who experience moderate to severe pain intensity (NRS score of ≥ 5) within 6 hours after surgery and who continue to meet all study entry criteria will be randomised

7.3.4 Dosing and Post-dose Assessments (Hour 0 through Hour 24)

- Subjects will re-assess their baseline pain intensity using the NRS immediately before receiving IMP (pre-dose, Time 0)
- Administer IMP at the timepoints in Table 3-2
- Subjects will assess their pain intensity (NRS) and pain relief (5 point categorical scale) at the following time points (pre-dose, if at one of the dosing timepoints of 0, 8, 12 or 16 hours): 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, if any. 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.
- Subjects will use the double stopwatch method to record the time to perceptible pain relief and time to meaningful pain relief during the 8 hours following the first dose or until subject takes rescue medication
- Subjects will complete a global evaluation of study drug 24 hours after Time 0 or immediately before the first dose of rescue medication (whichever occurs first)
- Vital signs will be recorded after the subject has been in a sitting position for 3 minutes at the following times: before surgery, within 30 minutes before Time 0, 12 and 24 hours after Time 0, and/or immediately before the first dose of rescue medication

- Concomitant medications
- Adverse events
- Subjects will remain at the study site overnight and will be discharged on Day 2.
- Upon discharge from the study site, provide prescription for pain medication.
- Schedule follow-up visit

7.4 Follow-up Visit (Day 8 ± 2 days) or Early Termination

- Abbreviated confirmatory physical assessment, including an examination of the subject's mouth and neck
- Vital signs
- Concomitant medications
- Record any post discharge adverse events

7.5 Unscheduled Visits

If unscheduled visits occur, the Investigator must record the reason for unscheduled visit, including any AEs, concomitant therapy changes, withdrawal (if deemed appropriate) and any clinical assessments deemed appropriate for the clinical care of the subject. Unscheduled visits should not alter the timing of the routine study schedule.

7.6 Study Restrictions

7.6.1 Prohibited Therapies

Subjects are not permitted to take any concomitant medications that might confound assessments of pain relief, such as psychotropic drugs, antidepressants, sedative-hypnotics (other than those permitted for conscious sedation), or other analgesics taken within five times of their elimination half-lives (other than those used at the surgery). Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) are permitted if the subject has been on a stable dose for at least four weeks prior to Visit 1 (screening).

7.6.2 General and Dietary Restrictions

Other restrictions include the following: alcohol use is prohibited from 24 hours before surgery until discharge on Day 2; nothing by mouth from midnight before surgery until 1 hour after surgery; clear liquids only are allowed starting 1 hour after surgery until 1 hour after dosing; 1 hour after dosing, the subject's diet may be advanced according to standard practice.

8 SAFETY REPORTING

8.1 Adverse Event Definitions

An Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. [ICH E6 1.2].

Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is classified as any untoward medical occurrence that:

- results in death
- is life-threatening
- requires in-patient hospitalization or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity or
- is a congenital anomaly/birth defect

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious.

[ICH E2A] Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Note: If the event is related to the investigational product and is both serious and unexpected, it is classified as a suspected unexpected serious adverse reaction (SUSAR). In case of double-blinded studies, unblinding is needed in order to determine a SUSAR.

8.2 Assessment of Adverse Events

Any untoward medical occurrences that arise after the subject has given informed consent will be recorded in the subject's source documents and electronic case report forms (eCRFs). Untoward medical occurrences can be reported spontaneously by the subject or in response to non-leading questioning or observation by the Investigator or be a significant laboratory abnormality.

Untoward medical occurrences, including all adverse events (AE) and all serious adverse events (SAEs) are collected, fully investigated and documented.

As the study will be conducted on subjects who have been through removal of impacted third molars, it is expected that they will present post-surgical symptoms, for example: swelling and bruising. For the purposes of this study, when at normal/expected magnitude, such occurrences will not be reported as AEs as they are expected and, therefore, are not “untoward” as in the AE standard definition.

SAEs should be followed until resolution or stabilisation. Participants with ongoing SAEs at study termination will be further followed up until recovery or until stabilisation of the disease after termination.

For each AE a causality assessment of the event to the study drug must be performed. The relationship to IMP must be determined by the Investigator (if medically qualified) or by a medically qualified Co-Investigator.

Table 8-1 AE Relationship Descriptions

Relationship	Description
Unassessable/ Unclassifiable	Insufficient information to be able to make an assessment
Conditional/ Unclassified	Insufficient information to make an assessment at present (causality is conditional on additional information)
Unrelated	No possibility that the AE was caused by the IMP
Unlikely	Slight, but remote, chance that the AE was caused by the IMP, but the balance of judgement is that it was most likely not due to the IMP
Possible	Reasonable suspicion that the AE was caused by the IMP
Probable	Most likely that the AE was caused by the IMP
Certain	The AE was definitely caused by the IMP

For each AE a severity description should be given.

Table 8-2 AE Severity Descriptions

Severity	Description
Mild	The AE does not limit usual activities; the subject may experience slight discomfort
Moderate	The AE results in some limitation of usual activities; the subject may experience significant discomfort
Severe	The AE results in an inability to carry out usual activities; the subject may experience intolerable discomfort or pain

Expectedness for each AE will be determined based on the information in Section 6.9 of the Investigator's Brochure.

All AEs will be coded by the Sponsor using the most up-to-date version of MedDRA.

8.3 Reporting of Adverse Events

In the event of a Serious Adverse Event (SAE), the Investigator must report the event using the SAE form to the Sponsor Global Vigilance Group (GVG), by contacting GVG by email: gvg@rb.com while copying in the contract research organisation (CRO) and Sponsor Project/Study Managers within 24 hours of knowledge of the event.

The out of hours emergency phone number is +44 (0)1482 326151. An alternative number may additionally be provided by Premier Research to give access to the study Medical Monitor our of hours.

This emergency phone number will be confirmed to the Investigator at the Study Initiation Visit.

All SAE Forms must be provided via email. Any inconsistencies in the information received from the Investigator will be clarified using the Adverse Event Data Clarification Form. The Investigator must retain a copy of all the SAE forms in the Investigator Site File.

The Investigator must inform their Institutional Review Board (IRB) of all SAEs occurring in the study within 7 days for fatal or life-threatening SAEs and 15 days for all other SAEs as per Sponsor instructions and as described in the Safety Management Plan.

The Investigator should not break the randomisation code except when it is necessary to do so in order to ensure the subject receives appropriate medical care.

SAEs and non-serious AEs will be reported to the appropriate regulatory authorities by the Sponsor in accordance with the authorities' requirements. The Sponsor is responsible for expedited reporting of all SUSARs/ SAEs to relevant authorities and IECs/IRBs as required by

regulations. If the event requires expedited reporting, a CIOMS (Council for International Organizations of Medical Sciences) form will be produced and GVG will take actions as per the study specific Safety Management Plan.

8.4 Follow-up of Adverse Events

All SAEs and all AEs that have not resolved by the end of the study will be followed up by the Investigator until resolution or until the Investigator believes there will be no further change, whichever is the earlier. This may involve the subject making additional visits to the site.

If a subject has unresolved AEs requiring follow-up, investigators must attempt to contact subjects by telephone or other means.

8.5 Overdose, Abuse, Misuse and Medication Errors

The Sponsor defines “overdose” as the administration of a quantity of an investigational IMP given per administration or cumulatively, which is above the maximum recommended dose according to the authorised product information.

The Sponsor defines “abuse” as the persistent or sporadic, intentional excessive use of an IMP, which is intended to produce harmful physical or psychological effects e.g. intentional overdose to experience psychological effects.

The Sponsor defines “misuse” as situations where the IMP is intentionally and inappropriately used not in accordance with the authorised product information.

Overdoses, abuse, misuse are reportable to the Sponsor irrespective of the presence of an associated AE / SAE. The overdose, abuse, misuse and any associated AE / SAE will be captured on an AE CRF (Case Report Form) page / SAE form.

Due to the full inpatient nature of this study, in which medication doses will be supervised by site staff, cases of overdose, abuse or misuse are not expected to occur.

Medication errors are any unintentional errors in dispensing or administration of the IMP which relates to:

- Taking / being administered an incorrect IMP
- Taking / being administered a drug by the wrong route of administration e.g. swallowing a suppository
- The accidental administration of the IMP to a person who is not a subject within the study

Medication errors are reportable to the Sponsor irrespective of the presence of an associated AE / SAE. Medication errors with or without an associated AE / SAE will be captured on the AE CRF page / SAE form.

8.6 Pregnancy

Pregnancy both in a female subject or the female partner of a male subject is considered a collectable event and will be recorded as an AE in all cases. It will be qualified as an SAE only if it fulfils SAE criteria.

Due to the full inpatient nature of this study, pregnancy cases are not expected to occur during the study.

9 STATISTICAL CONSIDERATIONS

This section presents a summary of the planned statistical analyses. A statistical analysis plan (SAP) that describes the details of the analyses to be conducted will be written prior to database lock.

Summary statistics for continuous variables will typically include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, summary statistics will typically include the number and percentage of subjects in each category. All data will be presented in listings.

Baseline values are defined as the last measurements taken before dosing with study drug.

9.1 Determination of Sample Size

The sample size determination is based on the primary efficacy variable, SPID12. According to Farrar 2001[(1)], 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 [(7)], 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 2×300-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 randomised into each of the PR and IR groups. Thus 280 subjects will be enrolled into the study.

9.2 Interim Analysis

No interim analysis is planned.

9.3 Analysis Datasets

The analysis populations include the following:

- The intent-to-treat (ITT) population will consist of all subjects who are treated with study drug and who have at least 1 pain relief assessment after Time 0. The ITT population is the primary population for the efficacy analysis.
- The per-protocol (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 utilized to evaluate the sensitivity of the primary efficacy analysis.
- The safety population will include all subjects who are treated with study drug. The safety population is the population for all safety assessments.

9.4 Subject Disposition and Characteristics

The numbers of subjects randomised, completing, and withdrawing, along with reasons for withdrawal, will be tabulated overall and by treatment group. The number of subjects in each analysis population will be reported. Demographic and baseline characteristics (including date of birth, sex, race, weight, height, BMI, medical history, and surgery duration) will be summarized for each treatment group and for the overall population using descriptive statistics. No formal statistical analyses will be performed.

9.5 Efficacy Analyses

The comparison of primary interest is between PR ibuprofen and placebo. In addition, the comparison between IR ibuprofen and placebo will be presented with p-values to demonstrate study sensitivity. Point estimates and 95% confidence intervals will be used to evaluate the clinical relevance of any differences between the PR and IR formulations. All treatment differences will be presented with 95% confidence intervals. No P value adjustment will be made for multiple endpoints or multiple comparisons. In the event of model assumptions for normality being violated, non-parametric methods will be used.

Each efficacy endpoint will be summarized descriptively by treatment group.

9.5.1 Primary Endpoint(s)

The primary endpoint, summed pain intensity difference (SPID) over 0 to 12 hours (SPID12), will be used to compare the test product (2×300 mg ibuprofen PR tablets) against the placebo product.

9.5.1.1 Primary Analysis

The primary efficacy null hypothesis is that SPID12 for placebo is equal to SPID12 for ibuprofen 2×300 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.

9.5.1.2 Secondary Analysis

The clinical relevance of the difference between placebo and PR ibuprofen over 12 hours after initial dose will be evaluated.

9.5.2 Secondary Endpoints

- The summed pain intensity difference (SPID) over 0 to 24 hours (SPID24) will be used to compare the test product (2×300 mg ibuprofen PR tablets twice daily [BID]) and comparator product (2×200 mg ibuprofen IR tablets three times a day [TID]).
- Summed pain intensity difference (SPID) over 0 to 4 hours (SPID4), over 0 to 8 hours (SPID8), and over 0 to 12 hours (SPID12) after Time 0
- 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 (a responder will be defined as a subject with ≥30% improvement in pain intensity without rescue medication during the first 8 hours)
- Numeric rating scale (NRS) pain intensity difference (PID) at each scheduled time point after Time 0
- Pain intensity score at each scheduled time point
- Pain relief score at each scheduled time point after Time 0
- Peak pain relief
- Time to onset of analgesia (measured as time to perceptible pain relief confirmed by time to meaningful pain relief) using double stopwatch
- 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

9.5.2.1 Secondary Endpoint Analyses

For continuous secondary endpoints such as pain intensity score, SPID at each scheduled time point, peak pain intensity, TOTPAR4, TOTPAR8, TOTPAR12, TOTPAR24, SPID4, SPID8, SPID24, SPRID4, SPRID8, SPRID12, and SPRID24, descriptive statistics (such as mean, standard deviation, median, minimum, and maximum) will be provided for each treatment regimen. P values from ANCOVA models comparing the placebo group with other treatment groups, including terms for treatment and a covariate for baseline pain will be provided for SPID, SPRID, and TOTPAR variables, but no formal statistical inferences will be drawn on the basis of these tests. In the event that normality assumptions are violated for a parameter, non-parametric analysis methods will be used.

For ordinal secondary endpoints, such as pain intensity difference at each scheduled time point, pain relief at each scheduled time point, peak pain relief, and global evaluation of study drug, descriptive summaries will be provided and will include the number and percentage of subjects within each category for each treatment group. Nominal P values from Fisher's exact tests (or chi-square tests, as appropriate) comparing the placebo group with other treatment groups will be provided for peak pain relief and global evaluation of study drug, but no formal statistical inferences will be drawn on the basis of these tests.

For each time-to-event endpoint, Kaplan-Meier methodology will be used to evaluate the treatment effect. Time to onset of analgesia (measured as time to perceptible pain relief confirmed by meaningful pain relief) will be based on data collected using the double stopwatch method. Time to onset of analgesia will be right-censored at 8 hours for subjects who do not experience both perceptible pain relief and meaningful pain relief during the 8-hour interval after Time 0. The summary tables will provide the number of subjects analysed, the number of subjects censored, estimates for the quartiles, and 95% confidence intervals (CIs) for the estimated median and the restricted mean estimate. P values comparing placebo to active treatment from Wilcoxon or log-rank tests (as appropriate) will also be used to examine treatment effect.

For time to onset of analgesia, the comparison of interest will be the ibuprofen 2×300 mg PR group versus the ibuprofen 2×200 mg IR group. The summary table for this comparison will provide the number of subjects analysed, the number of subjects censored, estimates for the quartiles, and 95% confidence intervals (CIs) for the estimated median and the restricted mean estimate.

For the proportion of subjects who are responders and the proportion of subjects using rescue medication, logistic regression models that adjust for baseline intensity and/or significant demographic variables, if appropriate, will be used to evaluate the treatment effect.

For the responder analysis, subjects will be censored at 8 hours and for the use of rescue medication/time to first rescue subjects will be censored at 24 hours.

9.6 Safety Analyses

9.6.1 Safety Endpoint(s)

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

9.6.1.1 Safety Endpoint Analyses

Data listings will be provided for protocol-specified safety data. The Medical Dictionary for Regulatory Activities (MedDRA) (Version 19.0 or higher) will be used to classify all AEs with respect to system organ class and preferred term. Adverse event summaries will include only TEAEs, which will be summarized for each treatment group.

For vital sign measurements, descriptive statistics will be provided at each scheduled time point for each treatment group. Changes from Baseline for vital signs will be calculated for each subject, and descriptive statistics will be provided on changes in vital signs from Baseline for each treatment group at each scheduled time point after Baseline. No formal statistical tests will be performed.

9.7 Handling of Missing Data and Drop-outs

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.

The primary analysis will use windowed worst observation carried forward (WOCF) methodology for subjects who use rescue medication. Any pain measurements taken during a period of time in which rescue medication (any intervention used by the participant intended to alleviate pain) is active (4 hours) will be replaced by the worst pain measurement from Time 0 up until when the first dose of rescue medication was taken. 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 the pain relief scores. Any other pain assessments impacted by the use of prohibited medications/therapies and thus needing to implement windowed WOCF will be identified prior to database lock and study unblinding. A sensitivity analysis will also be performed, in which all pain assessments recorded after the first dose of rescue medication has been taken will be disregarded and the rules outlined above will be used for missing data.

All data for assessments other than pain assessments will be analysed as collected; missing data due to premature termination or any other reason will be left as missing. Additional sensitivity analyses including use of rescue medication will be detailed in the Statistical Analysis Plan.

9.8 Changes to the Original Statistical Plan

If there are any deviations to the proposed statistical analysis as described in this protocol these will either be documented in the final SAP or in a protocol amendment prior to database lock with the rationale and impact of the changes addressed.

10 DATA HANDLING AND RECORD KEEPING

10.1 Case Report Forms (CRFs)

Data will be recorded in an electronic Case Report Form (eCRF). For each enrolled study subject an eCRF is maintained. The Investigator or designees is responsible for the quality of the data record in the eCRF. eCRFs must be kept current to reflect subject status at each

phase during the course of study. Subjects must not be identified in the eCRF by name or initials.

In the eCRF subjects will be identified by a subject number in combination with date of birth only, i.e., not by their name or initials. eCRF entries must be completed by appropriately trained site staff only. A log of trained and authorised staff able to complete the eCRF will be kept.

10.2 Specification of Source Documents

Source data must be available at the site to document the existence of the study subjects. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject. The investigator and study monitor will identify the data that will be recorded directly on the eCRF and for this data the eCRF will be considered the source document (i.e., no prior written or electronic record of the data). The study monitor will document this at the screening and it will also be documented in the Data Management Plan.

Source documents will include notes taken at the site and will include data such as demographic data, participation in study and ICF, medical history, SAEs, AEs and concomitant medication, results of examinations and assessments.

Where source data are in the form of a computer printout (e.g. medical records, laboratory data) they will be signed and dated by the investigator or designated person, confirming that the print out is a true and faithful record of the data for that subject. These print-outs will be filed in the study files.

The Investigator agrees to provide direct access to source data for study-related monitoring, audits, IRB review, and regulatory inspection(s). Direct access to source data requires that the subject gives written, documented consent to this.

10.3 Data Management

The data management group at Premier Research will be responsible for data management and eCRF activities.

Full details regarding data management will be described within the Data Management Plan.

10.4 Reporting of Protocol Deviations

Site staff should make the study monitor aware of any deviation from the protocol as soon as possible after occurrence. Waivers for inclusion / exclusion criteria are not allowed.

10.5 Retention of Essential Documentation

The Investigator should retain all essential documents (as defined in ICH E6 or according to other national and international regulations) until at least 5 years after the completion of the study (defined as last subject last visit in the study). These documents should be retained for

a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

Subject files and other source data must be kept for the maximum period of time permitted by the Clinical Unit. The Investigator must notify the Sponsor of the retention period if this is shorter than described above.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Monitoring

The Sponsor will organise regular monitoring visits to be performed at intervals agreed with the Investigator. The anticipated monitoring frequency will be stated in the Monitoring Plan. Monitoring will also involve, as appropriate, correspondence and telephone contacts.

On-site monitoring includes source data verification (SDV) which is the procedure whereby the data contained in the eCRFs are compared with the primary source data and thereby verified as accurate. It will be performed in such a way as to preserve subject confidentiality, taking into account all ethical and legislative requirements.

The Investigator, or a designated member of the Investigator's staff, must be available at some time during the monitoring visit to review the data and resolve any queries and to allow direct access to the subject's records for SDV).

SDV will include as a minimum verification for all subjects, subject identity (date of birth, sex, initials and subject number), record of entry into the study and signature of the informed consent. In addition, details of SAEs in the subject's notes will be verified. Details included in the subject's notes as a minimum:

- Study number, brief description or title of study
- Date that the subject gave written consent
- All visit dates
- All SAEs
- All concomitant medications

At a site visit the eCRFs should be complete and available in order that the accuracy of their completion may be checked. Each completed eCRF for each subject must be signed electronically by the Investigator, to verify the data and statements submitted. Similarly, all alterations on paper records must be initialled and dated by the Investigator or a designated person, explained as necessary, with the original mistake left legible.

11.2 Audits and Inspections

For the purpose of ensuring compliance with the protocol, ICH GCP and applicable regulatory requirements, clinical studies sponsored by RB may be subject to an independent audit at the study site which will be conducted by personnel from an appropriate Quality Assurance Unit. Full consultation with the Investigator will be made prior to and during such audit, which will be conducted according to Quality Assurance Unit Standard Operating Procedures.

As soon as the Investigator is notified of a planned inspection by a Regulatory Authority, he / she must inform the Sponsor promptly and allow the Sponsor to participate in the inspection as permitted by applicable regulations and local laws.

11.3 Sponsor Policy on Fraud in Clinical Studies

In accordance with GCP, it is the Sponsor's policy to always follow-up suspected cases of fraud.

12 ETHICAL AND REGULATORY ASPECTS

12.1 Ethics Review and Regulatory Authority Approval

Written approval to conduct the study by an independent and appropriately constituted IRB must be obtained and a copy provided to the Sponsor before any protocol-related procedures that do not form part of the subject's normal clinical treatment are performed. The approval letter must contain:

- Name and address of the IRB.
- Date of meeting.
- Sufficient information to identify the version of the Protocol and subject information/informed consent.
- Sufficient information to identify the version of other documents reviewed.

The investigator must also provide the Sponsor with a list of IRB members that includes each member's name and profession.

Any amendments to the Protocol must be submitted to the IRB for approval unless where necessary to eliminate apparent immediate hazards to study subjects, and any administrative changes must be notified.

This study will be submitted to the applicable Regulatory Authorities. The study will only be undertaken when regulatory authorisation has been obtained by the Sponsor.

The Sponsor will notify the Regulatory Authority within 90 days of the end of the study (within 15 days if the study is terminated prematurely).

Premier Research will notify the IRB within 90 days of the end of the study (within 15 days if the study is terminated prematurely).

12.2 Subject Information and Consent

Informed consent should be obtained by means of a patient information sheet and ICF, prepared in accordance with ICH E6 (R2) section 4.8.10 and the applicable local regulations, written in a non-technical language. All subjects will be provided with oral and written information describing the nature and duration of the study and the procedures to be performed. The subject will be asked to sign and date an ICF prior to any study-specific procedures being performed. No subject can enter the study before his/her informed consent has been obtained. A sample subject ICF used in the study will be included in the clinical study report for this protocol.

As part of administering the informed consent document, the Investigator must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician. The subject should understand the study, patient information sheet, and ICF before signing and dating the ICF. The Investigator or person obtaining consent must also sign and date the form. Each subject will be given a copy of the signed informed consent and written information.

12.3 Early / Premature Termination of the Study

In the unlikely event that this study generates an excessive frequency of adverse events, subjects' termination or suspension may be requested by the sponsor or the IRB or the Regulatory Authority.

The sponsor retains the right to terminate the study for non-safety reasons by giving an appropriate period of notice to all involved parties as per contractual agreements.

Any decisions to terminate or suspend the study will be notified in writing to the Investigator or designees, the IRB, Regulatory Authority and the clinicaltrials.gov database.

If the study is terminated early, study subjects who have attended screening will be informed that they are no longer required and if they have any questions, they should consult the study site staff. For subjects who have completed the study they will not be informed that the clinical study has been terminated. All data collected up to the point of study termination will be used in an abbreviated Clinical Investigation Report.

13 COMPENSATION, INDEMNITY AND INSURANCE

13.1 Clinical Study Agreement

Before the study commences, a contract between the Sponsor and Premier Research, who contracts with the Investigator, will be signed in which financial aspects of the study (including financial disclosure) as well as responsibilities and obligations are described.

13.2 Compensation

The Sponsor and the CRO carry insurance to pay compensation for injury, accident, ill health and death caused by participation in this study without regard to proof of negligence in accordance with the current local regulations and requirements. Details on finance and insurance will be provided in a separate agreement between the investigator and the sponsor.

13.3 Indemnity

The Sponsor will provide appropriate indemnity for the Investigator and staff who conduct part or all of this study, upon request. The request must be received before the first subject is recruited.

13.4 Insurance

If required and in accordance with applicable regulatory and legal requirements, the Sponsor will take out appropriate insurance policies on behalf of the Investigator and staff who conduct part or all of this study and/or on behalf of the subjects participating in the study.

14 REPORTING, PUBLICATION AND PRESENTATION

A clinical study report will be prepared according to ICH E3 (Structure and Content of Clinical Study Reports) as part of the Sponsor's commitment to Good Clinical Practice. The report will be a record of the total study conduct and findings and will be subject to approval by the Investigator who will sign the final report.

The study data will be owned by the Sponsor. The Sponsor retains the right to publish the data independently of the Investigator. The Sponsor agrees that before it publishes the results, it will provide the Investigator with at least 30 days for full review prior to submission of the manuscript to the publisher. The Investigator must submit any proposed manuscript to the Sponsor for approval prior to submission for publication.

15 REFERENCES

(1) Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain. 2001 Nov; 94(2):149-58.

(2) Summary of Product Characteristics for Nurofen 200 mg tablets Reckitt Benckiser Healthcare Ltd. (PL 00063/0385). 09 November 2015.

(3) Davies, NM Clinical pharmacokinetics of ibuprofen. The first 30 years. Clin. Pharmacokinetic. 1998, 34 (2), 101-154.

(4) Lisa Miles, Jessica Hall, Bartosz Jenner, Richard Addis & Simon Hutchings (2018) Predicting rapid analgesic onset of ibuprofen salts compared with ibuprofen acid: Tlag, Tlow, Tmed, and a novel parameter, TCmax Ref, Current Medical Research and Opinion, DOI: 10.1080/03007995.2018.1466697.

(5) Cooper SA, Desjardins PJ, Turk DC, et al. Research design considerations for single-dose analgesic clinical trials in acute pain: IMMPACT recommendations. Pain. 2016 Feb; 157(2):288-301. doi: 10.1097/j.pain.0000000000000375.

(6) Wyeth Consumer Healthcare. (2002). *NDAC Meeting on Risks of NSAIDs.* Available: https://www.fda.gov/ohrms/dockets/ac/02/briefing/3882b2_04_wyeth-ibuprophen.htm. Last accessed 13th March 2018

(7) Singla, Neil Kumar et al. “A comparison of the clinical and experimental characteristics of four acute surgical pain models: Dental extraction, bunionectomy, joint replacement, and soft tissue surgery.” PAIN® 155 (2014): 441-456.

HEALTH · HYGIENE · HOME	**Investigational Study Protocol Amendment**
	Page 1 of 6

Document Name:	Non-Substantial Protocol Amendment Number 2	
Version Number & Date:	Version 1.0 12 May 2020	
Study Number:	5003601	
Study Title:	A Randomised, 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	
EudraCT / IND / Other Number:	IND 141948	
Study Type:	Efficacy	
Protocol Version Number:	From:	3.0
	To:	4.0
Principal Investigator Name:	Todd Bertoch, M.D.	

Details of Amendment:	Amendments are required to the Study Synopsis: Statistical Evaluation section and section 9.7 Handling of Missing Data and Drop Outs. 1. Correction of the description of the windowed worst observation carried forward (WOCF) method and additional details of sensitivity analyses that will be documented in the statistical analysis plan 2. An update to the time window for pain measurements during rescue medication / therapies.	
Section(s) to be Changed:		
Study Synopsis: Statistical Evaluation	From:	The primary analysis will use windowed worst observation carried forward (WOCF) methodology for subjects who use rescue medication. Any pain measurements taken during a period of time in which rescue medication is active (4 hours) will be replaced by the last pain measurement before the rescue medication was taken. A sensitivity analysis will also be performed, in which all pain assessments recorded after the first dose of rescue medication has been taken will be disregarded and the rules outlined above will be used for missing data. All data for assessments other than pain assessments will be analysed as collected; missing data due to premature termination or any other reason will be left as missing.
	To:	The primary analysis will use windowed worst observation carried forward (WOCF) methodology for subjects who use rescue medication. Any pain measurements taken during a period of time in which rescue medication (any intervention used by the participant intended to alleviate pain) is active (4 hours) will be replaced by the worst pain measurement from time 0 up until when the first dose of rescue medication was taken. 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 the pain relief scores. Any pain assessments impacted by the use of prohibited medications/therapies and thus needing to implement windowed WOCF will be identified during the blinded Data Review Meeting (DRM) prior to database lock and study unblinding. A sensitivity analysis will also be performed, in which all pain assessments recorded after the first dose of rescue medication has been taken will be disregarded and the rules outlined above will be used for missing data. All data for assessments other than pain assessments will be analysed as collected; missing data due to premature termination or any other reason will be left as missing. Additional sensitivity analyses including use of rescue medication will be detailed in the Statistical Analysis Plan.
Section 9.7 Handling of	From:	The primary analysis will use windowed worst observation carried forward (WOCF) methodology for subjects who use rescue

Missing Data and Dropouts		medication. Any pain measurements taken during a period of time in which rescue medication is active (4 hours) will be replaced by the last pain measurement before the rescue medication was taken. A sensitivity analysis will also be performed, in which all pain assessments recorded after the first dose of rescue medication has been taken will be disregarded and the rules outlined above will be used for missing data. All data for assessments other than pain assessments will be analysed as collected; missing data due to premature termination or any other reason will be left as missing. In the event of a notable difference between treatment groups in the number of subjects using rescue medication, other sensitivity analyses may be performed. These will be detailed in the Statistical Analysis Plan (SAP).
	To:	The primary analysis will use windowed worst observation carried forward (WOCF) methodology for subjects who use rescue medication. Any pain measurements taken during a period of time in which rescue medication (any intervention used by the participant intended to alleviate pain) is active (4 hours) will be replaced by the worst pain measurement from Time 0 up until when the first dose of rescue medication was taken. 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 the pain relief scores. Any other pain assessments impacted by the use of prohibited medications/therapies and thus needing to implement windowed WOCF will be identified prior to database lock and study unblinding. A sensitivity analysis will also be performed, in which all pain assessments recorded after the first dose of rescue medication has been taken will be disregarded and the rules outlined above will be used for missing data. All data for assessments other than pain assessments will be analysed as collected; missing data due to premature termination or any other reason will be left as missing. Additional sensitivity analyses including use of rescue medication will be detailed in the Statistical Analysis Plan.
Reason for Changes (in green text):		These changes are not intended to change or replace the analysis planned for this study. The method for imputing data for participants who had taken rescue medication was correctly detailed in the Statistical Analysis Plan (V1.0 07 Oct 2019 Section 6.1.5 Analysis Windows) and the Evidence Brief (Feb 2018 Statistical Methods, Efficacy Analysis Section), both of which state “The primary analysis will use windowed worst observation carried forward (WOCF) methodology for subjects who use rescue medication.” However, in the protocol the description of the method for imputing data for participants who took rescue medication was incorrectly detailed in these sections. Therefore, these amendments have been made to correct these typographical errors aligning with the SAP, whilst also providing

	clarity to the description and application of the statistical methodology (windowed Worst Observation Carried Forward) to be used.
Reason for Change (in blue text):	The amendment details the intention to conduct multiple sensitivity analyses which will be conducted to assess the impact of rescue medication.
Reason for Change (in purple text):	This change acknowledges the fact that rescue medication and / or therapies other than those specified in the protocol at the discretion of the investigator may have been used.

SIGNATURE PAGE

Protocol Author

DocuSigned by:
Steve Fincham
Signer Name: Steve Fincham
Signing Reason: I am the author of this document
Signing Time: 12-05-2020 | 08:06 BST
BE7614371B734BEE96BB73959AA3DE4C

Mr Stephen Fincham Date
BSc, MSc
Associate Clinical Study Manager
RB

Protocol Statistician
(Statistics and DM sections reviewed and approved):

DocuSigned by:
Darren Targett
Signer Name: Darren Targett
Signing Reason: I approve this document
Signing Time: 12-05-2020 | 09:16 BST
AFBA8AD99F4542DDA7D194D987EF1679

Darren Targett Date
Consultant Statistician
RB Representative

Sponsor's Medical Expert
(Reviewed and approved):

DocuSigned by:
Neil Fawkes
Signer Name: Neil Fawkes
Signing Reason: I approve this document
Signing Time: 12-05-2020 | 10:55 BST
FBE2F9E6498A42529274F2FA9073AD21

Dr. Neil Fawkes, MBChB Date
Clinical Research Physician
RB

Senior Representative – Medical Science
(Approved to Proceed):

DocuSigned by:
Bruce Charlesworth
Signer Name: Bruce Charlesworth
Signing Reason: I have reviewed this document
Signing Time: 13-05-2020 | 14:24 BST
BD51A4AE69EE4498B7C482A182264320

Bruce Charlesworth, MBChB Date
Chief Medical Officer – Health Relief, Hygiene and Wellness
RB

INVESTIGATOR APPROVAL

I have read and understood this Clinical Study Protocol Amendment

Principal Investigator
(Reviewed and Accepted):

Todd Bertoch, MD Date
Chief Scientific Officer
JBR Clinical Research

13 MAY 2020

RECKITT BENCKISER

STUDY TITLE

A Randomised, 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

Short Study Title

Efficacy Study of 300mg Ibuprofen Prolonged-Release Tablets for the Treatment of Pain After Surgical Removal of Impacted Third Molars

IND (Investigational New Drug) Number:	141948
RB Study Number:	5003601
CRO Study Number:	RECK.177369
Protocol Version and Date:	FINAL V3.0 / 19-Nov-2019
Previous Versions / Date(s):	None
Confidentiality Statement:	The information contained in this document is privileged and confidential. Do not copy, circulate or otherwise distribute without written authority from Reckitt Benckiser

KEY CONTACTS

Name and title	Address	Phone	e-mail
Sponsor: RB Healthcare UK	Dansom Lane, Hull, HU8 7DS United Kingdom	+44 (0)1482 326151	5003601@rb.com
Sponsor's Medical Expert: Neil Fawkes	Dansom Lane, Hull, HU8 7DS United Kingdom	+44 (0)1482 5833242	neil.fawkes@rb.com
Principal / Chief / Coordinating Investigator(s): Dr Todd Bertoch	JBR Clinical Research 650 East 4500 South Suite 100 Salt Lake City Utah, 84107 USA	+ 1 928 8307354	tbertoch@jbrutah.com
Sponsors Statistician: Darren Targett	Dansom Lane, Hull, HU8 7DS United Kingdom	N/A	darren.targett@primoriscs.co.uk
Contract Research Organisation: Premier Research	One Park Drive, Suite 150 Durham, NC 27709 USA	+ 1 919 627 9100	N/A
CRO Project Manager: Paul Brittain	One Park Drive, Suite 150 Durham, NC 27709 USA	+ 1 617 934 2233	paul.brittain@premier-research.com
Clinical Laboratory: Quest Diagnostics, Inc.	3489 W 2100 S, Suite 200, West Valley City, Utah 84119 USA	N/A	N/A

SIGNATURE PAGE

Protocol Final Author

DocuSigned by:
Jane Thomas
Signer Name: Jane Thomas
Signing Reason: I am the author of this document
Signing Time: 19-Nov-2019 | 18:29:34 PM GMT
F09BC76EBAC349BDBA7BAD8C69B8DDD3

Mrs S. Jane Thomas Date
BSc (Hons)
Senior Clinical Study Manager
RB

Protocol Statistician
(Statistics and DM sections reviewed and approved):

DocuSigned by:
Darren Targett
Signer Name: Darren Targett
Signing Reason: I approve this document
Signing Time: 20-Nov-2019 | 08:02:57 AM GMT
AFBA8AD99F4542DDA7D194D987EF1679

Darren Targett Date
Consultant Statistician
RB Representative

Sponsor's Medical Expert
(Reviewed and approved):

DocuSigned by:
Neil Fawkes
Signer Name: Neil Fawkes
Signing Reason: I approve this document
Signing Time: 20-Nov-2019 | 10:37:34 AM GMT
FBE2F9E6498A42529274F2FA9073AD21

Dr. Neil Fawkes, MBChB Date
Clinical Research Physician
RB

Sponsor's Medical Director
(Approved to Proceed):

DocuSigned by:
Bruce Charlesworth
Signer Name: Bruce Charlesworth
Signing Reason: I approve this document
Signing Time: 25-Nov-2019 | 14:47:04 PM GMT
BD51A4AE69EE4498B7C482A182264320

Bruce Charlesworth, MBChB Date
Chief Medical Officer – Health Relief, Hygiene and Wellness
RB

INVESTIGATOR STATEMENT

I have read and understood this Clinical Study Protocol and agree:

- to conduct this clinical study in accordance with the protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). Amendments to the protocol are acceptable only upon mutual agreement with the exception of urgent safety measures that need to be taken to protect study subjects from any immediate hazard to their health and safety.
- to conduct this clinical study in accordance with the principles as set out in the Declaration of Helsinki and with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.
- to conduct this study only after a favourable opinion is obtained from the Independent Review Board and Regulatory Authority
- to report all information or data in accordance with the protocol.
- to report any serious adverse events as defined in the "Safety Reporting" section of this protocol.
- to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol.

I understand:

- that information that identifies me will be used and disclosed as described in the protocol and that such information may be transferred to countries that do not have laws protecting such information.
- that since the information in the protocol and the references in the Investigator's brochure (if applicable) are confidential, its disclosure to any third parties, other than those involved in approval, supervision or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

Principal Investigator
(Reviewed and Accepted):

02 Dec 2019

Todd Bertoch, MD — Date
Chief Scientific Officer
JBR Clinical Research

TABLE OF CONTENTS

List of Tables Contained in the Body of the Protocol

List of Figures Contained in the Body of the Protocol

LIST OF ABBREVIATIONS

Abbreviation	Abbreviation in Full
AE	Adverse Event
ANCOVA	Analysis of Covariance
AUC	Area Under the Plasma Concentration Curve
BID	Twice Daily
BMI	Body Mass Index
Cmax	Maximum Observed Plasma Concentration
CRF	Case Report Form
CRO	Contract Research Organisation
eCRF	Electronic Case Report Form
FDA	(US) Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GVG	Global Vigilance Group
HDL	High Density Lipoprotein
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IR	Immediate Release
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
IUS	Intrauterine System
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numeric Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
OTC	Over the Counter
PID	Pain Intensity Difference
PP	Per Protocol
PR	Prolonged Release
RB	Reckitt Benckiser
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SNRI	Serotonin and Noradrenaline Reuptake Inhibitor
SPID	Summed Pain Intensity Difference
SPRID	Summed Pain Relief and Intensity Difference
SSRI	Selective Serotonin Reuptake Inhibitor

Abbreviation	Abbreviation in Full
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent Adverse Event
TID	Three Times a Day
Tmax	Time to Maximum Plasma Concentration
TOTPAR	Sum of Total Pain Relief
WOCF	Worst Observation Carried Forward

STUDY SYNOPSIS

Study Title:	A randomised, 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
RB Study Number:	5003601
Background and Rationale:	Reckitt Benckiser (RB) is co-developing a new 300 mg ibuprofen prolonged release (PR) tablet with Strides Shasun Ltd. The product has been developed to meet consumer and patient needs to have access to longer acting over-the-counter analgesics. This PR formulation will reduce fluctuations in drug plasma concentrations and allow for a lower frequency of administration which is desirable in situations where pain duration is expected to be prolonged and require multiple doses of immediate release formulations. As a result, the product would be more consumer friendly, require less dosing and improve compliance with treatment. The proposed therapeutic indications of the PR product are for the short-term symptomatic treatment of mild to moderate pain such as dysmenorrhea, rheumatic pain, muscular pain, pain of non-serious arthritic conditions and backache. The proposed posology in adults over the age of 18 is: Ibuprofen 300 mg PR tablets. Two tablets to be taken every 12 hours when required for pain relief. No more than 2 doses in 24 hours. The maximum daily dose is 1200 mg and there is no proposed indication in the paediatric population. Therefore, the purpose of the proposed study is to provide supporting pivotal efficacy evidence for registration applications in Europe, Australia and Russia. The decision to progress to an efficacy clinical trial was determined on the basis of successful outcomes of the 2 phase 1 clinical trials (BE/17/279 and BE/17/281) in terms of bioavailability (BA) versus a reference ibuprofen immediate release (IR) product and bioequivalence (BE) versus comparator 600 mg ibuprofen PR.
Objectives:	**Primary Objective:** • To evaluate the superiority of 2×300 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. **Key Secondary Objectives:** • 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 2×300 mg ibuprofen PR tablets. **Additional Secondary Objectives:** • To evaluate the total analgesic effect, peak analgesic effect, onset and duration of action and the subject's overall assessment of the study medications.
Design:	This is a single centre, randomised, double-blind, double-dummy, parallel group, multiple-dose, active and placebo-controlled efficacy study to evaluate the efficacy and safety of 2×300 mg ibuprofen PR tablets in subjects with post-surgical dental pain.
Primary Endpoint:	The Summed Pain Intensity Difference (SPID) over 0 to 12 hours (SPID12) will be used to compare the test product (2×300 mg ibuprofen PR tablets) against the placebo product.
Confirmatory Evaluation:	Clinically relevant difference between placebo and PR ibuprofen over 12 hours after initial dose (for the purposes of this study, a difference of 30 % in PID scores over 12 hours after initial dose will be considered clinically relevant).[(1)]
Secondary Endpoints:	**Key secondary efficacy endpoint:** • The summed pain intensity difference (SPID) over 0 to 24 hours (SPID24) will be used to compare the test product (2×300 mg ibuprofen PR tablets twice daily [BID]) and active comparator product (2×200 mg ibuprofen IR tablets three times a day [TID]). **Efficacy endpoints:** • Summed pain intensity difference (SPID) over 0 to 4 hours (SPID4), over 0 to 8 hours (SPID8), and over 0 to 12 hours (SPID12) after Time 0 • 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 (a responder will be defined as a subject with ≥30 % improvement in pain intensity without rescue medication during the first 8 hours) • Numeric rating scale (NRS) pain intensity difference (PID) at each scheduled time point after Time 0 • Pain intensity score at each scheduled time point • Pain relief score at each scheduled time point after Time 0 • Peak pain relief • Time to onset of analgesia (measured as time to perceptible pain relief confirmed by time to meaningful pain relief) using double stopwatch • 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 **Exploratory endpoint:** • Patient's global evaluation of study drug
Safety Endpoints:	• Incidence of treatment-emergent adverse events (TEAEs) • Incidence of clinically relevant changes in vital sign measurements
Subjects:	**Inclusion Criteria** A subject will be eligible for study entry if all the following inclusion criteria are met: 1) Is male or female ≥ 18 and ≤ 50 years of age. 2) Requires extraction of 2 or more third molars. At least 1 of the third molars must be a fully or partially bone impacted mandibular molar. If only 2 molars are removed, then they must be ipsilateral. 3) Experiences moderate to severe pain intensity within 6 hours after surgery, as measured by a numeric rating scale (NRS) score of ≥ 5 on a 0-10 scale. 4) Has a body weight ≥ 45 kg and a body mass index (BMI) ≤ 35 kg/m^2. 5) Female subjects of child-bearing potential must have been using an acceptable method of contraception for at least 30 days prior to randomization and be willing to continue use until at least 48 hours post discharge from the clinic (see Section 4.4). To be considered not of child-bearing potential, females must be surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or post-menopausal (defined as no menses for 12 months without an alternative medical cause).

	6) Free of clinically significant abnormal findings as determined by medical history, physical examination, vital signs, laboratory tests and ECG. 7) Is able to provide written informed consent. 8) Is willing and able to comply with study requirements (including diet and smoking restrictions), complete the pain evaluations, remain at the study site overnight, and return for follow-up 7 (± 2) days after surgery, (Day 8 ± 2 days). **Exclusion Criteria** A subject will not be eligible for study entry if any of the following exclusion criteria are met: 1) Known hypersensitivity reactions or allergy (e.g. asthma, rhinitis, angioedema or urticaria) in response to nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen), acetylsalicylic acid (aspirin), ingredients of the study drug, or any other drugs used in the study, including anaesthetics and antibiotics that may be required on the day of surgery. 2) A history of active or previous peptic ulceration/ haemorrhage, gastrointestinal bleeding or perforation, heart failure, renal or hepatic failure, uncontrolled hypertension, asthma, nasal polyps, or chronic rhinitis. 3) Has complications from the tooth extraction or any other clinically significant medical history that, in the opinion of the investigator, would affect the subject's ability to comply or otherwise contraindicate study participation, including but not limited to the following: cardiac, respiratory, gastroenterological, neurological, psychological, immunological, haematological, oncological, or renal disease. 4) Has undergone another dental surgery within 60 days prior to the day of surgery. 5) A positive urine drugs of abuse screen or alcohol breathalyser test at screening and during the study (with the exception of a positive drugs of abuse screen that is a consequence of permitted prescription medicines). 6) If female, has a positive pregnancy test at screening (serum) or on the day of surgery prior to surgery (urine), or is lactating. 7) Has known or suspected, (in the opinion of the investigator), history of alcoholism or drug abuse within 2 years of screening or evidence of tolerance or physical dependence before dosing with study drug. 8) Taking any concomitant medications that might confound assessments of pain relief, such as psychotropic drugs, antidepressants, sedative-hypnotics (other than those permitted for

	conscious sedation), or other analgesics taken within five times of their elimination half-lives. Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) are permitted if the subject has been on a stable dose for at least four weeks prior to Visit 1 (screening). 9) Is considered by the investigator, for any reason (including, but not limited to the risks described as precautions, warnings and contraindications in the current version of the investigator's brochure for 300 mg ibuprofen PR tablets), to be an unsuitable candidate to receive the study drug. 10) Has a history of chronic use (defined as daily use for > 2 weeks) of nonsteroidal anti-inflammatory (NSAIDs), opiates, or glucocorticoids (except inhaled nasal steroids and topical corticosteroids), for any condition within 6 months before dosing with study drug. 11) Has significant difficulties swallowing capsules or tablets or is unable to tolerate oral medication. 12) Subject has received an investigational product or participated in another trial involving a marketed or investigational drug in the 30 days (or for investigational agents with a long half-life, a washout of 5 half-lives) prior to first drug administration (washout period between studies is defined as the period of time elapsed between the last dose of the previous study and first dose for this study). Or if the investigator believes that any previous participation in an investigational study would be to the detriment of the safety of the participant or the conduct of the study. 13) Enrolment of the Investigator, his / her family members, employees and other dependent persons. 14) Failure to satisfy the investigator of fitness to participate for any other reason.
Products to be Evaluated and Treatment Regimen:	**Test product:** • 300 mg ibuprofen PR tablets for oral administration **Reference products:** • 200 mg ibuprofen IR tablets for oral administration • Placebo (for blinding purposes, two types of placebo tablets will be made; one to look like the test product and one to look like the reference product) **Treatment regimens:** Eligible subjects meeting all study entry criteria will be randomised to receive 1 of the following treatments:

	• Treatment A: test product; 2×300 mg ibuprofen PR tablets, BID (total daily dose 1200 mg) • Treatment B: reference product; 2×200 mg ibuprofen IR tablets, TID (total daily dose 1200 mg) • Treatment C: matching placebo tablets
Methodology:	This is a single centre, randomised, double blind, double-dummy, parallel group-, multiple-dose, active and placebo controlled efficacy study to evaluate the efficacy and safety of ibuprofen 2×300 mg ibuprofen PR tablets in subjects with post-surgical dental pain. Eligible subjects will complete all screening procedures within 28 days before the surgery and randomisation. At Screening, subjects will provide written informed consent to participate in the study before any protocol specified procedures or assessments are completed. On Day 1, subjects who continue to be eligible for study participation after completing screening procedures and assessments will undergo extraction of 2 or more third molars. At least 1 of the third molars must be a fully or partially bone impacted mandibular molar. If only 2 molars are removed, then they must be ipsilateral. All subjects will receive local anaesthesia (2% lidocaine with 1:100,000 epinephrine). Nitrous oxide will be allowed at the discretion of the investigator. Subjects who experience moderate to severe pain intensity (a score of ≥ 5 on a numeric rating scale [NRS] from 0-10 where 0 = no pain, 10 = worst pain ever) within 6 hours after surgery and who continue to meet all study entry criteria will be randomised in a 3:3:1 ratio to receive 2×300 mg ibuprofen PR tablets every 12 hours (Q12h), 2×200 mg ibuprofen IR tablets every 8 hours (Q8h), or placebo. The randomisation 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). Subjects will re-assess their baseline pain intensity using the NRS immediately before receiving study drug (pre-dose, Time 0) and their pain intensity (NRS) and pain relief (5-point categorical scale) at the following time points (pre-dose, if at one of the dosing timepoints of 0, 8, 12 and/or 16 hours): 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, if any. 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. The double stopwatch method will be used to record the time to perceptible pain relief and time to meaningful pain relief during the 8 hours following the first dose or until subject takes rescue

	medication. Subjects will complete a global evaluation of study drug 24 hours (+/- 5 minutes) after Time 0 or immediately before the first dose of rescue medication (whichever occurs first). Vital signs will be recorded after the subject has been in a sitting position for 3 minutes at the following times: before surgery, within 30 minutes before Time 0, 12 and 24 hours after Time 0, and/or immediately before the first dose of rescue medication. Adverse events (AEs) will be monitored and recorded from the time of signing of the informed consent form (ICF) until the Follow up- Visit (or Early Termination Visit). During the 24 hours following Time 0, subjects will complete efficacy and safety assessments. Subjects will remain at the study site overnight and will be discharged on Day 2. Paracetamol / acetaminophen (1000 mg) will be permitted as the initial rescue medication. Subjects will be encouraged to wait at least 60 minutes after receiving study drug before taking rescue medication. If acetaminophen rescue medication is not effective in relieving the subject's pain, 5 mg oxycodone rescue medication may be administered at the discretion of the investigator. Subjects are not permitted to take any concomitant medications that might confound assessments of pain relief, such as psychotropic drugs, antidepressants, sedative-hypnotics (other than those permitted for conscious sedation), or other analgesics taken within five times of their elimination half-lives (other than those used at the surgery). Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) are permitted if the subject has been on a stable dose for at least four weeks prior to Visit 1 (screening). Other restrictions include the following: alcohol use is prohibited from 24 hours before surgery until discharge on Day 2; nothing by mouth from midnight before surgery until 1 hour after surgery; clear liquids only are allowed starting 1 hour after surgery until 1 hour after dosing; 1 hour after dosing, the subject's diet may be advanced according to standard practice. Upon discharge from the study site, subjects may be prescribed pain medication for use at home according to the standard practice of the study site. On Day 8 (± 2 days), subjects will return to the study site for an abbreviated confirmatory physical assessment and AE assessments.
Statistical Evaluation:	**Analysis Populations** The analysis populations include the following:

	• The intent-to-treat (ITT) population will consist of all subjects who are treated with study drug and who have at least 1 pain relief assessment after Time 0. The ITT population is the primary population for the efficacy analysis. • The per protocol- (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 utilized to evaluate the sensitivity of the primary efficacy analysis. • The safety population will include all subjects who are treated with study drug. The safety population is the population for all safety assessments. **Subject Characteristics** Demographic and baseline characteristics (including date of birth, sex, race, weight, height, BMI and medical history) will be summarized for each treatment group and for the overall population using descriptive statistics. No formal statistical analyses will be performed. **Efficacy Analyses** The primary efficacy null hypothesis is that SPID12 for placebo is equal to SPID12 for ibuprofen 2×300 mg PR tablets. The primary analysis will be an ANCOVA (Analysis of Covariance) model that includes the main effect of treatment and the baseline pain score as a covariate 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. All other comparisons between the treatment regimens, including ibuprofen 2×200 mg IR tablets versus placebo, will be considered secondary. No P value adjustment will be made for multiple endpoints or multiple comparisons. Each efficacy endpoint will be summarized descriptively by treatment group. For continuous secondary endpoints such as pain intensity score, SPID at each scheduled time point, peak pain intensity, TOTPAR4, TOTPAR8, TOTPAR12, TOTPAR24, SPID4, SPID8, SPID24, SPRID4, SPRID8, SPRID12, and SPRID24, descriptive statistics (such as mean, standard deviation, median, minimum, and maximum) will be provided for each treatment regimen. Nominal P values from ANCOVA models comparing the placebo group with other treatment groups, including terms for treatment and baseline pain will be provided for SPID, SPRID, and TOTPAR variables, but no formal statistical inferences will be drawn on the basis of these tests. For ordinal secondary endpoints, such as pain intensity difference at each scheduled time point, pain relief at each scheduled time point,

	peak pain relief, response to study drug, and global evaluation of study drug, descriptive summaries will be provided and will include the number and percentage of subjects within each category for each treatment group. Nominal P values from Fisher's exact tests (or chi-square- tests, as appropriate) comparing the placebo group with other treatment groups will be provided for peak pain relief and global evaluation of study drug, but no formal statistical inferences will be drawn on the basis of these tests. For each time to- event endpoint, Kaplan Meier methodology will be used to evaluate the treatment effect. Time to onset of analgesia (measured as time to perceptible pain relief confirmed by meaningful pain relief) will be based on data collected using the double stopwatch method. Time to onset of analgesia will be -right censored- at 8 hours for subjects who do not experience both perceptible pain relief and meaningful pain relief during the 8-hour interval after Time 0. For time to onset of analgesia, the comparison of interest will be the ibuprofen 2×300 mg PR group versus the ibuprofen 2×200 mg IR group. The summary tables will provide the number of subjects analysed, the number of subjects censored, estimates for the quartiles, and 95% confidence intervals (CIs) for the estimated median and the restricted mean estimate. P values from the Wilcoxon or log rank- tests (as appropriate) will also be used to compare placebo to the active treatments. For the responder analysis and the proportion of subjects using rescue medication, logistic regression models that adjust for baseline intensity and/or significant demographic variables, if appropriate, will be used to evaluate the treatment effect. Baseline values are defined as the last measurements taken before dosing with a study drug. 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. The primary analysis will use windowed worst observation carried forward (WOCF) methodology for subjects who use rescue medication. Any pain measurements taken during a period of time in which rescue

	medication is active (4 hours) will be replaced by the last pain measurement before the rescue medication was taken. A sensitivity analysis will also be performed, in which all pain assessments recorded after the first dose of rescue medication has been taken will be disregarded and the rules outlined above will be used for missing data. All data for assessments other than pain assessments will be analysed as collected; missing data due to premature termination or any other reason will be left as missing. **Safety Analysis** Data listings will be provided for protocol-specified safety data. The Medical Dictionary for Regulatory Activities (MedDRA) (Version 19.0 or higher) will be used to classify all AEs with respect to system organ class and preferred term. Adverse event summaries will include only TEAEs, which will be summarized for each treatment group. For vital sign measurements, descriptive statistics will be provided at each scheduled time point for each treatment group. Changes from Baseline for vital signs will be calculated for each subject, and descriptive statistics will be provided on changes in vital signs from Baseline for each treatment group at each scheduled time point after Baseline. No formal statistical tests will be performed.

1 BACKGROUND AND RATIONALE

1.1 Background for the Study and Rationale

Reckitt Benckiser (RB) is co-developing a new 300 mg ibuprofen prolonged release (PR) tablet with Strides Shasun Ltd. The product has been developed to meet consumer and patient needs to have access to longer acting over-the-counter analgesics. This PR formulation will reduce fluctuations in drug plasma concentrations and allow for a lower frequency of administration which is desirable in situations where pain duration is expected to be prolonged and require multiple doses of immediate release formulations. As a result, the product would be more consumer friendly, require less dosing and improve compliance with treatment.

The proposed therapeutic indications of the PR product are for the short-term symptomatic treatment of mild to moderate pain such as dysmenorrhea, rheumatic pain, muscular pain, pain of non-serious arthritic conditions and backache.

The proposed posology in adults over the age of 18 is:

Ibuprofen 300 mg PR tablets. Two tablets to be taken every 12 hours when required for pain relief. No more than 2 doses in 24 hours. The maximum daily dose is 1200 mg and there is no proposed indication in the paediatric population.

Therefore, the purpose of the proposed study is to provide supporting pivotal efficacy evidence for European, Russian, and Australian applications and not to support any application in the USA. This efficacy study will provide further evidence on the safety and efficacy of the product in addition to the data obtained in two bioequivalence studies BE/17/279 and BE/17/281.

1.2 Investigational Product

Ibuprofen [2-(4-isobutylphenyl) propionic acid] is a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and anti-pyretic properties [(2)]. It was initially available in 1969 as a prescription only medicine, indicated for rheumatoid arthritis, osteoarthritis and other chronic painful conditions such as ankylosing spondylitis. Following further research and the establishment of a reassuring safety profile, it was launched in 1983 as an over-the-counter (OTC) medication, marketed as Nurofen®.

Absorption of ibuprofen after oral administration is fairly rapid with peak serum concentrations occurring within 1 to 2 hours after administration. Ibuprofen is extensively bound to plasma proteins (99%) when administered at therapeutic levels and has a plasma half-life of about 2 hours. Excretion by the kidney is both rapid and complete, but only a small proportion of drug is excreted unchanged in urine, the majority being extensively metabolised in the liver to 2 major inactive metabolites. The pharmacokinetics of ibuprofen has been extensively reviewed by Davies [(3)].

1.3 Treatment Rationale

The treatment of the test product is in line with the proposed posology of the final product and the treatment of the active comparator is in line with the posology provided in the label of the product. The treatments will be administered orally, as this is the standard route of administration for these products.

The following are the treatment regimens of each product in the study:

- Treatment A: test product, 2x300 mg PR ibuprofen tablet, twice daily [total daily dose 1200 mg]
- Treatment B: reference product, 2x200 mg IR ibuprofen tablet, three times a day [total daily dose 1200 mg]
- Treatment C: matching placebo tablets for both the test and reference regimens

The active comparator (Treatment B) currently marketed in a number of geographies including a number of different European countries. It has therefore been chosen to fulfil requirements that when it is included in a marketing authorisation dossier as a comparator that it is licenced within the EU.

1.4 Study Population and Indication

The following study population will be invited to participate in this clinical trial:

Adult participants aged 18 to 50 requiring extraction of 2 or more third molars, at least 1 of which must be a fully or partially bone-impacted mandibular molar, (if only 2 molars are removed, then they must be ipsilateral), and who experience moderate to severe pain following surgery.

Such population is expected to present pain levels that will allow for assessing the magnitude of treatment effect in a low variability setting.

1.5 Non-Clinical Evidence

No non-clinical evidence is available for the PR tablet.

1.6 Clinical Evidence to Date

A total of 5 single and multiple-dose pharmacokinetic studies (139-15, BE-16-081, BE-16-295, BE-17-279, BE-17-281) have been performed with the test product. These studies demonstrated the oral bioavailability (BA) of the ibuprofen PR tablets (dosed at 2x300 mg) is comparable to Brufen® (Ibuprofen) IR Tablets (dosed at 3x200 mg) after a single dose and at steady state conditions. In terms of the release profile and absorption, C_{max} tends to be slightly higher in the IR formulation when compared with the PR formulation [21.96 ±3.87 µg/mL vs 14.51 ±3.1 µg/mL]. However the C_{max}, (Maximum Observed Plasma Concentration), T_{max}, (Time to Maximum Plasma Concentration) and $AUC_{0\text{-}Tmax}$ (Area Under the Plasma Concentration Curve) of the PR formulation suggest that's the onset of action should not be any slower than the IR reference when considering the minimum effective concentration of ibuprofen [(4)]. In terms of total exposure ($AUC_{0\text{-}\infty}$) the concentration profile is bioequivalent between the PR test product and the IR reference product [163.41 ±43.0 µg.h/mL vs 168.59 ±37.7 µg.h/mL]. A food effect is demonstrated when the test product is taken in the fed state, with an expected increase in the absorption rate.

In the 5 PK studies performed (over 200 subjects) only a limited number of mild, transient adverse events were reported.

Summary Outcomes:

- The Clinical data available for this reformulation (Ibuprofen 300 mg PR) suggests an adequate pharmacokinetic profile to achieve a sufficient therapeutic effect in the proposed study
- There are no safety concerns with the test product
- Ibuprofen 300 mg PR had an increased rate of absorption when administered with food.
- Ibuprofen 300 mg PR tablets had a comparable concentration profile to the comparator IR product and was bioequivalent based on $AUC_{0\text{-}\infty}$

1.7 Risks / Benefits

This study has been designed to confirm the therapeutic efficacy of ibuprofen 300 mg PR. Participants in this study are subjects aged 18-50 who require the extraction of 2 or more third molars, at least 1 of which must be a fully or partially bone impacted mandibular molar. Subjects will undergo dental surgery that is equivalent to that of the standard-of-care that would be expected for the above condition. They should be otherwise healthy and each subject will undergo a full health check as part of the enrolment into the study to confirm that they are healthy as defined in this protocol (see Section 4).

Participants randomised into the placebo arm would not be expected to derive any therapeutic benefit from the administration of the placebo tablets. The placebo arm is essential to the study

design as it ensures that any conclusion of non-inferiority from the trial is a reflection of the true properties of the treatments; that is, it demonstrates the assay sensitivity of the study. However, this obviously leaves the participants without adequate analgesia in the post-surgery procedure and from an ethical perspective this is mitigated in the study design by the use of rescue medication that would be in line with standards of treatment. Although it is hypothesised that the investigational medicinal product (IMP) will provide adequate analgesia in the study, this cannot be guaranteed, and therefore the use of rescue medication also addresses the potential of reduced or lack of efficacy.

Ibuprofen is an established pharmaceutical ingredient and the adverse reactions associated with administration of 1200 mg/24 hour (OTC doses) are well known and documented [(2)(5)]. The adverse reactions most frequently occurring with a single dose being nausea, gastrointestinal upset, vomiting, diarrhoea, light headedness, dizziness and headache. Rarely, more serious reactions have been reported including GI bleeding, ulceration and perforations, hypertension and renal failure. When OTC doses of ibuprofen (200-400 mg/dose; 1200 mg/day) are taken for acute episodes of pain there is an extremely low risk of causing serious gastrointestinal events [(5)].

The specific 200mg Ibuprofen tablet to be used in this study as the active comparator (Treatment B) is marketed in the EU under the Nurofen brand and has an excellent safety profile.

It is not anticipated that the safety profile of ibuprofen will be altered after administration of multiple single doses of ibuprofen 300 mg PR in the context of this study. There are not expected to be any drug-drug interactions with the non-investigational medicinal products included within the study design. A washout period of at least 6 days is deemed to be sufficient prior to the Follow-up/Early Termination Visit to ensure adequate safety monitoring of the IMP.

The investigation site will have adequate set up, experience and safety measures that would be expected of a centre able to perform regular molar extractions. They will also have adequate experience in the safety monitoring of participants post dose that would be expected in a clinical trial setting. Therefore, it is considered that the risk related to study procedures are low and limited to common adverse events (AEs) related to the dental procedure, administration of routine anaesthetics, and discomfort from vital sign measurements. Any subject that experiences immediate complications during the surgery will be excluded from the study.

Therefore, the overall benefit-risk profile for the use of the investigational product as defined in this protocol is considered favourable.

1.8 Ethical Conduct of the Study

This study will be conducted in accordance with this protocol and the principles set out in the Declaration of Helsinki. It will comply with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

2 STUDY OBJECTIVES

Primary Objective:

- To evaluate the superiority of 2×300 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.

Key Secondary Objectives:

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

Additional Secondary Objectives:

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

3 STUDY DESIGN AND RATIONALE FOR DESIGN

This is a single centre randomised, double-blind, double dummy, parallel group, multiple-dose, active and placebo-controlled efficacy study to evaluate the efficacy and safety of 2×300 mg ibuprofen PR tablets in subjects with post-surgical dental pain.

The dental pain model used in this study is a robust and well established post-surgical pain model that produces pain that is predictable in its character, duration, and intensity[(6)]. The model is widely accepted and has a proven record of assay sensitivity (i.e. separating active drugs from each other, as well as from placebo). The model is frequently used to evaluate NSAID type analgesics. Results from dental pain studies are accepted by the US Food and Drug Administration (FDA) and European authorities and have been widely extrapolated to other general pain conditions.

The decision to conduct the study in the United States was taken as suitably qualified and experienced test sites could not be found in Europe. The specific test site has been chosen to conduct the study as they have a proven history of quality and safety when conducting studies of this type.

The placebo products have two purposes:

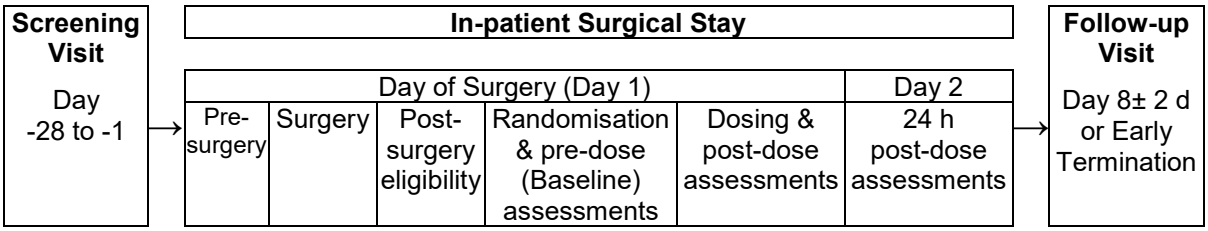
1. To mask the treatment identify for PR and IR arms
2. Act as a control arm

The dose of the test product is the proposed posology of the final product and the dose of the active comparator is the posology provided in the label of the product.

Eligible subjects will be randomised in a 3:3:1 ratio to receive 2×300 mg ibuprofen PR tablets Q12h, 2×200 mg ibuprofen IR tablets Q8h, or placebo. The randomisation 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 randomisation schedule will be prepared by a statistician not otherwise involved in the study. Randomisation will be performed using an interactive web response system (IWRS). 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.

Figure 3.1 Study Design Schematic



Note: Un-scheduled visits may occur at any point throughout the study

Table 3-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary Objective: To evaluate the superiority of 2×300 mg ibuprofen PR tablets compared with placebo in subjects experiencing acute dental pain after third molar extraction over 12 hours post initial dose.	**Primary Endpoint:** The primary efficacy endpoint is the summed pain intensity difference (SPID) over the 0 to 12 hours (SPID12) after Time 0 and will be used to compare the test product (2x300 mg PR ibuprofen) and the placebo product. The clinical relevance of the difference between placebo and PR ibuprofen over 12 hours after initial dose will be evaluated as confirmatory evidence (for the purposes of this study, a difference of 30% in PID scores over 12 hours after initial dose will be considered clinically relevant).
Secondary Efficacy Objectives: • To evaluate the analgesic performance of a total daily dose of 1200 mg of ibuprofen PR formulation compared to ibuprofen IR formulation over 24 hours post initial dose. • To evaluate the total analgesic effect, peak analgesic effect, onset and duration	**Key Secondary Efficacy Endpoints:** • The summed pain intensity difference (SPID) over 0 to 24 hours (SPID24) will be used to compare the test product (2×300 mg ibuprofen PR tablets twice daily [BID]) and comparator product (2×200 mg ibuprofen IR tablets three times a day [TID]).

of action and the subject's overall assessment of the study medications.	**Efficacy Endpoints:** • Summed pain intensity difference (SPID) over 0 to 4 hours (SPID4), over 0 to 8 hours (SPID8), over 0 to 12 hours (SPID12), and over 0 to 24 hours (SPID24) after Time 0 • 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 (a responder will be defined as a subject with ≥30% improvement in pain intensity without rescue medication during the first 8 hours) • NRS pain intensity difference (PID) at each scheduled time point after Time 0 • Pain intensity score at each scheduled time point • Pain relief score at each scheduled time point after Time 0 • Peak pain relief • Time to onset of analgesia (measured as time to perceptible pain relief confirmed by time to meaningful pain relief) using double stopwatch • 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

	Exploratory Endpoint: • Patient's global evaluation of study drug
Safety Objective: To evaluate the safety and tolerability of 2×300 mg ibuprofen PR tablets.	**Safety Endpoints:** • Incidence of treatment-emergent adverse events (TEAEs) • Incidence of clinically relevant changes in vital sign measurements

Subjects in the PR group will take 2×300 mg ibuprofen PR tablets at Hours 0 and 12. Subjects in the IR group will take 2×200 mg ibuprofen IR tablets at Hours 0, 8, and 16. To maintain double-blinding, at each dosing timepoint (Hours 0, 8, 12, and 16) all subjects will take a total of 4 tablets (placebo-only or active plus placebo, depending on randomised treatment group).

Table 3-2 Treatment Regimens

	PR Group	IR Group	Placebo Group
Hour 0	2 PR, 2 placebo for IR	2 placebo for PR, 2 IR	2 placebo for PR, 2 placebo for IR
Hour 8	2 placebo for PR, 2 placebo for IR	2 placebo for PR, 2 IR	2 placebo for PR, 2 placebo for IR
Hour 12	2 PR, 2 placebo for IR	2 placebo for PR, 2 placebo for IR	2 placebo for PR, 2 placebo for IR
Hour 16	2 placebo for PR, 2 placebo for IR	2 placebo for PR, 2 IR	2 placebo for PR, 2 placebo for IR
Hour 24	final assessments	final assessments	final assessments

The study will enrol approximately 280 male and female subjects 18-50 years of age who experience moderate to severe pain intensity within 6 hours after dental surgery to remove 2 or more third molars. At least 1 of the third molars must be a fully or partially bone impacted mandibular molar. If only 2 molars are removed, they must be ipsilateral. Subjects must satisfy all eligibility criteria including providing informed consent and willingness to remain at the clinic overnight.

The study will be conducted in 1 study site in the United States.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Study Population

The study will enrol approximately 280 male and female subjects.

4.2 Inclusion Criteria

Only subjects to whom all of the following conditions apply will be included:

1. Is male or female ≥ 18 and ≤ 50 years of age.
2. Requires extraction of 2 or more third molars. At least 1 of the third molars must be a fully or partially bone-impacted mandibular molar. If only 2 molars are removed, then they must be ipsilateral.
3. Experiences moderate to severe pain intensity within 6 hours after surgery, as measured by a numeric rating scale (NRS) score of ≥ 5 on a 0-10 scale.
4. Has a body weight ≥ 45 kg and a body mass index (BMI) ≤ 35 kg/m^2.
5. Female subjects of child-bearing potential must have been using an acceptable method of contraception for at least 30 days prior to randomization and be willing to continue use until at least 48 hours post discharge from the clinic (see Section 4.4). To be considered not of child-bearing potential, females must be surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or post-menopausal (defined as no menses for 12 months without an alternative medical cause).
6. Free of clinically significant abnormal findings as determined by medical history, physical examination, vital signs, laboratory tests and ECG.
7. Is able to provide written informed consent.
8. Is willing and able to comply with study requirements (including diet and smoking restrictions), complete the pain evaluations, remain at the study site overnight, and return for follow-up 7 (± 2) days after surgery, (Day 8 ± 2 days).

4.3 Exclusion Criteria

A subject will not be eligible for study entry if any of the following exclusion criteria are met:

1. Known hypersensitivity reactions or allergy (e.g., asthma, rhinitis, angioedema or urticaria) in response to nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen), acetylsalicylic acid (aspirin), ingredients of the study drug, or any other drugs used in the study, including anaesthetics and antibiotics that may be required on the day of surgery.
2. A history of active or previous peptic ulceration/ haemorrhage, gastrointestinal bleeding or perforation, heart failure, renal or hepatic failure, uncontrolled hypertension, asthma, nasal polyps, or chronic rhinitis.
3. Has complications from the tooth extraction or any other clinically significant medical history that, in the opinion of the investigator, would affect the subject's ability to comply or otherwise contraindicate study participation, including but not limited to the

following: cardiac, respiratory, gastroenterological, neurological, psychological, immunological, haematological, oncological, or renal disease.

4. Has undergone another dental surgery within 60 days prior to the day of surgery.
5. A positive urine drugs of abuse screen or alcohol breathalyser test at screening and during the study (with the exception of a positive drugs of abuse screen that is a consequence of permitted prescription medicines).
6. If female, has a positive pregnancy test at screening (serum) or on the day of surgery prior to surgery (urine), or is lactating.
7. Has known or suspected, (in the opinion of the investigator), history of alcoholism or drug abuse within 2 years of screening or evidence of tolerance or physical dependence before dosing with study drug.
8. Taking any concomitant medications that might confound assessments of pain relief, such as psychotropic drugs, antidepressants, sedative-hypnotics (other than those permitted for conscious sedation), or other analgesics taken within five times of their elimination half-lives. Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) are permitted if the subject has been on a stable dose for at least four weeks prior to Visit 1 (screening).
9. Is considered by the investigator, for any reason (including, but not limited to the risks described as precautions, warnings and contraindications in the current version of the investigator's brochure [IB] for 300 mg ibuprofen PR tablets), to be an unsuitable candidate to receive the study drug.
10. Has a history of chronic use (defined as daily use for > 2 weeks) of nonsteroidal anti-inflammatory (NSAIDs), opiates, or glucocorticoids (except inhaled nasal steroids and topical corticosteroids), for any condition within 6 months before dosing with study drug.
11. Has significant difficulties swallowing capsules or tablets or is unable to tolerate oral medication.
12. Subject has received an investigational product or participated in another trial involving a marketed or investigational drug in the 30 days (or for investigational agents with a long half-life, a washout of 5 half-lives) prior to first drug administration (washout period between studies is defined as the period of time elapsed between the last dose of the previous study and first dose for this study). Or if the investigator believes that any previous participation in an investigational study would be to the detriment of the safety of the participant or the conduct of the study.
13. Enrolment of the Investigator, his / her family members, employees and other dependent persons.
14. Failure to satisfy the investigator of fitness to participate for any other reason.

4.4 Subjects of Reproductive Potential

Female subjects of childbearing potential must have been using an acceptable method of contraception for at least 30 days prior to randomization and be willing to continue use until at least 48 hours post discharge from the clinic. An acceptable method of contraception includes:

a. Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action

b. Male or female condom with or without spermicide

c. Cap, diaphragm or sponge with spermicide

Alternatively, highly effective methods of contraception are also considered acceptable, such as:

d. Surgical sterilisation

e. Established use of oral, injected or implanted hormonal methods of contraception

f. Some intrauterine devices (IUDs) or intrauterine systems (IUSs)

g. Male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). [For female subjects on the study, the vasectomised male partner should be the sole partner for that subject]

h. True abstinence which is in line with the preferred and usual lifestyle of the subject. Periodic abstinence such as calendar, ovulation, symptothermal, or post-ovulation methods; declaration of abstinence for the duration of the trial; and withdrawal are not acceptable methods of contraception.

4.5 Discontinuation / Withdrawal and Replacement of Subjects

The Investigator may withdraw the subject from the study at any time. Reasons for removing a subject from the study include, but are not limited to:

- AEs that in the judgement of the Investigator may cause severe or permanent harm (significant clinical deterioration is an AE)
- Violation of the study protocol
- In the Investigator's judgement, it is in the subject's best interest
- Subject declines further study participation
- If applicable, randomisation code is broken

If subjects choose to prematurely stop the study prior to the scheduled discharge at Hour 24, safety and tolerability assessments must be performed prior to discharge, and, if possible, efficacy assessments should be performed.

If subjects choose to prematurely stop the study after clinic discharge but prior to the follow-up visit, at least 2 documented attempts should be made to contact the subjects for follow-up assessments which will include the assessments described for the follow-up visit (Section 7.4).

5 STUDY TREATMENT

5.1 Investigational Products

Active Test Product

Ibuprofen PR tablets 300 mg, single oral dose of 600 mg. A yellow to pale yellow coloured, film coated, caplet shaped tablet, debossed as 'N12' on one side and plain on the other side.

Table 5-1 Active Test Product

Name of Ingredient	Quantity/Tablet(mg)	Function	Reference
Ibuprofen	300.00	Active	Ph.Eur.
Silicon dioxide	3.00	Glidant/Anti-adherent	Ph.Eur.
Hypromellose K4M Premium	62.50	Rate Controlling Polymer	Ph.Eur.
Hypromellose K100 LV	32.50	Rate Controlling Polymer	Ph.Eur.
Silicified Microcrystalline cellulose 50	100.00	Filler/Binder	NF
Silicified Microcrystalline cellulose 90	50.00	Filler/Binder	NF
Croscarmellose sodium	17.50	Disintegrant	Ph.Eur.
Glycine	25.00	Release Modifier	Ph.Eur
Silicon dioxide	3.00	Glidant/Anti-adherent	Ph.Eur.
Stearic acid	6.00	Lubricant	Ph.Eur.
Total weight of core tablet	**599.50 mg**		
Film coating and Polishing			
Opadry Yellow 15B520019	7.50	Coating agent	In House
Purified water[#]	q.s.	Coating vehicle	Ph.Eur.
Carnauba Wax	0.025	Polishing Agent	Ph.Eur
Total weight	**607.025 mg**		

[#] Removed during the process.

Placebo for Test Product

A yellow to pale yellow coloured, film coated, caplet shaped tablet, debossed as 'N12' on one side and plain on the other side.

Table 5-2 Placebo for Test Product

Ingredient	mg/tablet	Function	Reference Standard
Core			
Hypromellose K4M Premium	125.10	Rate Controlling Polymer	Ph. Eur.
Hypromellose K100 Premium LV	65.05	Rate Controlling Polymer	Ph. Eur.
Silicified Microcrystalline Cellulose 50	200.17	Filler/ Binder	NF
Silicified Microcrystalline Cellulose 90	100.08	Filler/ Binder	NF
Croscarmellose Sodium	35.03	Disintegrant	Ph. Eur.
Glycine	50.04	Release Modifier	Ph. Eur.
Silica, Colloidal Hydrated	12.02	Glidant/ Anti-adherent	Ph. Eur.
Stearic Acid	12.01	Lubricant	Ph. Eur.
Coating and Polishing			
Opadry Yellow 15B520019	7.50	Coating Agent	In house
Carnauba Wax	0.025	Polishing Agent	Ph. Eur.
Processing agent			
Purified Water	q.s.*	Coating Vehicle	Ph. Eur.
Total	**607.025**		

* Does not remain in final product except traces. Removed during the coating process.

Comparator Product

Nurofen Ibuprofen acid tablets 200 mg, single oral dose of 400 mg. A white to off white, biconvex, round, sugar coated tablet.

Table 5-3 Comparator Product

Name of Ingredient	Unit Formula (mg/tablet)	Function	Reference to Standards
Active Ingredient			
Ibuprofen	200.0	Active ingredient	Ph.Eur.
Other Ingredients			
Croscarmellose Sodium	30.0	Disintegrating agent	Ph.Eur.
Sodium Lauryl Sulphate	0.5	Tablet lubricant	Ph.Eur.
Sodium Citrate	43.5	Bulk filler	Ph.Eur.
Stearic Acid	2.0	Tablet lubricant	Ph.Eur.
Colloidal Anhydrous Silica	1.0	Granule flow aid	Ph.Eur.
Tablet Core Weight	277.0		
Sugar Coat Ingredients			
Carmellose Sodium	0.7	Sugar coat binder	Ph.Eur.
Talc	33.0	Sugar coat bulking agent	Ph.Eur.
Acacia Spray Dried	0.6	Sugar coat binder	Ph.Eur.
Sucrose	116.1	Sugar coat	Ph.Eur.
Titanium Dioxide	1.4	Colour	Ph.Eur.
Macrogol 6000	0.2	Tablet polish	Ph.Eur.
Purified Water	ND	Sugar syrup solvent	Ph.Eur.
Coated Tablet Weight	429.0		

Placebo for Comparator Product

A white to off white, biconvex, round, sugar coated tablet.

Table 5-4 Placebo for Comparator Product

Ingredient	Quantity (%w/w)	Function	Reference Standard
Core			
Mannitol	46.81	Filler	Ph. Eur
Microcrystalline Cellulose	16.14	Filler	USP/NF
Magnesium Stearate	1.61	Lubricant	Ph. Eur.
Sugar coating			

Carmellose Sodium	0.16	Sugar coat binder	Ph. Eur
Talc	7.69	Sugar coat bulking agent	Ph. Eur
Acacia Spray Dried	0.14	Sugar coat binder	Ph. Eur
Sucrose	27.06	Sugar coat	Ph. Eur
Titanium Dioxide	0.33	Colour	Ph. Eur
Macrogol 6000	0.05	Tablet polish	Ph. Eur
Purified Water*	ND	Sugar syrup solvent	Ph. Eur

Test Product and Placebo for Test Product will be manufactured and packed (primary pack) to Good Manufacturing Practice (GMP) standards by Strides Shasun Limited, R.S No 32-34 PIMS Road, Periyakalpet, Kalapet, Pondicherry, 605014, India and shipped to Investigational Materials Supplies Unit (IMSU), RB, Dansom Lane, Hull, HU8 7DS.

Nurofen Ibuprofen acid (Comparator) and the Placebo for Comparator tablets will be manufactured to GMP standards by Reckitt Benckiser, Thane Road, Nottingham, NG90 2DB, UK. Both active and placebo tablets will be unprinted for blinding purpose.

Both the products (Comparator and Placebo) will be primary packed at Sharp Clinical Services, Elvicta Business Park, Crichowell, NP8 1DF, UK and shipped to Investigational Materials Supplies Unit (IMSU), RB, Dansom Lane, Hull, HU8 7DS.

The Test Product, Placebo for Test Product, Comparator Product and the Placebo for Comparator product will be assembled to GMP standards by the IMSU, RB, Dansom Lane, Hull HU8 7DS, and bulk certified by RB Research and Development Qualified Person. All the products will be shipped directly from IMSU to the study site.

5.2 Non-Investigational Products

In preparation for the surgery, subjects will receive local anaesthesia (2% lidocaine with 1:100,000 epinephrine). Nitrous oxide will be allowed at the discretion of the investigator.

5.3 Permitted Therapies

After randomisation and administration of study drug, paracetamol / acetaminophen (1000 mg) will be permitted as the initial rescue medication. Subjects will be encouraged to wait at least 60 minutes after receiving study drug before taking rescue medication. If acetaminophen rescue medication is not effective in relieving the subject's pain, 5 mg oxycodone rescue medication may be administered at the discretion of the investigator.

At the investigators discretion repeat doses of rescue medication may also be administered as required.

The Investigator or designees will record all medication taken by the subject at the screening visit in the subject's electronic Case Report Form (eCRF). Any medication taken by the subject

from the time of giving informed consent through to the end of the subject's participation in the study (last assessment) will be recorded on the concomitant medication page in the eCRF.

Upon discharge from the study site, subjects may be prescribed pain medication for use at home according to the standard practice of the study site.

5.4 Treatment Compliance

For the duration of each assessment the subject will remain at the study site under the supervision of the Investigator or designees. The Investigator or designees will provide supervised drug administration along with clear instructions and support to the subject to facilitate the best possible compliance with study requirements. Any non-compliance during the study will be observed and recorded by study site staff as a protocol deviation.

5.5 Packaging and Labelling and Supply / Resupply

For each subject one pack will be provided containing all required tablets for each dosing timepoint. Each tablet will be held in a blister within the pack. The pack will clearly show which tablets are to be taken at which timepoint.

All packs regardless of treatment regimen will be the same except for a kit number and will therefore not identify the treatment.

The IMP will be labelled in accordance with EudraLex Volume 4 Good Manufacturing Practice (GMP) Guidelines, Annex 13 - Manufacture of Investigational Medicinal Products, parts 26 to 33 (Labelling) and in accordance with directive 2003/94/EC as amended and including any other applicable national/state legislation. The IMP will be labelled in English

All IMP will be packed and labelled to GMP by the Investigational Material Supplies Unit (IMSU), Reckitt Benckiser Healthcare (UK) Ltd, Dansom Lane, Hull, HU8 7DS, UK. IMP will be shipped from the IMSU to the study site.

5.6 Storage Conditions

The Investigator or designated individual will keep all IMP(s) in a pharmacy or a secure storage facility, accessible only to those individuals authorised by the Investigator to dispense the medication.

The Investigator or designated individual will maintain an inventory. This will include the description and quantity of IMP(s) received during the course of this study, as well as a record of the materials that are dispensed and returned (how much, to whom and when). This inventory ("Drug Dispensing Log") will be subject to review by the study monitor during monitoring visits.

The Investigator agrees not to supply IMP(s) to any person except study personnel and patients enrolled in this study.

The IMP should be stored between 8-25 °C and is not to be refrigerated or frozen.

Temperatures must be constantly monitored and readings logged in a temperature log on working days.

The temperature in the secure storage facility will be recorded using a minimum/maximum thermometer. If the temperature falls outside the specified range of 8-25 °C, the Sponsor should be notified immediately and appropriate action should be agreed and documented. The temperature log will be reviewed by the study monitor at each monitoring visit.

5.7 Blinding

This study 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, colour and weight.

All subjects will receive 4 tablets at each dosing timepoint. At each timepoint each subject will receive 2 tablets that may be either PR or the placebo made to look like PR and 2 tablets that may be IR or the placebo made to look like IR. See Table 3-2 Treatment Regimens. This includes those in the placebo arm who will receive 2 placebo tablets designed to look like PR and 2 placebo tablets designed to look like IR at all dose timepoints.

All subject packs will be designed and labelled to ensure blinding is maintained.

Subjects, investigators and site staff will all be blind to the treatments.

Unblinding will only occur after database lock or in the case of emergency unblinding, see Section 5.8.

5.8 Emergency Unblinding Procedures

Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment.

For emergency unblinding, study personnel will use the IWRS. If treatment assignment is unblinded for an individual subject, study personnel will be notified of that subject's treatment assignment without unblinding the treatment assignments for the remaining subjects in the study. Thus, the overall study blind will not be compromised. If a subject's treatment assignment is unblinded, he/she may or may not be asked to withdraw from the study. The investigator should make this decision after consultation with the medical monitor.

5.9 Drug Accountability

The Investigator will keep all study medication (including rescue medication) in a pharmacy or a secure storage facility, accessible only to those individuals authorised by the Investigator to dispense the medication.

The Investigator or designated individual will maintain an inventory. This will include the description and quantity of study drug received during the course of the study, as well as a record of the materials that are dispensed and returned (how much, to whom and when). This inventory will be subject to review by the study monitor during monitoring visits.

The Investigator agrees not to supply study drug to any person except study personnel and subjects in this study.

5.10 Return and Destruction

The Investigator agrees to conduct a drug-supply inventory, to record the results of this inventory ("IMP Removal from Site" form) and to ensure all original IMP containers whether empty or containing IMP are sent to RB's representative at the end of the study.

RBs representative will then arrange for the appropriate and timely destruction of all containers and unused IMP upon confirmation from RB following provision of a full reconciliation by Premier (on finalisation of the study report).

6 STUDY PROCEDURES BY VARIABLE

6.1 Informed Consent

Prior to conducting any study-related activities, written informed consent must be obtained from the subject (Section 12.2).

6.2 Randomisation

Eligible subjects will be randomised in a 3:3:1 ratio to receive 2×300 mg ibuprofen PR tablets Q12h, 2x200 mg ibuprofen IR tablets Q8h, or placebo using permuted blocks of fixed size. The randomisation 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 randomisation schedule will be prepared by a statistician not otherwise involved in the study. Randomisation will be performed using an interactive web response system. 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.

6.3 Drug Administration

Subjects will be dosed under clinic supervision to ensure compliance. Prior to dosing, each subject will be instructed by the Investigator or clinic staff on how to take the medication.

6.4 Demographics

Demographic information will be recorded including gender, date of birth and race.

6.5 Medical History and Concomitant Medication

Relevant medical history, including history of current disease and information regarding underlying diseases will be recorded. The duration of surgery and all concomitant medication taken will be recorded as well as permitted therapies (see Section 5.3).

6.6 Physical Examination

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).

Height, weight, and BMI will be assessed at Screening.

6.7 Laboratory Tests

The following clinical laboratory tests will be performed at Screening.

Hematology:	hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count (or estimate), white blood cell count including differential
Serum Chemistry:	albumin, total bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, glucose, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase, uric acid, urea, inorganic phosphorous, cholesterol (total and High Density Lipoprotein (HDL)), triglycerides, gamma glutamyl transferase
Coagulation:	prothrombin time, partial thromboplastin time, fibrinogen
Urinalysis:	pH, specific gravity, blood, glucose, protein, ketones, leucocyte esterase, nitrites (in the event that the dipstick test is positive, red blood cells, white blood cells, epithelial cells, crystals, bacteria and casts will be examined microscopically)
Virology:	hepatitis B, hepatitis C, HIV

The following laboratory tests will also be performed:

- Alcohol breathalyzer test will be performed before surgery on Day 1.
- Urine drug screen samples will be collected at Screening and before surgery on Day 1 to test for amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine (PCP), and tetrahydrocannabinol (THC).

- For female subjects of childbearing potential, a blood sample for the serum pregnancy test will be collected at Screening and a urine pregnancy test sample will be collected before surgery on Day 1.

Blood and urine samples for hematology, serum chemistry, and urinalysis will be prepared using standard procedures and will be sent to a central laboratory for analyses.

6.8 Electrocardiograms

A 12-lead electrocardiogram will be performed at Screening.

6.9 Vital Signs

Vital signs will be recorded after the subject has been in a sitting position for 3 minutes. Vital sign assessments will include blood pressure, heart rate, respiratory rate, and body temperature. Clinically significant abnormalities in vital signs should be recorded as AEs.

6.10 Blood Sampling

Blood sampling will be performed according to the site's standard practices, as described in the study manual or other site documentation.

6.11 Oral Radiography

Oral radiographs (X-rays) will be taken at Screening (radiographs taken within 1 year before Screening will be acceptable and do not need to be repeated).

6.12 Pain Intensity

Subjects will rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever at the timepoints mentioned on Table 7-1.

6.13 Stopwatch Assessment

Two stopwatches will be started immediately after the subject has swallowed the study drug with 8 ounces of water. Each subject will be instructed, "Stop the first stopwatch when you first feel any pain relief whatsoever. This does not mean you feel completely better, although you might, but when you first feel any relief in the pain you have now" (perceptible pain relief). The subject will also be instructed, "Stop the second stopwatch when you feel the pain relief is meaningful to you" (meaningful pain relief). If the subject does not press the stopwatches within 8 hours after Time 0 the subject will discontinue use of the stopwatches.

6.14 Pain Relief Scale

Subjects will rate their pain relief relative to Time 0 using a 5-point categorical scale. Subjects will be asked "How much relief have you had since your starting pain?" with response choices of none = 0, a little = 1, some = 2, a lot = 3, and complete = 4. At each assessment time point, the pain intensity NRS 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.

6.15 Subject's Global Evaluation of Study Drug

For the global evaluation of study drug, the subject will be asked "How effective do you think the study drug is as a treatment for pain?" with response choices of 0 = poor, 1 = fair, 2 = good, 3 = very good, or 4 = excellent. Subjects will complete the global evaluation of study drug 24 hours after Time 0 or immediately before the first dose of rescue medication (whichever occurs first).

6.16 Adverse Events

During the study the Investigator will ask the subject: "Are you experiencing any symptoms or complaints?" at the baseline visit, and "Have you had any symptoms or complaints since the last time you were asked?" during the study. In addition, spontaneously reported AEs are collected.

The observation period for an individual subject will start after giving informed consent and will finish at the last visit (follow-up visit) for the given individual subject. All AEs that arise during the observation period will be recorded and an assessment of the AE will be performed as per Section 8.2 by a medically qualified Investigator. If a subject has an AE that is still ongoing at the last visit, an attempt will be made by the Investigator to follow this up as per Section 8.4.

If an untoward medical occurrence happens after the subject has signed the consent form but before administration of the IMP, it should be reported as an adverse event, including those associated with study procedures.

Note this does not include any pre-existing medical conditions or findings associated with medical history which are identified during the screening process.

7 STUDY PROCEDURES BY VISIT

7.1 Study Flow Chart / Table of Study Procedures and Assessments

Table 7-1 Schedule of Assessments

	Screening (Day -28 to Day -1)	Surgery (Day 1)						Day 2		Follow-up (Day 8 ±2 days) or ET[k]
			Post-surgery							
		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-surgery							
		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
Provide prescription for pain medication.									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;.

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.

i Subjects will complete a global evaluation of study drug 24 hours after Time 0 or immediately before the first dose of rescue medication (whichever occurs first).

j Adverse events will be monitored and recorded from the time of signing of the informed consent form until the Follow-up Visit (or Early Termination Visit).

k If an unscheduled visit occurs the Investigator should follow the activities detailed in Section 7.5.

7.2 Screening Visit (Day -28 to Day -1)

- Written informed consent
- Assign a screening number
- Inclusion/exclusion criteria
- Demographics
- Medical history
- Complete physical examination (excluding the genitourinary examination)
- Vital signs
- Electrocardiogram
- Height, weight, and BMI
- Clinical laboratory tests (haematology, chemistry, urinalysis)
- Serum pregnancy test for female subjects of childbearing potential
- Urine drug screen
- Oral radiography (oral radiographs taken within 1 year before Screening will be acceptable and do not need to be repeated)
- Review study restrictions with subject
- Schedule surgery

7.3 Day of Surgery (Day 1)

7.3.1 Pre-Surgery

- Inclusion/exclusion criteria review
- Medical history review
- Vital signs
- Urine pregnancy test for female subjects of childbearing potential
- Urine drug screen
- Alcohol breathalyzer test
- Concomitant medications

- Adverse events

7.3.2 Surgery

- Subjects who continue to be eligible for study participation after completing screening procedures and assessments will undergo extraction of 2 or more third molars. At least 1 of the third molars must be a fully or partially bone impacted mandibular molar. If only 2 molars are removed, then they must be ipsilateral.
- All subjects will receive local anesthesia (2% lidocaine with 1:100,000 epinephrine).
- Nitrous oxide will be allowed at the discretion of the investigator.

7.3.3 Post-surgery Eligibility Assessments and Randomisation

- Vital signs
- Concomitant medications
- Adverse events
- Pain intensity NRS
- Subjects who experience moderate to severe pain intensity (NRS score of ≥ 5) within 6 hours after surgery and who continue to meet all study entry criteria will be randomised

7.3.4 Dosing and Post-dose Assessments (Hour 0 through Hour 24)

- Subjects will re-assess their baseline pain intensity using the NRS immediately before receiving IMP (pre-dose, Time 0)
- Administer IMP at the timepoints in Table 3-2
- Subjects will assess their pain intensity (NRS) and pain relief (5 point categorical scale) at the following time points (pre-dose, if at one of the dosing timepoints of 0, 8, 12 or 16 hours): 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, if any. 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.
- Subjects will use the double stopwatch method to record the time to perceptible pain relief and time to meaningful pain relief during the 8 hours following the first dose or until subject takes rescue medication
- Subjects will complete a global evaluation of study drug 24 hours after Time 0 or immediately before the first dose of rescue medication (whichever occurs first)
- Vital signs will be recorded after the subject has been in a sitting position for 3 minutes at the following times: before surgery, within 30 minutes before Time 0, 12 and 24 hours after Time 0, and/or immediately before the first dose of rescue medication

- Concomitant medications
- Adverse events
- Subjects will remain at the study site overnight and will be discharged on Day 2.
- Upon discharge from the study site, provide prescription for pain medication.
- Schedule follow-up visit

7.4 Follow-up Visit (Day 8 ± 2 days) or Early Termination

- Abbreviated confirmatory physical assessment, including an examination of the subject's mouth and neck
- Vital signs
- Concomitant medications
- Record any post discharge adverse events

7.5 Unscheduled Visits

If unscheduled visits occur, the Investigator must record the reason for unscheduled visit, including any AEs, concomitant therapy changes, withdrawal (if deemed appropriate) and any clinical assessments deemed appropriate for the clinical care of the subject. Unscheduled visits should not alter the timing of the routine study schedule.

7.6 Study Restrictions

7.6.1 Prohibited Therapies

Subjects are not permitted to take any concomitant medications that might confound assessments of pain relief, such as psychotropic drugs, antidepressants, sedative-hypnotics (other than those permitted for conscious sedation), or other analgesics taken within five times of their elimination half-lives (other than those used at the surgery). Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) are permitted if the subject has been on a stable dose for at least four weeks prior to Visit 1 (screening).

7.6.2 General and Dietary Restrictions

Other restrictions include the following: alcohol use is prohibited from 24 hours before surgery until discharge on Day 2; nothing by mouth from midnight before surgery until 1 hour after surgery; clear liquids only are allowed starting 1 hour after surgery until 1 hour after dosing; 1 hour after dosing, the subject's diet may be advanced according to standard practice.

8 SAFETY REPORTING

8.1 Adverse Event Definitions

An Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. [ICH E6 1.2].

Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is classified as any untoward medical occurrence that:

- results in death
- is life-threatening
- requires in-patient hospitalization or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity or
- is a congenital anomaly/birth defect

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious.

[ICH E2A] Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Note: If the event is related to the investigational product and is both serious and unexpected, it is classified as a suspected unexpected serious adverse reaction (SUSAR). In case of double-blinded studies, unblinding is needed in order to determine a SUSAR.

8.2 Assessment of Adverse Events

Any untoward medical occurrences that arise after the subject has given informed consent will be recorded in the subject's source documents and electronic case report forms (eCRFs). Untoward medical occurrences can be reported spontaneously by the subject or in response to non-leading questioning or observation by the Investigator or be a significant laboratory abnormality.

Untoward medical occurrences, including all adverse events (AE) and all serious adverse events (SAEs) are collected, fully investigated and documented.

As the study will be conducted on subjects who have been through removal of impacted third molars, it is expected that they will present post-surgical symptoms, for example: swelling and bruising. For the purposes of this study, when at normal/expected magnitude, such occurrences will not be reported as AEs as they are expected and, therefore, are not “untoward” as in the AE standard definition.

SAEs should be followed until resolution or stabilisation. Participants with ongoing SAEs at study termination will be further followed up until recovery or until stabilisation of the disease after termination.

For each AE a causality assessment of the event to the study drug must be performed. The relationship to IMP must be determined by the Investigator (if medically qualified) or by a medically qualified Co-Investigator.

Table 8-1 AE Relationship Descriptions

Relationship	Description
Unassessable/ Unclassifiable	Insufficient information to be able to make an assessment
Conditional/ Unclassified	Insufficient information to make an assessment at present (causality is conditional on additional information)
Unrelated	No possibility that the AE was caused by the IMP
Unlikely	Slight, but remote, chance that the AE was caused by the IMP, but the balance of judgement is that it was most likely not due to the IMP
Possible	Reasonable suspicion that the AE was caused by the IMP
Probable	Most likely that the AE was caused by the IMP
Certain	The AE was definitely caused by the IMP

For each AE a severity description should be given.

Table 8-2 AE Severity Descriptions

Severity	Description
Mild	The AE does not limit usual activities; the subject may experience slight discomfort
Moderate	The AE results in some limitation of usual activities; the subject may experience significant discomfort
Severe	The AE results in an inability to carry out usual activities; the subject may experience intolerable discomfort or pain

Expectedness for each AE will be determined based on the information in Section 6.9 of the Investigator's Brochure.

All AEs will be coded by the Sponsor using the most up-to-date version of MedDRA.

8.3 Reporting of Adverse Events

In the event of a Serious Adverse Event (SAE), the Investigator must report the event using the SAE form to the Sponsor Global Vigilance Group (GVG), by contacting GVG by email: gvg@rb.com while copying in the contract research organisation (CRO) and Sponsor Project/Study Managers within 24 hours of knowledge of the event.

The out of hours emergency phone number is +44 (0)1482 326151. An alternative number may additionally be provided by Premier Research to give access to the study Medical Monitor our of hours.

This emergency phone number will be confirmed to the Investigator at the Study Initiation Visit.

All SAE Forms must be provided via email. Any inconsistencies in the information received from the Investigator will be clarified using the Adverse Event Data Clarification Form. The Investigator must retain a copy of all the SAE forms in the Investigator Site File.

The Investigator must inform their Institutional Review Board (IRB) of all SAEs occurring in the study within 7 days for fatal or life-threatening SAEs and 15 days for all other SAEs as per Sponsor instructions and as described in the Safety Management Plan.

The Investigator should not break the randomisation code except when it is necessary to do so in order to ensure the subject receives appropriate medical care.

SAEs and non-serious AEs will be reported to the appropriate regulatory authorities by the Sponsor in accordance with the authorities' requirements. The Sponsor is responsible for expedited reporting of all SUSARs/ SAEs to relevant authorities and IECs/IRBs as required by

regulations. If the event requires expedited reporting, a CIOMS (Council for International Organizations of Medical Sciences) form will be produced and GVG will take actions as per the study specific Safety Management Plan.

8.4 Follow-up of Adverse Events

All SAEs and all AEs that have not resolved by the end of the study will be followed up by the Investigator until resolution or until the Investigator believes there will be no further change, whichever is the earlier. This may involve the subject making additional visits to the site.

If a subject has unresolved AEs requiring follow-up, investigators must attempt to contact subjects by telephone or other means.

8.5 Overdose, Abuse, Misuse and Medication Errors

The Sponsor defines “overdose” as the administration of a quantity of an investigational IMP given per administration or cumulatively, which is above the maximum recommended dose according to the authorised product information.

The Sponsor defines “abuse” as the persistent or sporadic, intentional excessive use of an IMP, which is intended to produce harmful physical or psychological effects e.g. intentional overdose to experience psychological effects.

The Sponsor defines “misuse” as situations where the IMP is intentionally and inappropriately used not in accordance with the authorised product information.

Overdoses, abuse, misuse are reportable to the Sponsor irrespective of the presence of an associated AE / SAE. The overdose, abuse, misuse and any associated AE / SAE will be captured on an AE CRF (Case Report Form) page / SAE form.

Due to the full inpatient nature of this study, in which medication doses will be supervised by site staff, cases of overdose, abuse or misuse are not expected to occur.

Medication errors are any unintentional errors in dispensing or administration of the IMP which relates to:

- Taking / being administered an incorrect IMP
- Taking / being administered a drug by the wrong route of administration e.g. swallowing a suppository
- The accidental administration of the IMP to a person who is not a subject within the study

Medication errors are reportable to the Sponsor irrespective of the presence of an associated AE / SAE. Medication errors with or without an associated AE / SAE will be captured on the AE CRF page / SAE form.

8.6 Pregnancy

Pregnancy both in a female subject or the female partner of a male subject is considered a collectable event and will be recorded as an AE in all cases. It will be qualified as an SAE only if it fulfils SAE criteria.

Due to the full inpatient nature of this study, pregnancy cases are not expected to occur during the study.

9 STATISTICAL CONSIDERATIONS

This section presents a summary of the planned statistical analyses. A statistical analysis plan (SAP) that describes the details of the analyses to be conducted will be written prior to database lock.

Summary statistics for continuous variables will typically include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, summary statistics will typically include the number and percentage of subjects in each category. All data will be presented in listings.

Baseline values are defined as the last measurements taken before dosing with study drug.

9.1 Determination of Sample Size

The sample size determination is based on the primary efficacy variable, SPID12. According to Farrar 2001[(1)], 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 [(7)], 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 2×300-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 randomised into each of the PR and IR groups. Thus 280 subjects will be enrolled into the study.

9.2 Interim Analysis

No interim analysis is planned.

9.3 Analysis Datasets

The analysis populations include the following:

- The intent-to-treat (ITT) population will consist of all subjects who are treated with study drug and who have at least 1 pain relief assessment after Time 0. The ITT population is the primary population for the efficacy analysis.
- The per-protocol (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 utilized to evaluate the sensitivity of the primary efficacy analysis.
- The safety population will include all subjects who are treated with study drug. The safety population is the population for all safety assessments.

9.4 Subject Disposition and Characteristics

The numbers of subjects randomised, completing, and withdrawing, along with reasons for withdrawal, will be tabulated overall and by treatment group. The number of subjects in each analysis population will be reported. Demographic and baseline characteristics (including date of birth, sex, race, weight, height, BMI, medical history, and surgery duration) will be summarized for each treatment group and for the overall population using descriptive statistics. No formal statistical analyses will be performed.

9.5 Efficacy Analyses

The comparison of primary interest is between PR ibuprofen and placebo. In addition, the comparison between IR ibuprofen and placebo will be presented with p-values to demonstrate study sensitivity. Point estimates and 95% confidence intervals will be used to evaluate the clinical relevance of any differences between the PR and IR formulations. All treatment differences will be presented with 95% confidence intervals. No P value adjustment will be made for multiple endpoints or multiple comparisons. In the event of model assumptions for normality being violated, non-parametric methods will be used.

Each efficacy endpoint will be summarized descriptively by treatment group.

9.5.1 Primary Endpoint(s)

The primary endpoint, summed pain intensity difference (SPID) over 0 to 12 hours (SPID12), will be used to compare the test product (2×300 mg ibuprofen PR tablets) against the placebo product.

9.5.1.1 Primary Analysis

The primary efficacy null hypothesis is that SPID12 for placebo is equal to SPID12 for ibuprofen 2×300 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.

9.5.1.2 Secondary Analysis

The clinical relevance of the difference between placebo and PR ibuprofen over 12 hours after initial dose will be evaluated.

9.5.2 Secondary Endpoints

- The summed pain intensity difference (SPID) over 0 to 24 hours (SPID24) will be used to compare the test product (2×300 mg ibuprofen PR tablets twice daily [BID]) and comparator product (2×200 mg ibuprofen IR tablets three times a day [TID]).
- Summed pain intensity difference (SPID) over 0 to 4 hours (SPID4), over 0 to 8 hours (SPID8), and over 0 to 12 hours (SPID12) after Time 0
- 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 (a responder will be defined as a subject with ≥30% improvement in pain intensity without rescue medication during the first 8 hours)
- Numeric rating scale (NRS) pain intensity difference (PID) at each scheduled time point after Time 0
- Pain intensity score at each scheduled time point
- Pain relief score at each scheduled time point after Time 0
- Peak pain relief
- Time to onset of analgesia (measured as time to perceptible pain relief confirmed by time to meaningful pain relief) using double stopwatch
- 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

9.5.2.1 Secondary Endpoint Analyses

For continuous secondary endpoints such as pain intensity score, SPID at each scheduled time point, peak pain intensity, TOTPAR4, TOTPAR8, TOTPAR12, TOTPAR24, SPID4, SPID8, SPID24, SPRID4, SPRID8, SPRID12, and SPRID24, descriptive statistics (such as mean, standard deviation, median, minimum, and maximum) will be provided for each treatment regimen. P values from ANCOVA models comparing the placebo group with other treatment groups, including terms for treatment and a covariate for baseline pain will be provided for SPID, SPRID, and TOTPAR variables, but no formal statistical inferences will be drawn on the basis of these tests. In the event that normality assumptions are violated for a parameter, non-parametric analysis methods will be used.

For ordinal secondary endpoints, such as pain intensity difference at each scheduled time point, pain relief at each scheduled time point, peak pain relief, and global evaluation of study drug, descriptive summaries will be provided and will include the number and percentage of subjects within each category for each treatment group. Nominal P values from Fisher's exact tests (or chi-square tests, as appropriate) comparing the placebo group with other treatment groups will be provided for peak pain relief and global evaluation of study drug, but no formal statistical inferences will be drawn on the basis of these tests.

For each time-to-event endpoint, Kaplan-Meier methodology will be used to evaluate the treatment effect. Time to onset of analgesia (measured as time to perceptible pain relief confirmed by meaningful pain relief) will be based on data collected using the double stopwatch method. Time to onset of analgesia will be right-censored at 8 hours for subjects who do not experience both perceptible pain relief and meaningful pain relief during the 8-hour interval after Time 0. The summary tables will provide the number of subjects analysed, the number of subjects censored, estimates for the quartiles, and 95% confidence intervals (CIs) for the estimated median and the restricted mean estimate. P values comparing placebo to active treatment from Wilcoxon or log-rank tests (as appropriate) will also be used to examine treatment effect.

For time to onset of analgesia, the comparison of interest will be the ibuprofen 2×300 mg PR group versus the ibuprofen 2×200 mg IR group. The summary table for this comparison will provide the number of subjects analysed, the number of subjects censored, estimates for the quartiles, and 95% confidence intervals (CIs) for the estimated median and the restricted mean estimate.

For the proportion of subjects who are responders and the proportion of subjects using rescue medication, logistic regression models that adjust for baseline intensity and/or significant demographic variables, if appropriate, will be used to evaluate the treatment effect.

For the responder analysis, subjects will be censored at 8 hours and for the use of rescue medication/time to first rescue subjects will be censored at 24 hours.

9.6 Safety Analyses

9.6.1 Safety Endpoint(s)

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

9.6.1.1 Safety Endpoint Analyses

Data listings will be provided for protocol-specified safety data. The Medical Dictionary for Regulatory Activities (MedDRA) (Version 19.0 or higher) will be used to classify all AEs with respect to system organ class and preferred term. Adverse event summaries will include only TEAEs, which will be summarized for each treatment group.

For vital sign measurements, descriptive statistics will be provided at each scheduled time point for each treatment group. Changes from Baseline for vital signs will be calculated for each subject, and descriptive statistics will be provided on changes in vital signs from Baseline for each treatment group at each scheduled time point after Baseline. No formal statistical tests will be performed.

9.7 Handling of Missing Data and Drop-outs

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.

The primary analysis will use windowed worst observation carried forward (WOCF) methodology for subjects who use rescue medication. Any pain measurements taken during a period of time in which rescue medication is active (4 hours) will be replaced by the last pain measurement before the rescue medication was taken. A sensitivity analysis will also be performed, in which all pain assessments recorded after the first dose of rescue medication has been taken will be disregarded and the rules outlined above will be used for missing data.

All data for assessments other than pain assessments will be analysed as collected; missing data due to premature termination or any other reason will be left as missing. In the event of a notable difference between treatment groups in the number of subjects using rescue medication, other sensitivity analyses may be performed. These will be detailed in the Statistical Analysis Plan (SAP).

9.8 Changes to the Original Statistical Plan

If there are any deviations to the proposed statistical analysis as described in this protocol these will either be documented in the final SAP or in a protocol amendment prior to database lock with the rationale and impact of the changes addressed.

10 DATA HANDLING AND RECORD KEEPING

10.1 Case Report Forms (CRFs)

Data will be recorded in an electronic Case Report Form (eCRF). For each enrolled study subject an eCRF is maintained. The Investigator or designees is responsible for the quality of the data record in the eCRF. eCRFs must be kept current to reflect subject status at each phase during the course of study. Subjects must not be identified in the eCRF by name or initials.

In the eCRF subjects will be identified by a subject number in combination with date of birth only, i.e., not by their name or initials. eCRF entries must be completed by appropriately trained site staff only. A log of trained and authorised staff able to complete the eCRF will be kept.

10.2 Specification of Source Documents

Source data must be available at the site to document the existence of the study subjects. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject. The investigator and study monitor will identify the data that will be recorded directly on the eCRF and for this data the eCRF will be considered the source document (i.e., no prior written or electronic record of the data). The study monitor will document this at the screening and it will also be documented in the Data Management Plan.

Source documents will include notes taken at the site and will include data such as demographic data, participation in study and ICF, medical history, SAEs, AEs and concomitant medication, results of examinations and assessments.

Where source data are in the form of a computer printout (e.g. medical records, laboratory data) they will be signed and dated by the investigator or designated person, confirming that the print out is a true and faithful record of the data for that subject. These print-outs will be filed in the study files.

The Investigator agrees to provide direct access to source data for study-related monitoring, audits, IRB review, and regulatory inspection(s). Direct access to source data requires that the subject gives written, documented consent to this.

10.3 Data Management

The data management group at Premier Research will be responsible for data management and eCRF activities.

Full details regarding data management will be described within the Data Management Plan.

10.4 Reporting of Protocol Deviations

Site staff should make the study monitor aware of any deviation from the protocol as soon as possible after occurrence. Waivers for inclusion / exclusion criteria are not allowed.

10.5 Retention of Essential Documentation

The Investigator should retain all essential documents (as defined in ICH E6 or according to other national and international regulations) until at least 5 years after the completion of the study (defined as last subject last visit in the study). These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

Subject files and other source data must be kept for the maximum period of time permitted by the Clinical Unit. The Investigator must notify the Sponsor of the retention period if this is shorter than described above.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Monitoring

The Sponsor will organise regular monitoring visits to be performed at intervals agreed with the Investigator. The anticipated monitoring frequency will be stated in the Monitoring Plan. Monitoring will also involve, as appropriate, correspondence and telephone contacts.

On-site monitoring includes source data verification (SDV) which is the procedure whereby the data contained in the eCRFs are compared with the primary source data and thereby verified as accurate. It will be performed in such a way as to preserve subject confidentiality, taking into account all ethical and legislative requirements.

The Investigator, or a designated member of the Investigator's staff, must be available at some time during the monitoring visit to review the data and resolve any queries and to allow direct access to the subject's records for SDV).

SDV will include as a minimum verification for all subjects, subject identity (date of birth, sex, initials and subject number), record of entry into the study and signature of the informed consent. In addition, details of SAEs in the subject's notes will be verified. Details included in the subject's notes as a minimum:

- Study number, brief description or title of study
- Date that the subject gave written consent
- All visit dates
- All SAEs
- All concomitant medications

At a site visit the eCRFs should be complete and available in order that the accuracy of their completion may be checked. Each completed eCRF for each subject must be signed electronically by the Investigator, to verify the data and statements submitted. Similarly, all alterations on paper records must be initialled and dated by the Investigator or a designated person, explained as necessary, with the original mistake left legible.

11.2 Audits and Inspections

For the purpose of ensuring compliance with the protocol, ICH GCP and applicable regulatory requirements, clinical studies sponsored by RB may be subject to an independent audit at the study site which will be conducted by personnel from an appropriate Quality Assurance Unit.

Full consultation with the Investigator will be made prior to and during such audit, which will be conducted according to Quality Assurance Unit Standard Operating Procedures.

As soon as the Investigator is notified of a planned inspection by a Regulatory Authority, he / she must inform the Sponsor promptly and allow the Sponsor to participate in the inspection as permitted by applicable regulations and local laws.

11.3 Sponsor Policy on Fraud in Clinical Studies

In accordance with GCP, it is the Sponsor's policy to always follow-up suspected cases of fraud.

12 ETHICAL AND REGULATORY ASPECTS

12.1 Ethics Review and Regulatory Authority Approval

Written approval to conduct the study by an independent and appropriately constituted IRB must be obtained and a copy provided to the Sponsor before any protocol-related procedures that do not form part of the subject's normal clinical treatment are performed. The approval letter must contain:

- Name and address of the IRB.
- Date of meeting.
- Sufficient information to identify the version of the Protocol and subject information/informed consent.
- Sufficient information to identify the version of other documents reviewed.

The investigator must also provide the Sponsor with a list of IRB members that includes each member's name and profession.

Any amendments to the Protocol must be submitted to the IRB for approval unless where necessary to eliminate apparent immediate hazards to study subjects, and any administrative changes must be notified.

This study will be submitted to the applicable Regulatory Authorities. The study will only be undertaken when regulatory authorisation has been obtained by the Sponsor.

The Sponsor will notify the Regulatory Authority within 90 days of the end of the study (within 15 days if the study is terminated prematurely).

Premier Research will notify the IRB within 90 days of the end of the study (within 15 days if the study is terminated prematurely).

12.2 Subject Information and Consent

Informed consent should be obtained by means of a patient information sheet and ICF, prepared in accordance with ICH E6 (R2) section 4.8.10 and the applicable local regulations, written in a non-technical language. All subjects will be provided with oral and written information describing the nature and duration of the study and the procedures to be performed. The subject will be asked to sign and date an ICF prior to any study-specific procedures being performed. No subject can enter the study before his/her informed consent has been obtained. A sample subject ICF used in the study will be included in the clinical study report for this protocol.

As part of administering the informed consent document, the Investigator must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician. The subject should understand the study, patient information sheet, and ICF before signing and dating the ICF. The Investigator or person obtaining consent must also sign and date the form. Each subject will be given a copy of the signed informed consent and written information.

12.3 Early / Premature Termination of the Study

In the unlikely event that this study generates an excessive frequency of adverse events, subjects' termination or suspension may be requested by the sponsor or the IRB or the Regulatory Authority.

The sponsor retains the right to terminate the study for non-safety reasons by giving an appropriate period of notice to all involved parties as per contractual agreements.

Any decisions to terminate or suspend the study will be notified in writing to the Investigator or designees, the IRB, Regulatory Authority and the clinicaltrials.gov database.

If the study is terminated early, study subjects who have attended screening will be informed that they are no longer required and if they have any questions, they should consult the study site staff. For subjects who have completed the study they will not be informed that the clinical study has been terminated. All data collected up to the point of study termination will be used in an abbreviated Clinical Investigation Report.

13 COMPENSATION, INDEMNITY AND INSURANCE

13.1 Clinical Study Agreement

Before the study commences, a contract between the Sponsor and Premier Research, who contracts with the Investigator, will be signed in which financial aspects of the study (including financial disclosure) as well as responsibilities and obligations are described.

13.2 Compensation

The Sponsor and the CRO carry insurance to pay compensation for injury, accident, ill health and death caused by participation in this study without regard to proof of negligence in accordance with the current local regulations and requirements. Details on finance and insurance will be provided in a separate agreement between the investigator and the sponsor.

13.3 Indemnity

The Sponsor will provide appropriate indemnity for the Investigator and staff who conduct part or all of this study, upon request. The request must be received before the first subject is recruited.

13.4 Insurance

If required and in accordance with applicable regulatory and legal requirements, the Sponsor will take out appropriate insurance policies on behalf of the Investigator and staff who conduct part or all of this study and/or on behalf of the subjects participating in the study.

14 REPORTING, PUBLICATION AND PRESENTATION

A clinical study report will be prepared according to ICH E3 (Structure and Content of Clinical Study Reports) as part of the Sponsor's commitment to Good Clinical Practice. The report will be a record of the total study conduct and findings and will be subject to approval by the Investigator who will sign the final report.

The study data will be owned by the Sponsor. The Sponsor retains the right to publish the data independently of the Investigator. The Sponsor agrees that before it publishes the results, it will provide the Investigator with at least 30 days for full review prior to submission of the manuscript to the publisher. The Investigator must submit any proposed manuscript to the Sponsor for approval prior to submission for publication.

15 REFERENCES

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(2) Summary of Product Characteristics for Nurofen 200 mg tablets Reckitt Benckiser Healthcare Ltd. (PL 00063/0385). 09 November 2015.

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HEALTH · HYGIENE · HOME	**Investigational Study Protocol Amendment**
	Page 1 of 7

Document Name:	Substantial Amendment Number 1	
Version Number & Date:	Version 1.0 19-Nov-2019.	
Study Number:	5003601	
Study Title:	A Randomised, 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	
EudraCT / IND / Other Number:	IND 141948	
Protocol Version Number:	From:	2.0
	To:	3.0
Principal Investigator Name:	Todd Bertoch, M.D.	

Details of Amendment:	Updates to 1 inclusion criteria and 1 exclusion criteria and to align section 4.4 with the update to the inclusion criteria.	
Section(s) to be Changed:		
Study Synopsis and Section 4.2. Inclusion Criteria number 5. Pages 14 and 30.	From:	5) Female subjects of child-bearing potential must be willing to use a highly effective method of contraception throughout the study. A highly effective method of birth control is defined as one which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly, such as the following: a. Surgical sterilisation b. established use of oral, injected or implanted hormonal methods of contraception c. some intrauterine devices (IUDs) or intrauterine systems (IUSs) d. true sexual abstinence, when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence such as calendar, ovulation, symptothermal, or post-ovulation methods; declaration of abstinence for the duration of the trial; or withdrawal are not acceptable methods of contraception) e. vasectomised partner. To be considered not of child-bearing potential, females must be surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or post-menopausal (defined as no menses for 12 months in women not using hormonal contraception or hormone replacement therapy, confirmed by a follicle stimulating hormone [FSH] level in the postmenopausal range at Screening).
	To:	5) Female subjects of child-bearing potential must *have been using an acceptable method of contraception for at least 30 days prior to randomization and be willing to continue use until at least 48 hours post discharge from the clinic (see Section 4.4).* To be considered not of child-bearing potential, females must be surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or post-menopausal (defined as no menses for 12 months *without an alternative medical cause).*

	Reason for Change:	Due to delays in the study recruitment resulting from two temporary halts the Investigational Product (IP) is nearing its expiry date. It is felt that this change does not pose any risk to subjects or the study data whilst aiming to make recruitment easier and therefore faster subsequently allowing the study to reach Last Subject Last Visit (LSLV) prior to the expiry of the IP.
Section 4.4, original location page 32, new location page 31.	From:	Woman of childbearing potential must use a highly effective contraceptive method for the entire duration of study participation. A highly effective method of birth control is defined as one which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly, such as the following: • Surgical sterilisation • Established use of oral, injected or implanted hormonal methods of contraception • Some intrauterine devices (IUDs) or intrauterine systems (IUSs) • Male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). [For female subjects on the study, the vasectomised male partner should be the sole partner for that subject] • True abstinence which is in line with the preferred and usual lifestyle of the subject. Periodic abstinence such as calendar, ovulation, symptothermal, or post-ovulation methods; declaration of abstinence for the duration of the trial; and withdrawal are not acceptable methods of contraception.
	To:	*Female subjects* of childbearing potential must *have been using an acceptable method of contraception for at least 30 days prior to randomization and be willing to continue use until at least 48 hours post discharge from the clinic.* *An acceptable method of contraception includes:* a. *Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action* b. *Male or female condom with or*

		without spermicide c. *Cap, diaphragm or sponge with spermicide* *Alternatively, highly effective methods of contraception are also considered acceptable, such as:* *d.* Surgical sterilisation *e.* Established use of oral, injected or implanted hormonal methods of contraception *f.* Some intrauterine devices (IUDs) or intrauterine systems (IUSs) *g.* Male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). [For female subjects on the study, the vasectomised male partner should be the sole partner for that subject] *h.* True abstinence which is in line with the preferred and usual lifestyle of the subject. Periodic abstinence such as calendar, ovulation, symptothermal, or post-ovulation methods; declaration of abstinence for the duration of the trial; and withdrawal are not acceptable methods of contraception.
	Reason for Change:	To align with the changes to inclusion 5 above.
Study Synopsis and Section 4.3. Exclusion Criteria number 12. Original Locations: Pages 17 and 32, New Locations: Pages 16 and 31.	From:	12) Previously participated (randomised) in another clinical study of 300 mg ibuprofen PR tablets, or received any investigational drug, device, or therapy within 90 days before screening.
	To:	*12) Subject has received an investigational product or participated in another trial involving a marketed or investigational drug in the 30 days (or for investigational agents with a long half-life, a washout of 5 half-lives) prior to first drug administration (washout period between studies is defined as the period of time elapsed between the last dose of the previous study and first dose for this study). Or if the investigator believes that*

		any previous participation in an investigational study would be to the detriment of the safety of the participant or the conduct of the study.
	Reason for Change:	Due to delays in the study recruitment resulting from two temporary halts the Investigational Product (IP) is nearing its expiry date. This change does not pose any risk to subjects or the study data whilst aiming to make recruitment easier and therefore faster subsequently allowing the study to reach Last Subject Last Visit (LSLV) prior to the expiry of the IP.
Signature page, page 3	From:	Protocol Author
	To:	Protocol *Final* Author
	Reason for Change:	The changes in the protocol from v2.0 to v3.0 due to this Substantial Amendment have not been made by the original author. Therefore the title of the signatory has been updated. This is aligned with the signature page of this amendment.

SIGNATURE PAGE

Protocol Final Author

DocuSigned by:
Jane Thomas
Signer Name: Jane Thomas
Signing Reason: I am the author of this document
Signing Time: 19-Nov-2019 | 18:29:03 PM GMT
F09BC76EBAC349BDBA7BAD8C69B8DDD3

Mrs S. Jane Thomas Date
BSc (Hons)
Senior Clinical Study Manager
RB

Protocol Statistician
(Statistics and DM sections reviewed and approved):

DocuSigned by:
Darren Targett
Signer Name: Darren Targett
Signing Reason: I approve this document
Signing Time: 20-Nov-2019 | 08:02:29 AM GMT
AFBA8AD99F4542DDA7D194D987EF1679

Darren Targett Date
Consultant Statistician
RB Representative

Sponsor's Medical Expert
(Reviewed and approved):

DocuSigned by:
Neil Fawkes
Signer Name: Neil Fawkes
Signing Reason: I approve this document
Signing Time: 20-Nov-2019 | 10:36:59 AM GMT
FBE2F9E6498A42529274F2FA9073AD21

Dr Neil Fawkes, MBChB Date
Clinical Research Physician
RB

Senior Representative – Medical Science
(Approved to Proceed):

DocuSigned by:
Bruce Charlesworth
Signer Name: Bruce Charlesworth
Signing Reason: I approve this document
Signing Time: 25-Nov-2019 | 14:46:48 PM GMT
BD51A4AE69EE4498B7C482A182264320

Bruce Charlesworth, MBChB Date
Chief Medical Officer – Health Relief, Hygiene and Wellness
RB

INVESTIGATOR APPROVAL

I have read and understood this Clinical Study Protocol Amendment

Principal Investigator
(Reviewed and Accepted):

02 Dec 2019

Todd Bertoch, MD
Chief Scientific Officer
JBR Clinical Research

Date

RECKITT BENCKISER

STUDY TITLE

A Randomised, 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

Short Study Title

Efficacy Study of 300mg Ibuprofen Prolonged-Release Tablets for the Treatment of Pain After Surgical Removal of Impacted Third Molars

IND (Investigational New Drug) Number:	141948
RB Study Number:	5003601
CRO Study Number:	RECK.177369
Protocol Version and Date:	FINAL V2.0 / 19-Jul-2019
Previous Versions / Date(s):	None
Confidentiality Statement:	The information contained in this document is privileged and confidential. Do not copy, circulate or otherwise distribute without written authority from Reckitt Benckiser

KEY CONTACTS

Name and title	Address	Phone	e-mail
Sponsor: RB Healthcare UK	Dansom Lane, Hull, HU8 7DS United Kingdom	+44 (0)1482 326151	5003601@rb.com
Sponsor's Medical Expert: Neil Fawkes	Dansom Lane, Hull, HU8 7DS United Kingdom	+44 (0)1482 5833242	neil.fawkes@rb.com
Principal / Chief / Coordinating Investigator(s): Dr Todd Bertoch	JBR Clinical Research 650 East 4500 South Suite 100 Salt Lake City Utah, 84107 USA	+ 1 928 8307354	tbertoch@jbrutah.com
Sponsors Statistician: Darren Targett	Dansom Lane, Hull, HU8 7DS United Kingdom	N/A	darren.targett@primoriscs.co.uk
Contract Research Organisation: Premier Research	One Park Drive, Suite 150 Durham, NC 27709 USA	+ 1 919 627 9100	N/A
CRO Project Manager: Paul Brittain	One Park Drive, Suite 150 Durham, NC 27709 USA	+ 1 617 934 2233	paul.brittain@premier-research.com
Clinical Laboratory: Quest Diagnostics, Inc.	3489 W 2100 S, Suite 200, West Valley City, Utah 84119 USA	N/A	N/A

SIGNATURE PAGE

Protocol Author

DocuSigned by:
Signer Name: Donna Reed
Signing Reason: I approve this document
Signing Time: Jul 29, 2019 | 15:16 BST
EAB25C398D9E4208A54F62E0595D29FA

29-Jul-2019 | 07:16:13 AM PDT

Donna Reed, MA
Principal Medical Writer
Premier Research

Date

Protocol Statistician
(Statistics and DM sections reviewed and approved):

DocuSigned by:
Darren Targett
Signer Name: Darren Targett
Signing Reason: I approve this document
Signing Time: Jul 22, 2019 | 16:20 BST
AFBA8AD99F4542DDA7D194D987EF1679

22-Jul-2019 | 16:20:57 PM BST

Darren Targett
Consultant Statistician
RB Representative

Date

Sponsor's Medical Expert
(Reviewed and approved):

DocuSigned by:
Neil Fawkes
Signer Name: Neil Fawkes
Signing Reason: I approve this document
Signing Time: Jul 25, 2019 | 16:55 BST
FBE2F9E6498A42529274F2FA9073AD21

25-Jul-2019 | 16:55:40 PM BST

Dr. Neil Fawkes, MBChB
Clinical Research Physician
RB

Date

Sponsor's Medical Director
(Approved to Proceed):

DocuSigned by:
Robert Eichler
Signer Name: Robert Eichler
Signing Reason: I approve this document
Signing Time: Jul 22, 2019 | 16:26 BST
40BB1215263A447D822D9E4E2C48D131

22-Jul-2019 | 16:26:24 PM BST

Robert Eichler, Phd
Global Medical Affairs Head, Health
RB

Date

INVESTIGATOR STATEMENT

I have read and understood this Clinical Study Protocol and agree:

- to conduct this clinical study in accordance with the protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). Amendments to the protocol are acceptable only upon mutual agreement with the exception of urgent safety measures that need to be taken to protect study subjects from any immediate hazard to their health and safety.
- to conduct this clinical study in accordance with the principles as set out in the Declaration of Helsinki and with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.
- to conduct this study only after a favourable opinion is obtained from the Independent Review Board and Regulatory Authority
- to report all information or data in accordance with the protocol.
- to report any serious adverse events as defined in the “Safety Reporting” section of this protocol.
- to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol.

I understand:

- that information that identifies me will be used and disclosed as described in the protocol and that such information may be transferred to countries that do not have laws protecting such information.
- that since the information in the protocol and the references in the Investigator's brochure (if applicable) are confidential, its disclosure to any third parties, other than those involved in approval, supervision or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

Principal Investigator
(Reviewed and Accepted):

DocuSigned by:
Dr. Todd Bertoch
Signing Name: Dr. Todd Bertoch
Signing Reason: I have reviewed this document
Signing Time: 29-Jul-2019 | 15:35 EDT
B2AE4BF347AA4C1C95ABCA5CAF0104F2

29-Jul-2019 | 12:37:29 PDT

Todd Bertoch, MD
Chief Scientific Officer
JBR Clinical Research

Date

TABLE OF CONTENTS

List of Tables Contained in the Body of the Protocol

List of Figures Contained in the Body of the Protocol

LIST OF ABBREVIATIONS

Abbreviation	Abbreviation in Full
AE	Adverse Event
ANCOVA	Analysis of Covariance
AUC	Area Under the Plasma Concentration Curve
BID	Twice Daily
BMI	Body Mass Index
Cmax	Maximum Observed Plasma Concentration
CRF	Case Report Form
CRO	Contract Research Organisation
eCRF	Electronic Case Report Form
FDA	(US) Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GVG	Global Vigilance Group
HDL	High Density Lipoprotein
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IR	Immediate Release
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
IUS	Intrauterine System
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numeric Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
OTC	Over the Counter
PID	Pain Intensity Difference
PP	Per Protocol
PR	Prolonged Release
RB	Reckitt Benckiser
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SNRI	Serotonin and Noradrenaline Reuptake Inhibitor
SPID	Summed Pain Intensity Difference
SPRID	Summed Pain Relief and Intensity Difference

Abbreviation	Abbreviation in Full
SSRI	Selective Serotonin Reuptake Inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent Adverse Event
TID	Three Times a Day
Tmax	Time to Maximum Plasma Concentration
TOTPAR	Sum of Total Pain Relief
WOCF	Worst Observation Carried Forward

STUDY SYNOPSIS

Study Title:	A randomised, 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
RB Study Number:	5003601
Background and Rationale:	Reckitt Benckiser (RB) is co-developing a new 300 mg ibuprofen prolonged release (PR) tablet with Strides Shasun Ltd. The product has been developed to meet consumer and patient needs to have access to longer acting over-the-counter analgesics. This PR formulation will reduce fluctuations in drug plasma concentrations and allow for a lower frequency of administration which is desirable in situations where pain duration is expected to be prolonged and require multiple doses of immediate release formulations. As a result, the product would be more consumer friendly, require less dosing and improve compliance with treatment. The proposed therapeutic indications of the PR product are for the short-term symptomatic treatment of mild to moderate pain such as dysmenorrhea, rheumatic pain, muscular pain, pain of non-serious arthritic conditions and backache. The proposed posology in adults over the age of 18 is: Ibuprofen 300 mg PR tablets. Two tablets to be taken every 12 hours when required for pain relief. No more than 2 doses in 24 hours. The maximum daily dose is 1200 mg and there is no proposed indication in the paediatric population. Therefore, the purpose of the proposed study is to provide supporting pivotal efficacy evidence for registration applications in Europe, Australia and Russia. The decision to progress to an efficacy clinical trial was determined on the basis of successful outcomes of the 2 phase 1 clinical trials (BE/17/279 and BE/17/281) in terms of bioavailability (BA) versus a reference ibuprofen immediate release (IR) product and bioequivalence (BE) versus comparator 600 mg ibuprofen PR.
Objectives:	**Primary Objective:** • To evaluate the superiority of 2×300 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. **Key Secondary Objectives:** • 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 2×300 mg ibuprofen PR tablets. **Additional Secondary Objectives:** • To evaluate the total analgesic effect, peak analgesic effect, onset and duration of action and the subject's overall assessment of the study medications.
Design:	This is a single centre, randomised, double-blind, double-dummy, parallel group, multiple-dose, active and placebo-controlled efficacy study to evaluate the efficacy and safety of 2×300 mg ibuprofen PR tablets in subjects with post-surgical dental pain.
Primary Endpoint:	The Summed Pain Intensity Difference (SPID) over 0 to 12 hours (SPID12) will be used to compare the test product (2×300 mg ibuprofen PR tablets) against the placebo product.
Confirmatory Evaluation:	Clinically relevant difference between placebo and PR ibuprofen over 12 hours after initial dose (for the purposes of this study, a difference of 30 % in PID scores over 12 hours after initial dose will be considered clinically relevant).[(1)]
Secondary Endpoints:	**Key secondary efficacy endpoint:** • The summed pain intensity difference (SPID) over 0 to 24 hours (SPID24) will be used to compare the test product (2×300 mg ibuprofen PR tablets twice daily [BID]) and active comparator product (2×200 mg ibuprofen IR tablets three times a day [TID]). **Efficacy endpoints:** • Summed pain intensity difference (SPID) over 0 to 4 hours (SPID4), over 0 to 8 hours (SPID8), and over 0 to 12 hours (SPID12) after Time 0 • 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 (a responder will be defined as a subject with ≥30 % improvement in pain intensity without rescue medication during the first 8 hours) • Numeric rating scale (NRS) pain intensity difference (PID) at each scheduled time point after Time 0 • Pain intensity score at each scheduled time point • Pain relief score at each scheduled time point after Time 0 • Peak pain relief • Time to onset of analgesia (measured as time to perceptible pain relief confirmed by time to meaningful pain relief) using double stopwatch • 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 **Exploratory endpoint:** • Patient's global evaluation of study drug
Safety Endpoints:	• Incidence of treatment-emergent adverse events (TEAEs) • Incidence of clinically relevant changes in vital sign measurements
Subjects:	**Inclusion Criteria** A subject will be eligible for study entry if all the following inclusion criteria are met: 1) Is male or female ≥ 18 and ≤ 50 years of age. 2) Requires extraction of 2 or more third molars. At least 1 of the third molars must be a fully or partially bone impacted mandibular molar. If only 2 molars are removed, then they must be ipsilateral. 3) Experiences moderate to severe pain intensity within 6 hours after surgery, as measured by a numeric rating scale (NRS) score of ≥ 5 on a 0-10 scale. 4) Has a body weight ≥ 45 kg and a body mass index (BMI) ≤ 35 kg/m^2. 5) Female subjects of child-bearing potential must be willing to use a highly effective method of contraception throughout the study. A highly effective method of birth control is defined as one which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly, such as the following: a. Surgical sterilisation b. established use of oral, injected or implanted hormonal methods of contraception

	c. some intrauterine devices (IUDs) or intrauterine systems (IUSs) d. true sexual abstinence, when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence such as calendar, ovulation, symptothermal, or post-ovulation methods; declaration of abstinence for the duration of the trial; or withdrawal are not acceptable methods of contraception) e. vasectomised partner. To be considered not of child-bearing potential, females must be surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or post-menopausal (defined as no menses for 12 months in women not using hormonal contraception or hormone replacement therapy, confirmed by a follicle stimulating hormone [FSH] level in the postmenopausal range at Screening). 6) Free of clinically significant abnormal findings as determined by medical history, physical examination, vital signs, laboratory tests and ECG. 7) Is able to provide written informed consent. 8) Is willing and able to comply with study requirements (including diet and smoking restrictions), complete the pain evaluations, remain at the study site overnight, and return for follow-up 7 (± 2) days after surgery, (Day 8 ± 2 days). **Exclusion Criteria** A subject will not be eligible for study entry if any of the following exclusion criteria are met: 1) Known hypersensitivity reactions or allergy (e.g. asthma, rhinitis, angioedema or urticaria) in response to nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen), acetylsalicylic acid (aspirin), ingredients of the study drug, or any other drugs used in the study, including anaesthetics and antibiotics that may be required on the day of surgery. 2) A history of active or previous peptic ulceration/ haemorrhage, gastrointestinal bleeding or perforation, heart failure, renal or hepatic failure, uncontrolled hypertension, asthma, nasal polyps, or chronic rhinitis. 3) Has complications from the tooth extraction or any other clinically significant medical history that, in the opinion of the investigator, would affect the subject's ability to comply or otherwise contraindicate study participation, including but not limited to the following: cardiac, respiratory, gastroenterological, neurological, psychological, immunological, haematological, oncological, or renal disease.

	4) Has undergone another dental surgery within 60 days prior to the day of surgery. 5) A positive urine drugs of abuse screen or alcohol breathalyser test at screening and during the study (with the exception of a positive drugs of abuse screen that is a consequence of permitted prescription medicines). 6) If female, has a positive pregnancy test at screening (serum) or on the day of surgery prior to surgery (urine), or is lactating. 7) Has known or suspected, (in the opinion of the investigator), history of alcoholism or drug abuse within 2 years of screening or evidence of tolerance or physical dependence before dosing with study drug. 8) Taking any concomitant medications that might confound assessments of pain relief, such as psychotropic drugs, antidepressants, sedative-hypnotics (other than those permitted for conscious sedation), or other analgesics taken within five times of their elimination half-lives. Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) are permitted if the subject has been on a stable dose for at least four weeks prior to Visit 1 (screening). 9) Is considered by the investigator, for any reason (including, but not limited to the risks described as precautions, warnings and contraindications in the current version of the investigator's brochure for 300 mg ibuprofen PR tablets), to be an unsuitable candidate to receive the study drug. 10) Has a history of chronic use (defined as daily use for > 2 weeks) of nonsteroidal anti-inflammatory (NSAIDs), opiates, or glucocorticoids (except inhaled nasal steroids and topical corticosteroids), for any condition within 6 months before dosing with study drug. 11) Has significant difficulties swallowing capsules or tablets or is unable to tolerate oral medication. 12) Previously participated (randomised) in another clinical study of 300 mg ibuprofen PR tablets, or received any investigational drug, device, or therapy within 90 days before screening. 13) Enrolment of the Investigator, his / her family members, employees and other dependent persons. 14) Failure to satisfy the investigator of fitness to participate for any other reason.
Products to be Evaluated and	**Test product:** • 300 mg ibuprofen PR tablets for oral administration **Reference products:**

Treatment Regimen:	• 200 mg ibuprofen IR tablets for oral administration • Placebo (for blinding purposes, two types of placebo tablets will be made; one to look like the test product and one to look like the reference product) **Treatment regimens:** Eligible subjects meeting all study entry criteria will be randomised to receive 1 of the following treatments: • Treatment A: test product; 2×300 mg ibuprofen PR tablets, BID (total daily dose 1200 mg) • Treatment B: reference product; 2×200 mg ibuprofen IR tablets, TID (total daily dose 1200 mg) • Treatment C: matching placebo tablets
Methodology:	This is a single centre, randomised, double blind, double-dummy, parallel group-, multiple-dose, active and placebo controlled efficacy study to evaluate the efficacy and safety of ibuprofen 2×300 mg ibuprofen PR tablets in subjects with post-surgical dental pain. Eligible subjects will complete all screening procedures within 28 days before the surgery and randomisation. At Screening, subjects will provide written informed consent to participate in the study before any protocol specified procedures or assessments are completed. On Day 1, subjects who continue to be eligible for study participation after completing screening procedures and assessments will undergo extraction of 2 or more third molars. At least 1 of the third molars must be a fully or partially bone impacted mandibular molar. If only 2 molars are removed, then they must be ipsilateral. All subjects will receive local anaesthesia (2% lidocaine with 1:100,000 epinephrine). Nitrous oxide will be allowed at the discretion of the investigator. Subjects who experience moderate to severe pain intensity (a score of ≥ 5 on a numeric rating scale [NRS] from 0-10 where 0 = no pain, 10 = worst pain ever) within 6 hours after surgery and who continue to meet all study entry criteria will be randomised in a 3:3:1 ratio to receive 2×300 mg ibuprofen PR tablets every 12 hours (Q12h), 2×200 mg ibuprofen IR tablets every 8 hours (Q8h), or placebo. The randomisation 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). Subjects will re-assess their baseline pain intensity using the NRS immediately before receiving study drug (pre-dose, Time 0) and their pain intensity (NRS) and pain relief (5-point categorical scale) at the following time points (pre-dose, if at one of the dosing timepoints of 0,

	8, 12 and/or 16 hours): 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, if any. 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. The double stopwatch method will be used to record the time to perceptible pain relief and time to meaningful pain relief during the 8 hours following the first dose or until subject takes rescue medication. Subjects will complete a global evaluation of study drug 24 hours (+/- 5 minutes) after Time 0 or immediately before the first dose of rescue medication (whichever occurs first). Vital signs will be recorded after the subject has been in a sitting position for 3 minutes at the following times: before surgery, within 30 minutes before Time 0, 12 and 24 hours after Time 0, and/or immediately before the first dose of rescue medication. Adverse events (AEs) will be monitored and recorded from the time of signing of the informed consent form (ICF) until the Follow up- Visit (or Early Termination Visit). During the 24 hours following Time 0, subjects will complete efficacy and safety assessments. Subjects will remain at the study site overnight and will be discharged on Day 2. Paracetamol / acetaminophen (1000 mg) will be permitted as the initial rescue medication. Subjects will be encouraged to wait at least 60 minutes after receiving study drug before taking rescue medication. If acetaminophen rescue medication is not effective in relieving the subject's pain, 5 mg oxycodone rescue medication may be administered at the discretion of the investigator. Subjects are not permitted to take any concomitant medications that might confound assessments of pain relief, such as psychotropic drugs, antidepressants, sedative-hypnotics (other than those permitted for conscious sedation), or other analgesics taken within five times of their elimination half-lives (other than those used at the surgery). Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) are permitted if the subject has been on a stable dose for at least four weeks prior to Visit 1 (screening). Other restrictions include the following: alcohol use is prohibited from 24 hours before surgery until discharge on Day 2; nothing by mouth from midnight before surgery until 1 hour after surgery; clear liquids only are allowed starting 1 hour after surgery until 1 hour after dosing; 1 hour after dosing, the subject's diet may be advanced according to standard practice.

	Upon discharge from the study site, subjects may be prescribed pain medication for use at home according to the standard practice of the study site. On Day 8 (± 2 days), subjects will return to the study site for an abbreviated confirmatory physical assessment and AE assessments.
Statistical Evaluation:	**Analysis Populations** The analysis populations include the following: • The intent-to-treat (ITT) population will consist of all subjects who are treated with study drug and who have at least 1 pain relief assessment after Time 0. The ITT population is the primary population for the efficacy analysis. • The per protocol- (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 utilized to evaluate the sensitivity of the primary efficacy analysis. • The safety population will include all subjects who are treated with study drug. The safety population is the population for all safety assessments. **Subject Characteristics** Demographic and baseline characteristics (including date of birth, sex, race, weight, height, BMI and medical history) will be summarized for each treatment group and for the overall population using descriptive statistics. No formal statistical analyses will be performed. **Efficacy Analyses** The primary efficacy null hypothesis is that SPID12 for placebo is equal to SPID12 for ibuprofen 2×300 mg PR tablets. The primary analysis will be an ANCOVA (Analysis of Covariance) model that includes the main effect of treatment and the baseline pain score as a covariate 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. All other comparisons between the treatment regimens, including ibuprofen 2×200 mg IR tablets versus placebo, will be considered secondary. No P value adjustment will be made for multiple endpoints or multiple comparisons. Each efficacy endpoint will be summarized descriptively by treatment group. For continuous secondary endpoints such as pain intensity score, SPID at each scheduled time point, peak pain intensity, TOTPAR4, TOTPAR8, TOTPAR12, TOTPAR24, SPID4, SPID8, SPID24, SPRID4, SPRID8, SPRID12, and SPRID24, descriptive statistics

	(such as mean, standard deviation, median, minimum, and maximum) will be provided for each treatment regimen. Nominal P values from ANCOVA models comparing the placebo group with other treatment groups, including terms for treatment and baseline pain will be provided for SPID, SPRID, and TOTPAR variables, but no formal statistical inferences will be drawn on the basis of these tests. For ordinal secondary endpoints, such as pain intensity difference at each scheduled time point, pain relief at each scheduled time point, peak pain relief, response to study drug, and global evaluation of study drug, descriptive summaries will be provided and will include the number and percentage of subjects within each category for each treatment group. Nominal P values from Fisher's exact tests (or chi-square- tests, as appropriate) comparing the placebo group with other treatment groups will be provided for peak pain relief and global evaluation of study drug, but no formal statistical inferences will be drawn on the basis of these tests. For each time to- event endpoint, Kaplan Meier methodology will be used to evaluate the treatment effect. Time to onset of analgesia (measured as time to perceptible pain relief confirmed by meaningful pain relief) will be based on data collected using the double stopwatch method. Time to onset of analgesia will be -right censored- at 8 hours for subjects who do not experience both perceptible pain relief and meaningful pain relief during the 8-hour interval after Time 0. For time to onset of analgesia, the comparison of interest will be the ibuprofen 2×300 mg PR group versus the ibuprofen 2×200 mg IR group. The summary tables will provide the number of subjects analysed, the number of subjects censored, estimates for the quartiles, and 95% confidence intervals (CIs) for the estimated median and the restricted mean estimate. P values from the Wilcoxon or log rank- tests (as appropriate) will also be used to compare placebo to the active treatments. For the responder analysis and the proportion of subjects using rescue medication, logistic regression models that adjust for baseline intensity and/or significant demographic variables, if appropriate, will be used to evaluate the treatment effect. Baseline values are defined as the last measurements taken before dosing with a study drug. 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. The primary analysis will use windowed worst observation carried forward (WOCF) methodology for subjects who use rescue medication. Any pain measurements taken during a period of time in which rescue medication is active (4 hours) will be replaced by the last pain measurement before the rescue medication was taken. A sensitivity analysis will also be performed, in which all pain assessments recorded after the first dose of rescue medication has been taken will be disregarded and the rules outlined above will be used for missing data. All data for assessments other than pain assessments will be analysed as collected; missing data due to premature termination or any other reason will be left as missing. **Safety Analysis** Data listings will be provided for protocol-specified safety data. The Medical Dictionary for Regulatory Activities (MedDRA) (Version 19.0 or higher) will be used to classify all AEs with respect to system organ class and preferred term. Adverse event summaries will include only TEAEs, which will be summarized for each treatment group. For vital sign measurements, descriptive statistics will be provided at each scheduled time point for each treatment group. Changes from Baseline for vital signs will be calculated for each subject, and descriptive statistics will be provided on changes in vital signs from Baseline for each treatment group at each scheduled time point after Baseline. No formal statistical tests will be performed.

1 BACKGROUND AND RATIONALE

1.1 Background for the Study and Rationale

Reckitt Benckiser (RB) is co-developing a new 300 mg ibuprofen prolonged release (PR) tablet with Strides Shasun Ltd. The product has been developed to meet consumer and patient needs to have access to longer acting over-the-counter analgesics. This PR formulation will reduce fluctuations in drug plasma concentrations and allow for a lower frequency of administration which is desirable in situations where pain duration is expected to be prolonged and require multiple doses of immediate release formulations. As a result, the product would be more consumer friendly, require less dosing and improve compliance with treatment.

The proposed therapeutic indications of the PR product are for the short-term symptomatic treatment of mild to moderate pain such as dysmenorrhea, rheumatic pain, muscular pain, pain of non-serious arthritic conditions and backache.

The proposed posology in adults over the age of 18 is:

Ibuprofen 300 mg PR tablets. Two tablets to be taken every 12 hours when required for pain relief. No more than 2 doses in 24 hours. The maximum daily dose is 1200 mg and there is no proposed indication in the paediatric population.

Therefore, the purpose of the proposed study is to provide supporting pivotal efficacy evidence for European, Russian, and Australian applications and not to support any application in the USA. This efficacy study will provide further evidence on the safety and efficacy of the product in addition to the data obtained in two bioequivalence studies BE/17/279 and BE/17/281.

1.2 Investigational Product

Ibuprofen [2-(4-isobutylphenyl) propionic acid] is a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and anti-pyretic properties [(2)]. It was initially available in 1969 as a prescription only medicine, indicated for rheumatoid arthritis, osteoarthritis and other chronic painful conditions such as ankylosing spondylitis. Following further research and the establishment of a reassuring safety profile, it was launched in 1983 as an over-the-counter (OTC) medication, marketed as Nurofen®.

Absorption of ibuprofen after oral administration is fairly rapid with peak serum concentrations occurring within 1 to 2 hours after administration. Ibuprofen is extensively bound to plasma proteins (99%) when administered at therapeutic levels and has a plasma half-life of about 2 hours. Excretion by the kidney is both rapid and complete, but only a small proportion of drug is excreted unchanged in urine, the majority being extensively metabolised in the liver to 2 major inactive metabolites. The pharmacokinetics of ibuprofen has been extensively reviewed by Davies [(3)].

1.3 Treatment Rationale

The treatment of the test product is in line with the proposed posology of the final product and the treatment of the active comparator is in line with the posology provided in the label of the product. The treatments will be administered orally, as this is the standard route of administration for these products.

The following are the treatment regimens of each product in the study:

- Treatment A: test product, 2x300 mg PR ibuprofen tablet, twice daily [total daily dose 1200 mg]
- Treatment B: reference product, 2x200 mg IR ibuprofen tablet, three times a day [total daily dose 1200 mg]
- Treatment C: matching placebo tablets for both the test and reference regimens

The active comparator (Treatment B) currently marketed in a number of geographies including a number of different European countries. It has therefore been chosen to fulfil requirements that when it is included in a marketing authorisation dossier as a comparator that it is licenced within the EU.

1.4 Study Population and Indication

The following study population will be invited to participate in this clinical trial:

Adult participants aged 18 to 50 requiring extraction of 2 or more third molars, at least 1 of which must be a fully or partially bone-impacted mandibular molar, (if only 2 molars are removed, then they must be ipsilateral), and who experience moderate to severe pain following surgery.

Such population is expected to present pain levels that will allow for assessing the magnitude of treatment effect in a low variability setting.

1.5 Non-Clinical Evidence

No non-clinical evidence is available for the PR tablet.

1.6 Clinical Evidence to Date

A total of 5 single and multiple-dose pharmacokinetic studies (139-15, BE-16-081, BE-16-295, BE-17-279, BE-17-281) have been performed with the test product. These studies demonstrated the oral bioavailability (BA) of the ibuprofen PR tablets (dosed at 2x300 mg) is comparable to Brufen® (Ibuprofen) IR Tablets (dosed at 3x200 mg) after a single dose and at steady state conditions. In terms of the release profile and absorption, C_{max} tends to be slightly higher in the IR formulation when compared with the PR formulation [21.96 ±3.87 µg/mL vs 14.51 ±3.1 µg/mL]. However the C_{max}, (Maximum Observed Plasma Concentration), T_{max}, (Time to Maximum Plasma Concentration) and $AUC_{0\text{-}Tmax}$ (Area Under the Plasma Concentration Curve) of the PR formulation suggest that's the onset of action should not be any slower than the IR reference when considering the minimum effective concentration of ibuprofen [(4)]. In terms of total exposure ($AUC_{0\text{-}\infty}$) the concentration profile is bioequivalent between the PR test product and the IR reference product [163.41 ±43.0 µg.h/mL vs 168.59 ±37.7 µg.h/mL]. A food effect is demonstrated when the test product is taken in the fed state, with an expected increase in the absorption rate.

In the 5 PK studies performed (over 200 subjects) only a limited number of mild, transient adverse events were reported.

Summary Outcomes:

- The Clinical data available for this reformulation (Ibuprofen 300 mg PR) suggests an adequate pharmacokinetic profile to achieve a sufficient therapeutic effect in the proposed study
- There are no safety concerns with the test product
- Ibuprofen 300 mg PR had an increased rate of absorption when administered with food.
- Ibuprofen 300 mg PR tablets had a comparable concentration profile to the comparator IR product and was bioequivalent based on $AUC_{0\text{-}\infty}$

1.7 Risks / Benefits

This study has been designed to confirm the therapeutic efficacy of ibuprofen 300 mg PR. Participants in this study are subjects aged 18-50 who require the extraction of 2 or more third molars, at least 1 of which must be a fully or partially bone impacted mandibular molar. Subjects will undergo dental surgery that is equivalent to that of the standard-of-care that would be expected for the above condition. They should be otherwise healthy and each subject will undergo a full health check as part of the enrolment into the study to confirm that they are healthy as defined in this protocol (see Section 4).

Participants randomised into the placebo arm would not be expected to derive any therapeutic benefit from the administration of the placebo tablets. The placebo arm is essential to the study

design as it ensures that any conclusion of non-inferiority from the trial is a reflection of the true properties of the treatments; that is, it demonstrates the assay sensitivity of the study. However, this obviously leaves the participants without adequate analgesia in the post-surgery procedure and from an ethical perspective this is mitigated in the study design by the use of rescue medication that would be in line with standards of treatment. Although it is hypothesised that the investigational medicinal product (IMP) will provide adequate analgesia in the study, this cannot be guaranteed, and therefore the use of rescue medication also addresses the potential of reduced or lack of efficacy.

Ibuprofen is an established pharmaceutical ingredient and the adverse reactions associated with administration of 1200 mg/24 hour (OTC doses) are well known and documented [(2)(5)]. The adverse reactions most frequently occurring with a single dose being nausea, gastrointestinal upset, vomiting, diarrhoea, light headedness, dizziness and headache. Rarely, more serious reactions have been reported including GI bleeding, ulceration and perforations, hypertension and renal failure. When OTC doses of ibuprofen (200-400 mg/dose; 1200 mg/day) are taken for acute episodes of pain there is an extremely low risk of causing serious gastrointestinal events [(5)].

The specific 200mg Ibuprofen tablet to be used in this study as the active comparator (Treatment B) is marketed in the EU under the Nurofen brand and has an excellent safety profile.

It is not anticipated that the safety profile of ibuprofen will be altered after administration of multiple single doses of ibuprofen 300 mg PR in the context of this study. There are not expected to be any drug-drug interactions with the non-investigational medicinal products included within the study design. A washout period of at least 6 days is deemed to be sufficient prior to the Follow-up/Early Termination Visit to ensure adequate safety monitoring of the IMP.

The investigation site will have adequate set up, experience and safety measures that would be expected of a centre able to perform regular molar extractions. They will also have adequate experience in the safety monitoring of participants post dose that would be expected in a clinical trial setting. Therefore, it is considered that the risk related to study procedures are low and limited to common adverse events (AEs) related to the dental procedure, administration of routine anaesthetics, and discomfort from vital sign measurements. Any subject that experiences immediate complications during the surgery will be excluded from the study.

Therefore, the overall benefit-risk profile for the use of the investigational product as defined in this protocol is considered favourable.

1.8 Ethical Conduct of the Study

This study will be conducted in accordance with this protocol and the principles set out in the Declaration of Helsinki. It will comply with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

2 STUDY OBJECTIVES

Primary Objective:

- To evaluate the superiority of 2×300 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.

Key Secondary Objectives:

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

Additional Secondary Objectives:

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

3 STUDY DESIGN AND RATIONALE FOR DESIGN

This is a single centre randomised, double-blind, double dummy, parallel group, multiple-dose, active and placebo-controlled efficacy study to evaluate the efficacy and safety of 2×300 mg ibuprofen PR tablets in subjects with post-surgical dental pain.

The dental pain model used in this study is a robust and well established post-surgical pain model that produces pain that is predictable in its character, duration, and intensity[(6)]. The model is widely accepted and has a proven record of assay sensitivity (i.e. separating active drugs from each other, as well as from placebo). The model is frequently used to evaluate NSAID type analgesics. Results from dental pain studies are accepted by the US Food and Drug Administration (FDA) and European authorities and have been widely extrapolated to other general pain conditions.

The decision to conduct the study in the United States was taken as suitably qualified and experienced test sites could not be found in Europe. The specific test site has been chosen to conduct the study as they have a proven history of quality and safety when conducting studies of this type.

The placebo products have two purposes:

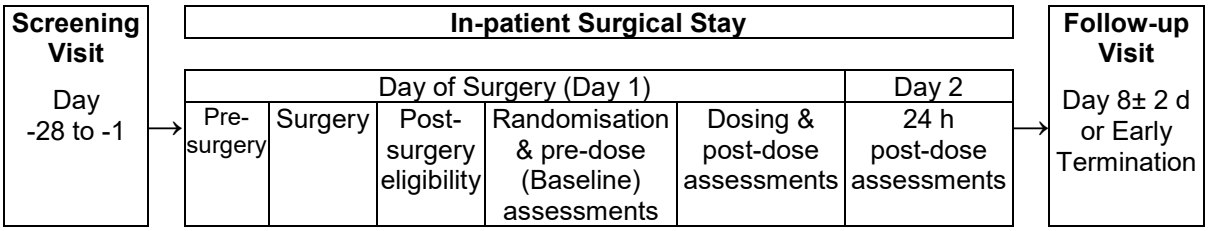
1. To mask the treatment identify for PR and IR arms
2. Act as a control arm

The dose of the test product is the proposed posology of the final product and the dose of the active comparator is the posology provided in the label of the product.

Eligible subjects will be randomised in a 3:3:1 ratio to receive 2×300 mg ibuprofen PR tablets Q12h, 2×200 mg ibuprofen IR tablets Q8h, or placebo. The randomisation 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 randomisation schedule will be prepared by a statistician not otherwise involved in the study. Randomisation will be performed using an interactive web response system (IWRS). 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.

Figure 3.1 Study Design Schematic



Note: Un-scheduled visits may occur at any point throughout the study

Table 3-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary Objective: To evaluate the superiority of 2×300 mg ibuprofen PR tablets compared with placebo in subjects experiencing acute dental pain after third molar extraction over 12 hours post initial dose.	**Primary Endpoint:** The primary efficacy endpoint is the summed pain intensity difference (SPID) over the 0 to 12 hours (SPID12) after Time 0 and will be used to compare the test product (2x300 mg PR ibuprofen) and the placebo product. The clinical relevance of the difference between placebo and PR ibuprofen over 12 hours after initial dose will be evaluated as confirmatory evidence (for the purposes of this study, a difference of 30% in PID scores over 12 hours after initial dose will be considered clinically relevant).
Secondary Efficacy Objectives: • To evaluate the analgesic performance of a total daily dose of 1200 mg of ibuprofen PR formulation compared to ibuprofen IR formulation over 24 hours post initial dose. • To evaluate the total analgesic effect, peak analgesic effect, onset and duration	**Key Secondary Efficacy Endpoints:** • The summed pain intensity difference (SPID) over 0 to 24 hours (SPID24) will be used to compare the test product (2×300 mg ibuprofen PR tablets twice daily [BID]) and comparator product (2×200 mg ibuprofen IR tablets three times a day [TID]).

of action and the subject's overall assessment of the study medications.	**Efficacy Endpoints:** • Summed pain intensity difference (SPID) over 0 to 4 hours (SPID4), over 0 to 8 hours (SPID8), over 0 to 12 hours (SPID12), and over 0 to 24 hours (SPID24) after Time 0 • 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 (a responder will be defined as a subject with ≥30% improvement in pain intensity without rescue medication during the first 8 hours) • NRS pain intensity difference (PID) at each scheduled time point after Time 0 • Pain intensity score at each scheduled time point • Pain relief score at each scheduled time point after Time 0 • Peak pain relief • Time to onset of analgesia (measured as time to perceptible pain relief confirmed by time to meaningful pain relief) using double stopwatch • 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

	Exploratory Endpoint: • Patient's global evaluation of study drug
Safety Objective: To evaluate the safety and tolerability of 2×300 mg ibuprofen PR tablets.	**Safety Endpoints:** • Incidence of treatment-emergent adverse events (TEAEs) • Incidence of clinically relevant changes in vital sign measurements

Subjects in the PR group will take 2×300 mg ibuprofen PR tablets at Hours 0 and 12. Subjects in the IR group will take 2×200 mg ibuprofen IR tablets at Hours 0, 8, and 16. To maintain double-blinding, at each dosing timepoint (Hours 0, 8, 12, and 16) all subjects will take a total of 4 tablets (placebo-only or active plus placebo, depending on randomised treatment group).

Table 3-2 Treatment Regimens

	PR Group	IR Group	Placebo Group
Hour 0	2 PR, 2 placebo for IR	2 placebo for PR, 2 IR	2 placebo for PR, 2 placebo for IR
Hour 8	2 placebo for PR, 2 placebo for IR	2 placebo for PR, 2 IR	2 placebo for PR, 2 placebo for IR
Hour 12	2 PR, 2 placebo for IR	2 placebo for PR, 2 placebo for IR	2 placebo for PR, 2 placebo for IR
Hour 16	2 placebo for PR, 2 placebo for IR	2 placebo for PR, 2 IR	2 placebo for PR, 2 placebo for IR
Hour 24	final assessments	final assessments	final assessments

The study will enrol approximately 280 male and female subjects 18-50 years of age who experience moderate to severe pain intensity within 6 hours after dental surgery to remove 2 or more third molars. At least 1 of the third molars must be a fully or partially bone impacted mandibular molar. If only 2 molars are removed, they must be ipsilateral. Subjects must satisfy all eligibility criteria including providing informed consent and willingness to remain at the clinic overnight.

The study will be conducted in 1 study site in the United States.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Study Population

The study will enrol approximately 280 male and female subjects.

4.2 Inclusion Criteria

Only subjects to whom all of the following conditions apply will be included:

1. Is male or female ≥ 18 and ≤ 50 years of age.
2. Requires extraction of 2 or more third molars. At least 1 of the third molars must be a fully or partially bone-impacted mandibular molar. If only 2 molars are removed, then they must be ipsilateral.
3. Experiences moderate to severe pain intensity within 6 hours after surgery, as measured by a numeric rating scale (NRS) score of ≥ 5 on a 0-10 scale.
4. Has a body weight ≥ 45 kg and a body mass index (BMI) ≤ 35 kg/m^2.
5. Female subjects of child-bearing potential must be willing to use a highly effective method of contraception throughout the study. A highly effective method of birth control is defined as one which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly, such as the following:
    a. surgical sterilisation
    b. contraceptive implants or injectables
    c. combined oral contraceptives
    d. some IUDs (intrauterine devices)
    e. true sexual abstinence, when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence such as calendar, ovulation, symptothermal, or post-ovulation methods; declaration of abstinence for the duration of the trial; or withdrawal are not acceptable methods of contraception), or
    f. vasectomised partner.

    To be considered not of child-bearing potential, females must be surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or post-menopausal (defined as no menses for 12 months in women not using hormonal contraception or hormone replacement therapy, confirmed by a follicle stimulating hormone [FSH] level in the postmenopausal range at Screening).
6. Free of clinically significant abnormal findings as determined by medical history, physical examination, vital signs, laboratory tests and ECG.
7. Is able to provide written informed consent.
8. Is willing and able to comply with study requirements (including diet and smoking restrictions), complete the pain evaluations, remain at the study site overnight, and return for follow-up 7 (± 2) days after surgery, (Day 8 ± 2 days).

4.3 Exclusion Criteria

A subject will not be eligible for study entry if any of the following exclusion criteria are met:

1. Known hypersensitivity reactions or allergy (e.g., asthma, rhinitis, angioedema or urticaria) in response to nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen), acetylsalicylic acid (aspirin), ingredients of the study drug, or any other drugs used in the study, including anaesthetics and antibiotics that may be required on the day of surgery.
2. A history of active or previous peptic ulceration/ haemorrhage, gastrointestinal bleeding or perforation, heart failure, renal or hepatic failure, uncontrolled hypertension, asthma, nasal polyps, or chronic rhinitis.
3. Has complications from the tooth extraction or any other clinically significant medical history that, in the opinion of the investigator, would affect the subject's ability to comply or otherwise contraindicate study participation, including but not limited to the following: cardiac, respiratory, gastroenterological, neurological, psychological, immunological, haematological, oncological, or renal disease.
4. Has undergone another dental surgery within 60 days prior to the day of surgery.
5. A positive urine drugs of abuse screen or alcohol breathalyser test at screening and during the study (with the exception of a positive drugs of abuse screen that is a consequence of permitted prescription medicines).
6. If female, has a positive pregnancy test at screening (serum) or on the day of surgery prior to surgery (urine), or is lactating.
7. Has known or suspected, (in the opinion of the investigator), history of alcoholism or drug abuse within 2 years of screening or evidence of tolerance or physical dependence before dosing with study drug.
8. Taking any concomitant medications that might confound assessments of pain relief, such as psychotropic drugs, antidepressants, sedative-hypnotics (other than those permitted for conscious sedation), or other analgesics taken within five times of their elimination half-lives. Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) are permitted if the subject has been on a stable dose for at least four weeks prior to Visit 1 (screening).
9. Is considered by the investigator, for any reason (including, but not limited to the risks described as precautions, warnings and contraindications in the current version of the investigator's brochure [IB] for 300 mg ibuprofen PR tablets), to be an unsuitable candidate to receive the study drug.
10. Has a history of chronic use (defined as daily use for > 2 weeks) of nonsteroidal anti-inflammatory (NSAIDs), opiates, or glucocorticoids (except inhaled nasal steroids and topical corticosteroids), for any condition within 6 months before dosing with study drug.
11. Has significant difficulties swallowing capsules or tablets or is unable to tolerate oral medication.

12. Previously participated (randomised) in another clinical study of 300 mg ibuprofen PR tablets, or received any investigational drug, device, or therapy within 90 days before screening.
13. Enrolment of the Investigator, his / her family members, employees and other dependent persons.
14. Failure to satisfy the investigator of fitness to participate for any other reason.

4.4 Subjects of Reproductive Potential

Woman of childbearing potential must use a highly effective contraceptive method for the entire duration of study participation.

A highly effective method of birth control is defined as one which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly, such as the following:

- Surgical sterilisation
- Established use of oral, injected or implanted hormonal methods of contraception
- Some intrauterine devices (IUDs) or intrauterine systems (IUSs)
- Male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). [For female subjects on the study, the vasectomised male partner should be the sole partner for that subject]
- True abstinence which is in line with the preferred and usual lifestyle of the subject. Periodic abstinence such as calendar, ovulation, symptothermal, or post-ovulation methods; declaration of abstinence for the duration of the trial; and withdrawal are not acceptable methods of contraception.

4.5 Discontinuation / Withdrawal and Replacement of Subjects

The Investigator may withdraw the subject from the study at any time. Reasons for removing a subject from the study include, but are not limited to:

- AEs that in the judgement of the Investigator may cause severe or permanent harm (significant clinical deterioration is an AE)
- Violation of the study protocol
- In the Investigator's judgement, it is in the subject's best interest
- Subject declines further study participation
- If applicable, randomisation code is broken

If subjects choose to prematurely stop the study prior to the scheduled discharge at Hour 24, safety and tolerability assessments must be performed prior to discharge, and, if possible, efficacy assessments should be performed.

If subjects choose to prematurely stop the study after clinic discharge but prior to the follow-up visit, at least 2 documented attempts should be made to contact the subjects for follow-up assessments which will include the assessments described for the follow-up visit (Section 7.4).

5 STUDY TREATMENT

5.1 Investigational Products

Active Test Product

Ibuprofen PR tablets 300 mg, single oral dose of 600 mg. A yellow to pale yellow coloured, film coated, caplet shaped tablet, debossed as 'N12' on one side and plain on the other side.

Table 5-1 Active Test Product

Name of Ingredient	Quantity/Tablet(mg)	Function	Reference
Ibuprofen	300.00	Active	Ph.Eur.
Silicon dioxide	3.00	Glidant/Anti-adherent	Ph.Eur.
Hypromellose K4M Premium	62.50	Rate Controlling Polymer	Ph.Eur.
Hypromellose K100 LV	32.50	Rate Controlling Polymer	Ph.Eur.
Silicified Microcrystalline cellulose 50	100.00	Filler/Binder	NF
Silicified Microcrystalline cellulose 90	50.00	Filler/Binder	NF
Croscarmellose sodium	17.50	Disintegrant	Ph.Eur.
Glycine	25.00	Release Modifier	Ph.Eur
Silicon dioxide	3.00	Glidant/Anti-adherent	Ph.Eur.
Stearic acid	6.00	Lubricant	Ph.Eur.
Total weight of core tablet	**599.50 mg**		
Film coating and Polishing			
Opadry Yellow 15B520019	7.50	Coating agent	In House
Purified water[#]	q.s.	Coating vehicle	Ph.Eur.
Carnauba Wax	0.025	Polishing Agent	Ph.Eur
Total weight	**607.025 mg**		

[#] Removed during the process.

Placebo for Test Product

A yellow to pale yellow coloured, film coated, caplet shaped tablet, debossed as 'N12' on one side and plain on the other side.

Table 5-2 Placebo for Test Product

Ingredient	mg/tablet	Function	Reference Standard
Core			
Hypromellose K4M Premium	125.10	Rate Controlling Polymer	Ph. Eur.
Hypromellose K100 Premium LV	65.05	Rate Controlling Polymer	Ph. Eur.
Silicified Microcrystalline Cellulose 50	200.17	Filler/ Binder	NF
Silicified Microcrystalline Cellulose 90	100.08	Filler/ Binder	NF
Croscarmellose Sodium	35.03	Disintegrant	Ph. Eur.
Glycine	50.04	Release Modifier	Ph. Eur.
Silica, Colloidal Hydrated	12.02	Glidant/ Anti-adherent	Ph. Eur.
Stearic Acid	12.01	Lubricant	Ph. Eur.
Coating and Polishing			
Opadry Yellow 15B520019	7.50	Coating Agent	In house
Carnauba Wax	0.025	Polishing Agent	Ph. Eur.
Processing agent			
Purified Water	q.s.*	Coating Vehicle	Ph. Eur.
Total	**607.025**		

* Does not remain in final product except traces. Removed during the coating process.

Comparator Product

Nurofen Ibuprofen acid tablets 200 mg, single oral dose of 400 mg. A white to off white, biconvex, round, sugar coated tablet.

Table 5-3 Comparator Product

Name of Ingredient	Unit Formula (mg/tablet)	Function	Reference to Standards
Active Ingredient			
Ibuprofen	200.0	Active ingredient	Ph.Eur.
Other Ingredients			
Croscarmellose Sodium	30.0	Disintegrating agent	Ph.Eur.
Sodium Lauryl Sulphate	0.5	Tablet lubricant	Ph.Eur.
Sodium Citrate	43.5	Bulk filler	Ph.Eur.
Stearic Acid	2.0	Tablet lubricant	Ph.Eur.
Colloidal Anhydrous Silica	1.0	Granule flow aid	Ph.Eur.
Tablet Core Weight	277.0		
Sugar Coat Ingredients			
Carmellose Sodium	0.7	Sugar coat binder	Ph.Eur.
Talc	33.0	Sugar coat bulking agent	Ph.Eur.
Acacia Spray Dried	0.6	Sugar coat binder	Ph.Eur.
Sucrose	116.1	Sugar coat	Ph.Eur.
Titanium Dioxide	1.4	Colour	Ph.Eur.
Macrogol 6000	0.2	Tablet polish	Ph.Eur.
Purified Water	ND	Sugar syrup solvent	Ph.Eur.
Coated Tablet Weight	429.0		

Placebo for Comparator Product

A white to off white, biconvex, round, sugar coated tablet.

Table 5-4 Placebo for Comparator Product

Ingredient	Quantity (%w/w)	Function	Reference Standard
Core			
Mannitol	46.81	Filler	Ph. Eur
Microcrystalline Cellulose	16.14	Filler	USP/NF
Magnesium Stearate	1.61	Lubricant	Ph. Eur.
Sugar coating			

Carmellose Sodium	0.16	Sugar coat binder	Ph. Eur
Talc	7.69	Sugar coat bulking agent	Ph. Eur
Acacia Spray Dried	0.14	Sugar coat binder	Ph. Eur
Sucrose	27.06	Sugar coat	Ph. Eur
Titanium Dioxide	0.33	Colour	Ph. Eur
Macrogol 6000	0.05	Tablet polish	Ph. Eur
Purified Water*	ND	Sugar syrup solvent	Ph. Eur

Test Product and Placebo for Test Product will be manufactured and packed (primary pack) to Good Manufacturing Practice (GMP) standards by Strides Shasun Limited, R.S No 32-34 PIMS Road, Periyakalpet, Kalapet, Pondicherry, 605014, India and shipped to Investigational Materials Supplies Unit (IMSU), RB, Dansom Lane, Hull, HU8 7DS.

Nurofen Ibuprofen acid (Comparator) and the Placebo for Comparator tablets will be manufactured to GMP standards by Reckitt Benckiser, Thane Road, Nottingham, NG90 2DB, UK. Both active and placebo tablets will be unprinted for blinding purpose.

Both the products (Comparator and Placebo) will be primary packed at Sharp Clinical Services, Elvicta Business Park, Crichowell, NP8 1DF, UK and shipped to Investigational Materials Supplies Unit (IMSU), RB, Dansom Lane, Hull, HU8 7DS.

The Test Product, Placebo for Test Product, Comparator Product and the Placebo for Comparator product will be assembled to GMP standards by the IMSU, RB, Dansom Lane, Hull HU8 7DS, and bulk certified by RB Research and Development Qualified Person. All the products will be shipped directly from IMSU to the study site.

5.2 Non-Investigational Products

In preparation for the surgery, subjects will receive local anaesthesia (2% lidocaine with 1:100,000 epinephrine). Nitrous oxide will be allowed at the discretion of the investigator.

5.3 Permitted Therapies

After randomisation and administration of study drug, paracetamol / acetaminophen (1000 mg) will be permitted as the initial rescue medication. Subjects will be encouraged to wait at least 60 minutes after receiving study drug before taking rescue medication. If acetaminophen rescue medication is not effective in relieving the subject's pain, 5 mg oxycodone rescue medication may be administered at the discretion of the investigator.

At the investigators discretion repeat doses of rescue medication may also be administered as required.

The Investigator or designees will record all medication taken by the subject at the screening visit in the subject's electronic Case Report Form (eCRF). Any medication taken by the subject

from the time of giving informed consent through to the end of the subject's participation in the study (last assessment) will be recorded on the concomitant medication page in the eCRF.

Upon discharge from the study site, subjects may be prescribed pain medication for use at home according to the standard practice of the study site.

5.4 Treatment Compliance

For the duration of each assessment the subject will remain at the study site under the supervision of the Investigator or designees. The Investigator or designees will provide supervised drug administration along with clear instructions and support to the subject to facilitate the best possible compliance with study requirements. Any non-compliance during the study will be observed and recorded by study site staff as a protocol deviation.

5.5 Packaging and Labelling and Supply / Resupply

For each subject one pack will be provided containing all required tablets for each dosing timepoint. Each tablet will be held in a blister within the pack. The pack will clearly show which tablets are to be taken at which timepoint.

All packs regardless of treatment regimen will be the same except for a kit number and will therefore not identify the treatment.

The IMP will be labelled in accordance with EudraLex Volume 4 Good Manufacturing Practice (GMP) Guidelines, Annex 13 - Manufacture of Investigational Medicinal Products, parts 26 to 33 (Labelling) and in accordance with directive 2003/94/EC as amended and including any other applicable national/state legislation. The IMP will be labelled in English

All IMP will be packed and labelled to GMP by the Investigational Material Supplies Unit (IMSU), Reckitt Benckiser Healthcare (UK) Ltd, Dansom Lane, Hull, HU8 7DS, UK. IMP will be shipped from the IMSU to the study site.

5.6 Storage Conditions

The Investigator or designated individual will keep all IMP(s) in a pharmacy or a secure storage facility, accessible only to those individuals authorised by the Investigator to dispense the medication.

The Investigator or designated individual will maintain an inventory. This will include the description and quantity of IMP(s) received during the course of this study, as well as a record of the materials that are dispensed and returned (how much, to whom and when). This inventory ("Drug Dispensing Log") will be subject to review by the study monitor during monitoring visits.

The Investigator agrees not to supply IMP(s) to any person except study personnel and patients enrolled in this study.

The IMP should be stored between 8-25 °C and is not to be refrigerated or frozen.

Temperatures must be constantly monitored and readings logged in a temperature log on working days.

The temperature in the secure storage facility will be recorded using a minimum/maximum thermometer. If the temperature falls outside the specified range of 8-25 °C, the Sponsor should be notified immediately and appropriate action should be agreed and documented. The temperature log will be reviewed by the study monitor at each monitoring visit.

5.7 Blinding

This study 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, colour and weight.

All subjects will receive 4 tablets at each dosing timepoint. At each timepoint each subject will receive 2 tablets that may be either PR or the placebo made to look like PR and 2 tablets that may be IR or the placebo made to look like IR. See Table 3-2 Treatment Regimens. This includes those in the placebo arm who will receive 2 placebo tablets designed to look like PR and 2 placebo tablets designed to look like IR at all dose timepoints.

All subject packs will be designed and labelled to ensure blinding is maintained.

Subjects, investigators and site staff will all be blind to the treatments.

Unblinding will only occur after database lock or in the case of emergency unblinding, see Section 5.8.

5.8 Emergency Unblinding Procedures

Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment.

For emergency unblinding, study personnel will use the IWRS. If treatment assignment is unblinded for an individual subject, study personnel will be notified of that subject's treatment assignment without unblinding the treatment assignments for the remaining subjects in the study. Thus, the overall study blind will not be compromised. If a subject's treatment assignment is unblinded, he/she may or may not be asked to withdraw from the study. The investigator should make this decision after consultation with the medical monitor.

5.9 Drug Accountability

The Investigator will keep all study medication (including rescue medication) in a pharmacy or a secure storage facility, accessible only to those individuals authorised by the Investigator to dispense the medication.

The Investigator or designated individual will maintain an inventory. This will include the description and quantity of study drug received during the course of the study, as well as a record of the materials that are dispensed and returned (how much, to whom and when). This inventory will be subject to review by the study monitor during monitoring visits.

The Investigator agrees not to supply study drug to any person except study personnel and subjects in this study.

5.10 Return and Destruction

The Investigator agrees to conduct a drug-supply inventory, to record the results of this inventory ("IMP Removal from Site" form) and to ensure all original IMP containers whether empty or containing IMP are sent to RB's representative at the end of the study.

RBs representative will then arrange for the appropriate and timely destruction of all containers and unused IMP upon confirmation from RB following provision of a full reconciliation by Premier (on finalisation of the study report).

6 STUDY PROCEDURES BY VARIABLE

6.1 Informed Consent

Prior to conducting any study-related activities, written informed consent must be obtained from the subject (Section 12.2).

6.2 Randomisation

Eligible subjects will be randomised in a 3:3:1 ratio to receive 2×300 mg ibuprofen PR tablets Q12h, 2x200 mg ibuprofen IR tablets Q8h, or placebo using permuted blocks of fixed size. The randomisation 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 randomisation schedule will be prepared by a statistician not otherwise involved in the study. Randomisation will be performed using an interactive web response system. 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.

6.3 Drug Administration

Subjects will be dosed under clinic supervision to ensure compliance. Prior to dosing, each subject will be instructed by the Investigator or clinic staff on how to take the medication.

6.4 Demographics

Demographic information will be recorded including gender, date of birth and race.

6.5 Medical History and Concomitant Medication

Relevant medical history, including history of current disease and information regarding underlying diseases will be recorded. The duration of surgery and all concomitant medication taken will be recorded as well as permitted therapies (see Section 5.3).

6.6 Physical Examination

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).

Height, weight, and BMI will be assessed at Screening.

6.7 Laboratory Tests

The following clinical laboratory tests will be performed at Screening.

Hematology:	hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count (or estimate), white blood cell count including differential
Serum Chemistry:	albumin, total bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, glucose, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase, uric acid, urea, inorganic phosphorous, cholesterol (total and High Density Lipoprotein (HDL)), triglycerides, gamma glutamyl transferase
Coagulation:	prothrombin time, partial thromboplastin time, fibrinogen
Urinalysis:	pH, specific gravity, blood, glucose, protein, ketones, leucocyte esterase, nitrites (in the event that the dipstick test is positive, red blood cells, white blood cells, epithelial cells, crystals, bacteria and casts will be examined microscopically)
Virology:	hepatitis B, hepatitis C, HIV

The following laboratory tests will also be performed:

- Alcohol breathalyzer test will be performed before surgery on Day 1.
- Urine drug screen samples will be collected at Screening and before surgery on Day 1 to test for amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine (PCP), and tetrahydrocannabinol (THC).

- For female subjects of childbearing potential, a blood sample for the serum pregnancy test will be collected at Screening and a urine pregnancy test sample will be collected before surgery on Day 1.

Blood and urine samples for hematology, serum chemistry, and urinalysis will be prepared using standard procedures and will be sent to a central laboratory for analyses.

6.8 Electrocardiograms

A 12-lead electrocardiogram will be performed at Screening.

6.9 Vital Signs

Vital signs will be recorded after the subject has been in a sitting position for 3 minutes. Vital sign assessments will include blood pressure, heart rate, respiratory rate, and body temperature. Clinically significant abnormalities in vital signs should be recorded as AEs.

6.10 Blood Sampling

Blood sampling will be performed according to the site's standard practices, as described in the study manual or other site documentation.

6.11 Oral Radiography

Oral radiographs (X-rays) will be taken at Screening (radiographs taken within 1 year before Screening will be acceptable and do not need to be repeated).

6.12 Pain Intensity

Subjects will rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever at the timepoints mentioned on Table 7-1.

6.13 Stopwatch Assessment

Two stopwatches will be started immediately after the subject has swallowed the study drug with 8 ounces of water. Each subject will be instructed, "Stop the first stopwatch when you first feel any pain relief whatsoever. This does not mean you feel completely better, although you might, but when you first feel any relief in the pain you have now" (perceptible pain relief). The subject will also be instructed, "Stop the second stopwatch when you feel the pain relief is meaningful to you" (meaningful pain relief). If the subject does not press the stopwatches within 8 hours after Time 0 the subject will discontinue use of the stopwatches.

6.14 Pain Relief Scale

Subjects will rate their pain relief relative to Time 0 using a 5-point categorical scale. Subjects will be asked "How much relief have you had since your starting pain?" with response choices of none = 0, a little = 1, some = 2, a lot = 3, and complete = 4. At each assessment time point, the pain intensity NRS 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.

6.15 Subject's Global Evaluation of Study Drug

For the global evaluation of study drug, the subject will be asked "How effective do you think the study drug is as a treatment for pain?" with response choices of 0 = poor, 1 = fair, 2 = good, 3 = very good, or 4 = excellent. Subjects will complete the global evaluation of study drug 24 hours after Time 0 or immediately before the first dose of rescue medication (whichever occurs first).

6.16 Adverse Events

During the study the Investigator will ask the subject: "Are you experiencing any symptoms or complaints?" at the baseline visit, and "Have you had any symptoms or complaints since the last time you were asked?" during the study. In addition, spontaneously reported AEs are collected.

The observation period for an individual subject will start after giving informed consent and will finish at the last visit (follow-up visit) for the given individual subject. All AEs that arise during the observation period will be recorded and an assessment of the AE will be performed as per Section 8.2 by a medically qualified Investigator. If a subject has an AE that is still ongoing at the last visit, an attempt will be made by the Investigator to follow this up as per Section 8.4.

If an untoward medical occurrence happens after the subject has signed the consent form but before administration of the IMP, it should be reported as an adverse event, including those associated with study procedures.

Note this does not include any pre-existing medical conditions or findings associated with medical history which are identified during the screening process.

7 STUDY PROCEDURES BY VISIT

7.1 Study Flow Chart / Table of Study Procedures and Assessments

Table 7-1 Schedule of Assessments

	Screening (Day -28 to Day -1)	Surgery (Day 1)						Day 2		Follow-up (Day 8 ±2 days) or ET[k]
			Post-surgery							
		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-surgery							
		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
Provide prescription for pain medication.									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;.

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.

i Subjects will complete a global evaluation of study drug 24 hours after Time 0 or immediately before the first dose of rescue medication (whichever occurs first).

j Adverse events will be monitored and recorded from the time of signing of the informed consent form until the Follow-up Visit (or Early Termination Visit).

k If an unscheduled visit occurs the Investigator should follow the activities detailed in Section 7.5.

7.2 Screening Visit (Day -28 to Day -1)

- Written informed consent
- Assign a screening number
- Inclusion/exclusion criteria
- Demographics
- Medical history
- Complete physical examination (excluding the genitourinary examination)
- Vital signs
- Electrocardiogram
- Height, weight, and BMI
- Clinical laboratory tests (haematology, chemistry, urinalysis)
- Serum pregnancy test for female subjects of childbearing potential
- Urine drug screen
- Oral radiography (oral radiographs taken within 1 year before Screening will be acceptable and do not need to be repeated)
- Review study restrictions with subject
- Schedule surgery

7.3 Day of Surgery (Day 1)

7.3.1 Pre-Surgery

- Inclusion/exclusion criteria review
- Medical history review
- Vital signs
- Urine pregnancy test for female subjects of childbearing potential
- Urine drug screen
- Alcohol breathalyzer test
- Concomitant medications

- Adverse events

7.3.2 Surgery

- Subjects who continue to be eligible for study participation after completing screening procedures and assessments will undergo extraction of 2 or more third molars. At least 1 of the third molars must be a fully or partially bone impacted mandibular molar. If only 2 molars are removed, then they must be ipsilateral.
- All subjects will receive local anesthesia (2% lidocaine with 1:100,000 epinephrine).
- Nitrous oxide will be allowed at the discretion of the investigator.

7.3.3 Post-surgery Eligibility Assessments and Randomisation

- Vital signs
- Concomitant medications
- Adverse events
- Pain intensity NRS
- Subjects who experience moderate to severe pain intensity (NRS score of ≥ 5) within 6 hours after surgery and who continue to meet all study entry criteria will be randomised

7.3.4 Dosing and Post-dose Assessments (Hour 0 through Hour 24)

- Subjects will re-assess their baseline pain intensity using the NRS immediately before receiving IMP (pre-dose, Time 0)
- Administer IMP at the timepoints in Table 3-2
- Subjects will assess their pain intensity (NRS) and pain relief (5 point categorical scale) at the following time points (pre-dose, if at one of the dosing timepoints of 0, 8, 12 or 16 hours): 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, if any. 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.
- Subjects will use the double stopwatch method to record the time to perceptible pain relief and time to meaningful pain relief during the 8 hours following the first dose or until subject takes rescue medication
- Subjects will complete a global evaluation of study drug 24 hours after Time 0 or immediately before the first dose of rescue medication (whichever occurs first)
- Vital signs will be recorded after the subject has been in a sitting position for 3 minutes at the following times: before surgery, within 30 minutes before Time 0, 12 and 24 hours after Time 0, and/or immediately before the first dose of rescue medication

- Concomitant medications
- Adverse events
- Subjects will remain at the study site overnight and will be discharged on Day 2.
- Upon discharge from the study site, provide prescription for pain medication.
- Schedule follow-up visit

7.4 Follow-up Visit (Day 8 ± 2 days) or Early Termination

- Abbreviated confirmatory physical assessment, including an examination of the subject's mouth and neck
- Vital signs
- Concomitant medications
- Record any post discharge adverse events

7.5 Unscheduled Visits

If unscheduled visits occur, the Investigator must record the reason for unscheduled visit, including any AEs, concomitant therapy changes, withdrawal (if deemed appropriate) and any clinical assessments deemed appropriate for the clinical care of the subject. Unscheduled visits should not alter the timing of the routine study schedule.

7.6 Study Restrictions

7.6.1 Prohibited Therapies

Subjects are not permitted to take any concomitant medications that might confound assessments of pain relief, such as psychotropic drugs, antidepressants, sedative-hypnotics (other than those permitted for conscious sedation), or other analgesics taken within five times of their elimination half-lives (other than those used at the surgery). Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) are permitted if the subject has been on a stable dose for at least four weeks prior to Visit 1 (screening).

7.6.2 General and Dietary Restrictions

Other restrictions include the following: alcohol use is prohibited from 24 hours before surgery until discharge on Day 2; nothing by mouth from midnight before surgery until 1 hour after surgery; clear liquids only are allowed starting 1 hour after surgery until 1 hour after dosing; 1 hour after dosing, the subject's diet may be advanced according to standard practice.

8 SAFETY REPORTING

8.1 Adverse Event Definitions

An Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. [ICH E6 1.2].

Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is classified as any untoward medical occurrence that:

- results in death
- is life-threatening
- requires in-patient hospitalization or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity or
- is a congenital anomaly/birth defect

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious.

[ICH E2A] Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Note: If the event is related to the investigational product and is both serious and unexpected, it is classified as a suspected unexpected serious adverse reaction (SUSAR). In case of double-blinded studies, unblinding is needed in order to determine a SUSAR.

8.2 Assessment of Adverse Events

Any untoward medical occurrences that arise after the subject has given informed consent will be recorded in the subject's source documents and electronic case report forms (eCRFs). Untoward medical occurrences can be reported spontaneously by the subject or in response to non-leading questioning or observation by the Investigator or be a significant laboratory abnormality.

Untoward medical occurrences, including all adverse events (AE) and all serious adverse events (SAEs) are collected, fully investigated and documented.

As the study will be conducted on subjects who have been through removal of impacted third molars, it is expected that they will present post-surgical symptoms, for example: swelling and bruising. For the purposes of this study, when at normal/expected magnitude, such occurrences will not be reported as AEs as they are expected and, therefore, are not “untoward” as in the AE standard definition.

SAEs should be followed until resolution or stabilisation. Participants with ongoing SAEs at study termination will be further followed up until recovery or until stabilisation of the disease after termination.

For each AE a causality assessment of the event to the study drug must be performed. The relationship to IMP must be determined by the Investigator (if medically qualified) or by a medically qualified Co-Investigator.

Table 8-1 AE Relationship Descriptions

Relationship	Description
Unassessable/ Unclassifiable	Insufficient information to be able to make an assessment
Conditional/ Unclassified	Insufficient information to make an assessment at present (causality is conditional on additional information)
Unrelated	No possibility that the AE was caused by the IMP
Unlikely	Slight, but remote, chance that the AE was caused by the IMP, but the balance of judgement is that it was most likely not due to the IMP
Possible	Reasonable suspicion that the AE was caused by the IMP
Probable	Most likely that the AE was caused by the IMP
Certain	The AE was definitely caused by the IMP

For each AE a severity description should be given.

Table 8-2 AE Severity Descriptions

Severity	Description
Mild	The AE does not limit usual activities; the subject may experience slight discomfort
Moderate	The AE results in some limitation of usual activities; the subject may experience significant discomfort
Severe	The AE results in an inability to carry out usual activities; the subject may experience intolerable discomfort or pain

Expectedness for each AE will be determined based on the information in Section 6.9 of the Investigator's Brochure.

All AEs will be coded by the Sponsor using the most up-to-date version of MedDRA.

8.3 Reporting of Adverse Events

In the event of a Serious Adverse Event (SAE), the Investigator must report the event using the SAE form to the Sponsor Global Vigilance Group (GVG), by contacting GVG by email: gvg@rb.com while copying in the contract research organisation (CRO) and Sponsor Project/Study Managers within 24 hours of knowledge of the event.

The out of hours emergency phone number is +44 (0)1482 326151. An alternative number may additionally be provided by Premier Research to give access to the study Medical Monitor our of hours.

This emergency phone number will be confirmed to the Investigator at the Study Initiation Visit.

All SAE Forms must be provided via email. Any inconsistencies in the information received from the Investigator will be clarified using the Adverse Event Data Clarification Form. The Investigator must retain a copy of all the SAE forms in the Investigator Site File.

The Investigator must inform their Institutional Review Board (IRB) of all SAEs occurring in the study within 7 days for fatal or life-threatening SAEs and 15 days for all other SAEs as per Sponsor instructions and as described in the Safety Management Plan.

The Investigator should not break the randomisation code except when it is necessary to do so in order to ensure the subject receives appropriate medical care.

SAEs and non-serious AEs will be reported to the appropriate regulatory authorities by the Sponsor in accordance with the authorities' requirements. The Sponsor is responsible for expedited reporting of all SUSARs/ SAEs to relevant authorities and IECs/IRBs as required by

regulations. If the event requires expedited reporting, a CIOMS (Council for International Organizations of Medical Sciences) form will be produced and GVG will take actions as per the study specific Safety Management Plan.

8.4 Follow-up of Adverse Events

All SAEs and all AEs that have not resolved by the end of the study will be followed up by the Investigator until resolution or until the Investigator believes there will be no further change, whichever is the earlier. This may involve the subject making additional visits to the site.

If a subject has unresolved AEs requiring follow-up, investigators must attempt to contact subjects by telephone or other means.

8.5 Overdose, Abuse, Misuse and Medication Errors

The Sponsor defines “overdose” as the administration of a quantity of an investigational IMP given per administration or cumulatively, which is above the maximum recommended dose according to the authorised product information.

The Sponsor defines “abuse” as the persistent or sporadic, intentional excessive use of an IMP, which is intended to produce harmful physical or psychological effects e.g. intentional overdose to experience psychological effects.

The Sponsor defines “misuse” as situations where the IMP is intentionally and inappropriately used not in accordance with the authorised product information.

Overdoses, abuse, misuse are reportable to the Sponsor irrespective of the presence of an associated AE / SAE. The overdose, abuse, misuse and any associated AE / SAE will be captured on an AE CRF (Case Report Form) page / SAE form.

Due to the full inpatient nature of this study, in which medication doses will be supervised by site staff, cases of overdose, abuse or misuse are not expected to occur.

Medication errors are any unintentional errors in dispensing or administration of the IMP which relates to:

- Taking / being administered an incorrect IMP
- Taking / being administered a drug by the wrong route of administration e.g. swallowing a suppository
- The accidental administration of the IMP to a person who is not a subject within the study

Medication errors are reportable to the Sponsor irrespective of the presence of an associated AE / SAE. Medication errors with or without an associated AE / SAE will be captured on the AE CRF page / SAE form.

8.6 Pregnancy

Pregnancy both in a female subject or the female partner of a male subject is considered a collectable event and will be recorded as an AE in all cases. It will be qualified as an SAE only if it fulfils SAE criteria.

Due to the full inpatient nature of this study, pregnancy cases are not expected to occur during the study.

9 STATISTICAL CONSIDERATIONS

This section presents a summary of the planned statistical analyses. A statistical analysis plan (SAP) that describes the details of the analyses to be conducted will be written prior to database lock.

Summary statistics for continuous variables will typically include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, summary statistics will typically include the number and percentage of subjects in each category. All data will be presented in listings.

Baseline values are defined as the last measurements taken before dosing with study drug.

9.1 Determination of Sample Size

The sample size determination is based on the primary efficacy variable, SPID12. According to Farrar 2001[(1)], 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 [(7)], 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 2×300-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 randomised into each of the PR and IR groups. Thus 280 subjects will be enrolled into the study.

9.2 Interim Analysis

No interim analysis is planned.

9.3 Analysis Datasets

The analysis populations include the following:

- The intent-to-treat (ITT) population will consist of all subjects who are treated with study drug and who have at least 1 pain relief assessment after Time 0. The ITT population is the primary population for the efficacy analysis.
- The per-protocol (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 utilized to evaluate the sensitivity of the primary efficacy analysis.
- The safety population will include all subjects who are treated with study drug. The safety population is the population for all safety assessments.

9.4 Subject Disposition and Characteristics

The numbers of subjects randomised, completing, and withdrawing, along with reasons for withdrawal, will be tabulated overall and by treatment group. The number of subjects in each analysis population will be reported. Demographic and baseline characteristics (including date of birth, sex, race, weight, height, BMI, medical history, and surgery duration) will be summarized for each treatment group and for the overall population using descriptive statistics. No formal statistical analyses will be performed.

9.5 Efficacy Analyses

The comparison of primary interest is between PR ibuprofen and placebo. In addition, the comparison between IR ibuprofen and placebo will be presented with p-values to demonstrate study sensitivity. Point estimates and 95% confidence intervals will be used to evaluate the clinical relevance of any differences between the PR and IR formulations. All treatment differences will be presented with 95% confidence intervals. No P value adjustment will be made for multiple endpoints or multiple comparisons. In the event of model assumptions for normality being violated, non-parametric methods will be used.

Each efficacy endpoint will be summarized descriptively by treatment group.

9.5.1 Primary Endpoint(s)

The primary endpoint, summed pain intensity difference (SPID) over 0 to 12 hours (SPID12), will be used to compare the test product (2×300 mg ibuprofen PR tablets) against the placebo product.

9.5.1.1 Primary Analysis

The primary efficacy null hypothesis is that SPID12 for placebo is equal to SPID12 for ibuprofen 2×300 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.

9.5.1.2 Secondary Analysis

The clinical relevance of the difference between placebo and PR ibuprofen over 12 hours after initial dose will be evaluated.

9.5.2 Secondary Endpoints

- The summed pain intensity difference (SPID) over 0 to 24 hours (SPID24) will be used to compare the test product (2×300 mg ibuprofen PR tablets twice daily [BID]) and comparator product (2×200 mg ibuprofen IR tablets three times a day [TID]).
- Summed pain intensity difference (SPID) over 0 to 4 hours (SPID4), over 0 to 8 hours (SPID8), and over 0 to 12 hours (SPID12) after Time 0
- 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 (a responder will be defined as a subject with ≥30% improvement in pain intensity without rescue medication during the first 8 hours)
- Numeric rating scale (NRS) pain intensity difference (PID) at each scheduled time point after Time 0
- Pain intensity score at each scheduled time point
- Pain relief score at each scheduled time point after Time 0
- Peak pain relief
- Time to onset of analgesia (measured as time to perceptible pain relief confirmed by time to meaningful pain relief) using double stopwatch
- 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

9.5.2.1 Secondary Endpoint Analyses

For continuous secondary endpoints such as pain intensity score, SPID at each scheduled time point, peak pain intensity, TOTPAR4, TOTPAR8, TOTPAR12, TOTPAR24, SPID4, SPID8, SPID24, SPRID4, SPRID8, SPRID12, and SPRID24, descriptive statistics (such as mean, standard deviation, median, minimum, and maximum) will be provided for each treatment regimen. P values from ANCOVA models comparing the placebo group with other treatment groups, including terms for treatment and a covariate for baseline pain will be provided for SPID, SPRID, and TOTPAR variables, but no formal statistical inferences will be drawn on the basis of these tests. In the event that normality assumptions are violated for a parameter, non-parametric analysis methods will be used.

For ordinal secondary endpoints, such as pain intensity difference at each scheduled time point, pain relief at each scheduled time point, peak pain relief, and global evaluation of study drug, descriptive summaries will be provided and will include the number and percentage of subjects within each category for each treatment group. Nominal P values from Fisher's exact tests (or chi-square tests, as appropriate) comparing the placebo group with other treatment groups will be provided for peak pain relief and global evaluation of study drug, but no formal statistical inferences will be drawn on the basis of these tests.

For each time-to-event endpoint, Kaplan-Meier methodology will be used to evaluate the treatment effect. Time to onset of analgesia (measured as time to perceptible pain relief confirmed by meaningful pain relief) will be based on data collected using the double stopwatch method. Time to onset of analgesia will be right-censored at 8 hours for subjects who do not experience both perceptible pain relief and meaningful pain relief during the 8-hour interval after Time 0. The summary tables will provide the number of subjects analysed, the number of subjects censored, estimates for the quartiles, and 95% confidence intervals (CIs) for the estimated median and the restricted mean estimate. P values comparing placebo to active treatment from Wilcoxon or log-rank tests (as appropriate) will also be used to examine treatment effect.

For time to onset of analgesia, the comparison of interest will be the ibuprofen 2×300 mg PR group versus the ibuprofen 2×200 mg IR group. The summary table for this comparison will provide the number of subjects analysed, the number of subjects censored, estimates for the quartiles, and 95% confidence intervals (CIs) for the estimated median and the restricted mean estimate.

For the proportion of subjects who are responders and the proportion of subjects using rescue medication, logistic regression models that adjust for baseline intensity and/or significant demographic variables, if appropriate, will be used to evaluate the treatment effect.

For the responder analysis, subjects will be censored at 8 hours and for the use of rescue medication/time to first rescue subjects will be censored at 24 hours.

9.6 Safety Analyses

9.6.1 Safety Endpoint(s)

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

9.6.1.1 Safety Endpoint Analyses

Data listings will be provided for protocol-specified safety data. The Medical Dictionary for Regulatory Activities (MedDRA) (Version 19.0 or higher) will be used to classify all AEs with respect to system organ class and preferred term. Adverse event summaries will include only TEAEs, which will be summarized for each treatment group.

For vital sign measurements, descriptive statistics will be provided at each scheduled time point for each treatment group. Changes from Baseline for vital signs will be calculated for each subject, and descriptive statistics will be provided on changes in vital signs from Baseline for each treatment group at each scheduled time point after Baseline. No formal statistical tests will be performed.

9.7 Handling of Missing Data and Drop-outs

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.

The primary analysis will use windowed worst observation carried forward (WOCF) methodology for subjects who use rescue medication. Any pain measurements taken during a period of time in which rescue medication is active (4 hours) will be replaced by the last pain measurement before the rescue medication was taken. A sensitivity analysis will also be performed, in which all pain assessments recorded after the first dose of rescue medication has been taken will be disregarded and the rules outlined above will be used for missing data.

All data for assessments other than pain assessments will be analysed as collected; missing data due to premature termination or any other reason will be left as missing. In the event of a notable difference between treatment groups in the number of subjects using rescue medication, other sensitivity analyses may be performed. These will be detailed in the Statistical Analysis Plan (SAP).

9.8 Changes to the Original Statistical Plan

If there are any deviations to the proposed statistical analysis as described in this protocol these will either be documented in the final SAP or in a protocol amendment prior to database lock with the rationale and impact of the changes addressed.

10 DATA HANDLING AND RECORD KEEPING

10.1 Case Report Forms (CRFs)

Data will be recorded in an electronic Case Report Form (eCRF). For each enrolled study subject an eCRF is maintained. The Investigator or designees is responsible for the quality of the data record in the eCRF. eCRFs must be kept current to reflect subject status at each phase during the course of study. Subjects must not be identified in the eCRF by name or initials.

In the eCRF subjects will be identified by a subject number in combination with date of birth only, i.e., not by their name or initials. eCRF entries must be completed by appropriately trained site staff only. A log of trained and authorised staff able to complete the eCRF will be kept.

10.2 Specification of Source Documents

Source data must be available at the site to document the existence of the study subjects. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject. The investigator and study monitor will identify the data that will be recorded directly on the eCRF and for this data the eCRF will be considered the source document (i.e., no prior written or electronic record of the data). The study monitor will document this at the screening and it will also be documented in the Data Management Plan.

Source documents will include notes taken at the site and will include data such as demographic data, participation in study and ICF, medical history, SAEs, AEs and concomitant medication, results of examinations and assessments.

Where source data are in the form of a computer printout (e.g. medical records, laboratory data) they will be signed and dated by the investigator or designated person, confirming that the print out is a true and faithful record of the data for that subject. These print-outs will be filed in the study files.

The Investigator agrees to provide direct access to source data for study-related monitoring, audits, IRB review, and regulatory inspection(s). Direct access to source data requires that the subject gives written, documented consent to this.

10.3 Data Management

The data management group at Premier Research will be responsible for data management and eCRF activities.

Full details regarding data management will be described within the Data Management Plan.

10.4 Reporting of Protocol Deviations

Site staff should make the study monitor aware of any deviation from the protocol as soon as possible after occurrence. Waivers for inclusion / exclusion criteria are not allowed.

10.5 Retention of Essential Documentation

The Investigator should retain all essential documents (as defined in ICH E6 or according to other national and international regulations) until at least 5 years after the completion of the study (defined as last subject last visit in the study). These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

Subject files and other source data must be kept for the maximum period of time permitted by the Clinical Unit. The Investigator must notify the Sponsor of the retention period if this is shorter than described above.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Monitoring

The Sponsor will organise regular monitoring visits to be performed at intervals agreed with the Investigator. The anticipated monitoring frequency will be stated in the Monitoring Plan. Monitoring will also involve, as appropriate, correspondence and telephone contacts.

On-site monitoring includes source data verification (SDV) which is the procedure whereby the data contained in the eCRFs are compared with the primary source data and thereby verified as accurate. It will be performed in such a way as to preserve subject confidentiality, taking into account all ethical and legislative requirements.

The Investigator, or a designated member of the Investigator's staff, must be available at some time during the monitoring visit to review the data and resolve any queries and to allow direct access to the subject's records for SDV).

SDV will include as a minimum verification for all subjects, subject identity (date of birth, sex, initials and subject number), record of entry into the study and signature of the informed consent. In addition, details of SAEs in the subject's notes will be verified. Details included in the subject's notes as a minimum:

- Study number, brief description or title of study
- Date that the subject gave written consent
- All visit dates
- All SAEs
- All concomitant medications

At a site visit the eCRFs should be complete and available in order that the accuracy of their completion may be checked. Each completed eCRF for each subject must be signed electronically by the Investigator, to verify the data and statements submitted. Similarly, all alterations on paper records must be initialled and dated by the Investigator or a designated person, explained as necessary, with the original mistake left legible.

11.2 Audits and Inspections

For the purpose of ensuring compliance with the protocol, ICH GCP and applicable regulatory requirements, clinical studies sponsored by RB may be subject to an independent audit at the study site which will be conducted by personnel from an appropriate Quality Assurance Unit.

Full consultation with the Investigator will be made prior to and during such audit, which will be conducted according to Quality Assurance Unit Standard Operating Procedures.

As soon as the Investigator is notified of a planned inspection by a Regulatory Authority, he / she must inform the Sponsor promptly and allow the Sponsor to participate in the inspection as permitted by applicable regulations and local laws.

11.3 Sponsor Policy on Fraud in Clinical Studies

In accordance with GCP, it is the Sponsor's policy to always follow-up suspected cases of fraud.

12 ETHICAL AND REGULATORY ASPECTS

12.1 Ethics Review and Regulatory Authority Approval

Written approval to conduct the study by an independent and appropriately constituted IRB must be obtained and a copy provided to the Sponsor before any protocol-related procedures that do not form part of the subject's normal clinical treatment are performed. The approval letter must contain:

- Name and address of the IRB.
- Date of meeting.
- Sufficient information to identify the version of the Protocol and subject information/informed consent.
- Sufficient information to identify the version of other documents reviewed.

The investigator must also provide the Sponsor with a list of IRB members that includes each member's name and profession.

Any amendments to the Protocol must be submitted to the IRB for approval unless where necessary to eliminate apparent immediate hazards to study subjects, and any administrative changes must be notified.

This study will be submitted to the applicable Regulatory Authorities. The study will only be undertaken when regulatory authorisation has been obtained by the Sponsor.

The Sponsor will notify the Regulatory Authority within 90 days of the end of the study (within 15 days if the study is terminated prematurely).

Premier Research will notify the IRB within 90 days of the end of the study (within 15 days if the study is terminated prematurely).

12.2 Subject Information and Consent

Informed consent should be obtained by means of a patient information sheet and ICF, prepared in accordance with ICH E6 (R2) section 4.8.10 and the applicable local regulations, written in a non-technical language. All subjects will be provided with oral and written information describing the nature and duration of the study and the procedures to be performed. The subject will be asked to sign and date an ICF prior to any study-specific procedures being performed. No subject can enter the study before his/her informed consent has been obtained. A sample subject ICF used in the study will be included in the clinical study report for this protocol.

As part of administering the informed consent document, the Investigator must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician. The subject should understand the study, patient information sheet, and ICF before signing and dating the ICF. The Investigator or person obtaining consent must also sign and date the form. Each subject will be given a copy of the signed informed consent and written information.

12.3 Early / Premature Termination of the Study

In the unlikely event that this study generates an excessive frequency of adverse events, subjects' termination or suspension may be requested by the sponsor or the IRB or the Regulatory Authority.

The sponsor retains the right to terminate the study for non-safety reasons by giving an appropriate period of notice to all involved parties as per contractual agreements.

Any decisions to terminate or suspend the study will be notified in writing to the Investigator or designees, the IRB, Regulatory Authority and the clinicaltrials.gov database.

If the study is terminated early, study subjects who have attended screening will be informed that they are no longer required and if they have any questions, they should consult the study site staff. For subjects who have completed the study they will not be informed that the clinical study has been terminated. All data collected up to the point of study termination will be used in an abbreviated Clinical Investigation Report.

13 COMPENSATION, INDEMNITY AND INSURANCE

13.1 Clinical Study Agreement

Before the study commences, a contract between the Sponsor and Premier Research, who contracts with the Investigator, will be signed in which financial aspects of the study (including financial disclosure) as well as responsibilities and obligations are described.

13.2 Compensation

The Sponsor and the CRO carry insurance to pay compensation for injury, accident, ill health and death caused by participation in this study without regard to proof of negligence in accordance with the current local regulations and requirements. Details on finance and insurance will be provided in a separate agreement between the investigator and the sponsor.

13.3 Indemnity

The Sponsor will provide appropriate indemnity for the Investigator and staff who conduct part or all of this study, upon request. The request must be received before the first subject is recruited.

13.4 Insurance

If required and in accordance with applicable regulatory and legal requirements, the Sponsor will take out appropriate insurance policies on behalf of the Investigator and staff who conduct part or all of this study and/or on behalf of the subjects participating in the study.

14 REPORTING, PUBLICATION AND PRESENTATION

A clinical study report will be prepared according to ICH E3 (Structure and Content of Clinical Study Reports) as part of the Sponsor's commitment to Good Clinical Practice. The report will be a record of the total study conduct and findings and will be subject to approval by the Investigator who will sign the final report.

The study data will be owned by the Sponsor. The Sponsor retains the right to publish the data independently of the Investigator. The Sponsor agrees that before it publishes the results, it will provide the Investigator with at least 30 days for full review prior to submission of the manuscript to the publisher. The Investigator must submit any proposed manuscript to the Sponsor for approval prior to submission for publication.

15 REFERENCES

(1) Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain. 2001 Nov; 94(2):149-58.

(2) Summary of Product Characteristics for Nurofen 200 mg tablets Reckitt Benckiser Healthcare Ltd. (PL 00063/0385). 09 November 2015.

(3) Davies, NM Clinical pharmacokinetics of ibuprofen. The first 30 years. Clin. Pharmacokinetic. 1998, 34 (2), 101-154.

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(6) Wyeth Consumer Healthcare. (2002). *NDAC Meeting on Risks of NSAIDs.* Available: https://www.fda.gov/ohrms/dockets/ac/02/briefing/3882b2_04_wyeth-ibuprophen.htm. Last accessed 13th March 2018

(7) Singla, Neil Kumar et al. “A comparison of the clinical and experimental characteristics of four acute surgical pain models: Dental extraction, bunionectomy, joint replacement, and soft tissue surgery.” PAIN® 155 (2014): 441-456.

HEALTH · HYGIENE · HOME	**Investigational Study Protocol Amendment**
	Page 1 of 9

Document Name:	Non-Substantial Protocol Amendment Number 1	
Version Number & Date:	Version 1.0, 19-Jul-2019.	
Study Number:	5003601	
Study Title:	A Randomised, 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	
EudraCT / IND / Other Number:	IND 141948	
Protocol Version Number:	From:	1.0
	To:	2.0
Principal Investigator Name:	Todd Bertoch, MD	

Details of Amendment:	Amendment to Adverse Event definition (section 8.1) not affecting the safety of subjects, with additional administrative updates.	
Section(s) to be Changed:		
Throughout protocol	From:	Post-operative or Post-op or postoperative Pre-operative or pre-op
	To:	*Post-surgery or post-surgical* *Pre-surgery or pre-surgical* Note: Also, removal of the expansion of the term Post-op in the footnote to Table 7.1 Schedule of Assessments.
	Reason for Change:	To ensure consistency of terminology throughout the protocol.
Section 7.3.4 Dosing and Post-dose Assessments (Hour 0 through Hour 24), page 48.	From:	Dispense/prescribe
	To:	*provide prescription for pain medication*
	Reason for Change:	As the site will only provide a prescription for the pain medication, to be used at home, and not provide / dispense the medication the wording has been updated. This is consistent with other sections of the protocol (study synopsis page 19 & 5.3 page 37).
Table 7.1 Schedule of Assessments, page 44	From:	Dispense/ prescribe pain medication for use at home, as needed
	To:	*Provide prescription for pain medication*
	Reason for Change:	As the site will only provide a prescription for the pain medication, to be used at home, and not provide / dispense the medication the wording has been updated.
7.4 Follow up Visit (Day 8 ± 2 days) or Early Termination and Table 7.1 Schedule of Assessments	From:	Section 7.4 • Abbreviated confirmatory physical assessment, including an examination of the subject's mouth and neck • Vital signs • Concomitant medications • Collect unused pain medications • Record any post discharge adverse events

		Table 7.1 'Collect unused home pain medications, as needed'
	To:	Section 7.4 • Abbreviated confirmatory physical assessment, including an examination of the subject's mouth and neck • Vital signs • Concomitant medications • Record any post discharge adverse events Table 7.1 Row deleted
	Reason for Change:	As pain medications are not being dispensed from the site they will not be returned to the site.
Section 6.7 Laboratory Tests, page 40.	From:	The following fasting clinical laboratory tests will be performed at Screening.
	To:	The following clinical laboratory tests will be performed at Screening.
	Reason for Change:	The laboratory tests being conducted are not impacted by food, therefore the requirement for fasting has been removed to ease the requirements placed on subjects at screening.
Section 8.1 Adverse Event Definitions, page 49	From:	An adverse event (AE) is any untoward medical occurrence in a patient or a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study procedure.
	To:	An adverse event (AE) is any untoward medical occurrence in a patient or a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with ***this treatment***.
	Reason for Change:	To ensure full alignment with ICH E2A.
Section 8.2 Assessment of Adverse Events, page 49	From:	All AEs that arise after the subject has given informed consent will be recorded in the subject's source documents and electronic case report forms (eCRFs). AEs can be reported spontaneously by the subject or in response to non-leading questioning or observation by the Investigator or be a significant laboratory

		abnormality. All adverse events (AE) and all serious adverse events (SAEs) are collected, fully investigated and documented.
	To:	*Any untoward medical occurrences* that arise after the subject has given informed consent will be recorded in the subject's source documents and electronic case report forms (eCRFs). Untoward medical occurrences can be reported spontaneously by the subject or in response to non-leading questioning or observation by the Investigator or be a significant laboratory abnormality. *Untoward medical occurrences, including* all adverse events (AE) and all serious adverse events (SAEs) are collected, fully investigated and documented.
	Reason for Change:	To ensure full alignment with ICH E2A.
Study Synopsis – Subjects, Pages 14 - 15	From:	5) Female subjects of child-bearing potential must be willing to use a highly effective method of contraception throughout the study. A highly effective method of birth control is defined as one which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly, such as the following: a. established use of oral, injected or implanted hormonal methods of contraception b. some intrauterine devices (IUDs) or intrauterine systems (IUSs) c. true sexual abstinence, when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence such as calendar, ovulation, symptothermal, or post-ovulation methods; declaration of abstinence for the duration of the trial; or withdrawal are not acceptable methods of

		contraception) d. vasectomised partner.
	To:	5) Female subjects of child-bearing potential must be willing to use a highly effective method of contraception throughout the study. A highly effective method of birth control is defined as one which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly, such as the following: *a. Surgical sterilisation* *b.* established use of oral, injected or implanted hormonal methods of contraception *c.* some intrauterine devices (IUDs) or intrauterine systems (IUSs) *d.* true sexual abstinence, when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence such as calendar, ovulation, symptothermal, or post-ovulation methods; declaration of abstinence for the duration of the trial; or withdrawal are not acceptable methods of contraception) *e.* vasectomised partner.
	Reason for Change:	Consistency with section 4.2 Inclusion Criteria in main body of protocol.
Inclusion Criteria Number 8 (Study Synopsis – Subjects, Page 15 and Section 4.2, Page 30)	From:	8. Is willing and able to comply with study requirements (including diet and smoking restrictions), complete the pain evaluations, remain at the study site overnight, and return for follow up 7 (± 2) days after surgery.
	To:	8. Is willing and able to comply with study requirements (including diet and smoking restrictions), complete the pain evaluations, remain at the study site overnight, and return for follow up 7 (± 2) days after surgery, *(Day 8 ± 2*

			days).
	Reason for Change:		To clarify the timing of the follow-up visit and ensure consistency with other sections of the protocol.
Section 8.3, Page 51	From:		The out of hours emergency phone number is +44 (0)1482 326151.
	To:		The out of hours emergency phone number is +44 (0)1482 326151. *An alternative number may additionally be provided by Premier Research to give access to the study Medical Monitor our of hours.*
	Reason for Change:		Concern from CRO that many people in the US do not know how to make an international call. Hence alternative number may be provided to give immediate access to the Medical Monitor at the CRO.
Header Pages 43-45 and Pages 46-63	From:	Pages 43-45	Protocol Version: 07 June 2018, draft Version 10
		Pages 46-63	Protocol Version: 22 August 2018, draft Version 0.17
	To:	Pages 43-45	Protocol Version: *19-July-2019, FINAL* Version *2.0*
		Pages 46-63	Protocol Version: *19-July-2019, FINAL* Version *2.0*
	Reason for Change:		Correction to both document date and version.
Exclusion Criteria Pages 16 & 32	From:		12) Previously participated in another clinical study of 300 mg ibuprofen PR tablets, or received any investigational drug, device, or therapy within 90 days before screening.
	To:		12) Previously participated *(randomised)* in another clinical study of 300 mg ibuprofen PR tablets, or received any investigational drug, device, or therapy within 90 days before screening.
	Reason for Change:		To ensure full clarity that participated does not include screening process.
Section 6.16 Adverse Event, page 42.	From:		If an untoward medical occurrence happens after the subject has signed the consent form but before administration of the IMP, it should be reported as an adverse event, including those associated with study procedures.
	To:		If an untoward medical occurrence happens after the subject has signed the consent form but before administration of the IMP, it should be

		reported as an adverse event, including those associated with study procedures. *Note this does not include any pre-existing medical conditions or findings associated with medical history which are identified during the screening process.*
	Reason for Change:	To prevent any misunderstanding that because the consent form has been signed, any conditions identified following procedures during screening, that in the opinion of the investigator are deemed to be pre-existing should not be reported as AEs.

SIGNATURE PAGE

Protocol Author

DocuSigned by:
Donna Reed
Signer Name: Donna Reed
Signing Reason: I approve this document
Signing Time: Jul 26, 2019 | 16:01 BST
EAB25C398D9E4208A54F62E0595D29FA

26-Jul-2019 | 08:01:20 AM PDT

Donna Reed, MA
Principal Medical Writer
Premier Research

Date

Protocol Statistician

(Statistics and DM sections reviewed and approved):

DocuSigned by:
Darren Targett
Signer Name: Darren Targett
Signing Reason: I approve this document
Signing Time: Jul 22, 2019 | 13:50 BST
AFBA8AD99F4542DDA7D194D987EF1679

22-Jul-2019 | 13:50:32 PM BST

Darren Targett
Consultant Statistician
RB Representative

Date

Sponsor's Medical Expert

(Reviewed and approved):

DocuSigned by:
Neil Fawkes
Signer Name: Neil Fawkes
Signing Reason: I approve this document
Signing Time: Jul 22, 2019 | 14:05 BST
FBE2F9E6498A42529274F2FA9073AD21

22-Jul-2019 | 14:05:32 PM BST

Dr. Neil Fawkes, MBChB
Clinical Research Physician
RB

Date

Sponsor's Medical Director

(Approved to Proceed):

DocuSigned by:
Robert Eichler
Signer Name: Robert Eichler
Signing Reason: I approve this document
Signing Time: Jul 22, 2019 | 16:03 BST
46BB1215283A447D822D9E4E2C48D131

22-Jul-2019 | 16:03:56 PM BST

Robert Eichler, PhD
Global Medical Affairs Head, Health
RB

Date

INVESTIGATOR APPROVAL

I have read and understood this Clinical Study Protocol Amendment

Principal Investigator
(Reviewed and Accepted):

DocuSigned by:
Dr. Todd Bertoch
Signer Name: Dr. Todd Bertoch
Signing Reason: I have reviewed this document
Signing Time: 07-Aug-2019 | 10:18 PDT 07-Aug-2019 | 07:18:33 PDT
B2AE4BF347AA4C1C95ABCA5CAF0104F2

Todd Bertoch, MD Date
Chief Scientific Officer
JBR Clinical Research
650 East 4500 South
Suite 100
Salt Lake City
Utah, 84107
USA

HEALTH · HYGIENE · HOME	**File Note Template** Page 1 of 1

File Note Number:	02
Study Number:	5003601
Description:	This File Note has been created to document the fact that the header in Protocol v1.0, 20-Nov-2018 contains the incorrect information from page 43 onwards. The header incorrectly shows draft and incorrect version numbers and dates, (see below) Pages 43-45 • Protocol Version: 07 June 2018, draft Version 10 Pages 46-63 • Protocol Version: 22 August 2018, draft Version 0.17 The information contained within those pages however is consistent and correct for Protocol v1.0 20-Nov.2018. The headers from pages 43-63 will be corrected if an amendment is made to the protocol.

SIGNATURE:	
NAME:	Jane Thomas
POSITION:	Senior Clinical Study Manager
DATE:	18-DEC-2018

RECKITT BENCKISER

STUDY TITLE

A Randomised, 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

Short Study Title

Efficacy Study of 300mg Ibuprofen Prolonged-Release Tablets for the Treatment of Pain After Surgical Removal of Impacted Third Molars

IND (Investigational New Drug) Number:	141948
RB Study Number:	5003601
CRO Study Number:	RECK.177369
Protocol Version and Date:	FINAL V1.0 / 20-November-2018
Previous Versions / Date(s):	None
Confidentiality Statement:	The information contained in this document is privileged and confidential. Do not copy, circulate or otherwise distribute without written authority from Reckitt Benckiser

KEY CONTACTS

Name and title	Address	Phone	e-mail
Sponsor: RB Healthcare UK	Dansom Lane, Hull, HU8 7DS United Kingdom	+44 (0)1482 326151	5003601@rb.com
Sponsor's Medical Expert: Neil Fawkes	Dansom Lane, Hull, HU8 7DS United Kingdom	+44 (0)1482 5833242	neil.fawkes@rb.com
Principal / Chief / Coordinating Investigator(s): Dr Todd Bertoch	JBR Clinical Research 650 East 4500 South Suite 100 Salt Lake City Utah, 84107 USA	+ 1 928 8307354	tbertoch@jbrutah.com
Sponsors Statistician: Darren Targett	Dansom Lane, Hull, HU8 7DS United Kingdom	N/A	darren.targett@primoriscs.co.uk
Contract Research Organisation: Premier Research	One Park Drive, Suite 150 Durham, NC 27709 USA	+ 1 919 627 9100	N/A
CRO Project Manager: Paul Brittain	One Park Drive, Suite 150 Durham, NC 27709 USA	+ 1 617 934 2233	paul.brittain@premier-research.com
Clinical Laboratory: Quest Diagnostics, Inc.	3489 W 2100 S, Suite 200, West Valley City, Utah 84119 USA	N/A	N/A

SIGNATURE PAGE

Protocol Author

DocuSigned by:
Signer Name: Donna Reed
Signing Reason: I approve this document
Signing Time: 21-Nov-2018 | 13:39 EST
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21-Nov-2018 | 13:40:08 EST

Donna Reed, MA — Date
Principal Medical Writer
Premier Research

Protocol Statistician
(Statistics and DM sections reviewed and approved):

DocuSigned by:
Darren Targett
Signer Name: Darren Targett
Signing Reason: I approve this document
Signing Time: Nov 20, 2018 | 15:42 GMT
AEBA8AD99F4542DDA7D194D987EF1679

Darren Targett — Date
Consultant Statistician
RB Representative

Sponsor's Medical Expert
(Reviewed and approved):

DocuSigned by:
Neil Fawkes
Signer Name: Neil Fawkes
Signing Reason: I approve this document
Signing Time: Nov 20, 2018 | 22:31 GMT
FBE2F9F6498A42529274F2FA9073AD21

Dr. Neil Fawkes, MBChB — Date
Clinical Research Physician
RB

Sponsor's Medical Director
(Approved to Proceed):

DocuSigned by:
Dalma Sugar
Signer Name: Dalma Sugar
Signing Reason: I approve this document
Signing Time: Nov 20, 2018 | 16:27 GMT
027391627634499E91BBE47C652BAF72

Dr. Dalma Sugar VetD — Date
R&D Director, Medical
Affairs Analgesics & Respiratory
RB

INVESTIGATOR STATEMENT

I have read and understood this Clinical Study Protocol and agree:

- to conduct this clinical study in accordance with the protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). Amendments to the protocol are acceptable only upon mutual agreement with the exception of urgent safety measures that need to be taken to protect study subjects from any immediate hazard to their health and safety.
- to conduct this clinical study in accordance with the principles as set out in the Declaration of Helsinki and with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.
- to conduct this study only after a favourable opinion is obtained from the Independent Review Board and Regulatory Authority
- to report all information or data in accordance with the protocol.
- to report any serious adverse events as defined in the “Safety Reporting” section of this protocol.
- to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol.

I understand:

- that information that identifies me will be used and disclosed as described in the protocol and that such information may be transferred to countries that do not have laws protecting such information.
- that since the information in the protocol and the references in the Investigator's brochure (if applicable) are confidential, its disclosure to any third parties, other than those involved in approval, supervision or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

Principal Investigator
(Reviewed and Accepted):

_____ _____

Todd Bertoch, MD Date
Chief Scientific Officer
JBR Clinical Research

TABLE OF CONTENTS

List of Tables Contained in the Body of the Protocol

List of Figures Contained in the Body of the Protocol

LIST OF ABBREVIATIONS

Abbreviation	Abbreviation in Full
AE	Adverse Event
ANCOVA	Analysis of Covariance
AUC	Area Under the Plasma Concentration Curve
BID	Twice Daily
BMI	Body Mass Index
Cmax	Maximum Observed Plasma Concentration
CRF	Case Report Form
CRO	Contract Research Organisation
eCRF	Electronic Case Report Form
FDA	(US) Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GVG	Global Vigilance Group
HDL	High Density Lipoprotein
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IR	Immediate Release
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
IUS	Intrauterine System
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numeric Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
OTC	Over the Counter
PID	Pain Intensity Difference
PP	Per Protocol
PR	Prolonged Release
RB	Reckitt Benckiser
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SNRI	Serotonin and Noradrenaline Reuptake Inhibitor
SPID	Summed Pain Intensity Difference
SPRID	Summed Pain Relief and Intensity Difference

Abbreviation	Abbreviation in Full
SSRI	Selective Serotonin Reuptake Inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent Adverse Event
TID	Three Times a Day
Tmax	Time to Maximum Plasma Concentration
TOTPAR	Sum of Total Pain Relief
WOCF	Worst Observation Carried Forward

STUDY SYNOPSIS

Study Title:	A randomised, 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
RB Study Number:	5003601
Background and Rationale:	Reckitt Benckiser (RB) is co-developing a new 300 mg ibuprofen prolonged release (PR) tablet with Strides Shasun Ltd. The product has been developed to meet consumer and patient needs to have access to longer acting over-the-counter analgesics. This PR formulation will reduce fluctuations in drug plasma concentrations and allow for a lower frequency of administration which is desirable in situations where pain duration is expected to be prolonged and require multiple doses of immediate release formulations. As a result, the product would be more consumer friendly, require less dosing and improve compliance with treatment. The proposed therapeutic indications of the PR product are for the short-term symptomatic treatment of mild to moderate pain such as dysmenorrhea, rheumatic pain, muscular pain, pain of non-serious arthritic conditions and backache. The proposed posology in adults over the age of 18 is: Ibuprofen 300 mg PR tablets. Two tablets to be taken every 12 hours when required for pain relief. No more than 2 doses in 24 hours. The maximum daily dose is 1200 mg and there is no proposed indication in the paediatric population. Therefore, the purpose of the proposed study is to provide supporting pivotal efficacy evidence for registration applications in Europe, Australia and Russia. The decision to progress to an efficacy clinical trial was determined on the basis of successful outcomes of the 2 phase 1 clinical trials (BE/17/279 and BE/17/281) in terms of bioavailability (BA) versus a reference ibuprofen immediate release (IR) product and bioequivalence (BE) versus comparator 600 mg ibuprofen PR.
Objectives:	**Primary Objective:** • To evaluate the superiority of 2×300 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. **Key Secondary Objectives:** • 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 2×300 mg ibuprofen PR tablets. **Additional Secondary Objectives:** • To evaluate the total analgesic effect, peak analgesic effect, onset and duration of action and the subject's overall assessment of the study medications.
Design:	This is a single centre, randomised, double-blind, double-dummy, parallel group, multiple-dose, active and placebo-controlled efficacy study to evaluate the efficacy and safety of 2×300 mg ibuprofen PR tablets in subjects with postoperative dental pain.
Primary Endpoint:	The Summed Pain Intensity Difference (SPID) over 0 to 12 hours (SPID12) will be used to compare the test product (2×300 mg ibuprofen PR tablets) against the placebo product.
Confirmatory Evaluation:	Clinically relevant difference between placebo and PR ibuprofen over 12 hours after initial dose (for the purposes of this study, a difference of 30 % in PID scores over 12 hours after initial dose will be considered clinically relevant).[(1)]
Secondary Endpoints:	**Key secondary efficacy endpoint:** • The summed pain intensity difference (SPID) over 0 to 24 hours (SPID24) will be used to compare the test product (2×300 mg ibuprofen PR tablets twice daily [BID]) and active comparator product (2×200 mg ibuprofen IR tablets three times a day [TID]). **Efficacy endpoints:** • Summed pain intensity difference (SPID) over 0 to 4 hours (SPID4), over 0 to 8 hours (SPID8), and over 0 to 12 hours (SPID12) after Time 0 • 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 (a responder will be defined as a subject with ≥30 % improvement in pain intensity without rescue medication during the first 8 hours) • Numeric rating scale (NRS) pain intensity difference (PID) at each scheduled time point after Time 0 • Pain intensity score at each scheduled time point • Pain relief score at each scheduled time point after Time 0 • Peak pain relief • Time to onset of analgesia (measured as time to perceptible pain relief confirmed by time to meaningful pain relief) using double stopwatch • 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 **Exploratory endpoint:** • Patient's global evaluation of study drug
Safety Endpoints:	• Incidence of treatment-emergent adverse events (TEAEs) • Incidence of clinically relevant changes in vital sign measurements
Subjects:	**Inclusion Criteria** A subject will be eligible for study entry if all the following inclusion criteria are met: 1) Is male or female ≥ 18 and ≤ 50 years of age. 2) Requires extraction of 2 or more third molars. At least 1 of the third molars must be a fully or partially bone impacted mandibular molar. If only 2 molars are removed, then they must be ipsilateral. 3) Experiences moderate to severe pain intensity within 6 hours after surgery, as measured by a numeric rating scale (NRS) score of ≥ 5 on a 0-10 scale. 4) Has a body weight ≥ 45 kg and a body mass index (BMI) ≤ 35 kg/m^2. 5) Female subjects of child-bearing potential must be willing to use a highly effective method of contraception throughout the study. A highly effective method of birth control is defined as one which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly, such as the following: a. established use of oral, injected or implanted hormonal methods of contraception b. some intrauterine devices (IUDs) or intrauterine systems (IUSs) c. true sexual abstinence, when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence such as

	calendar, ovulation, symptothermal, or post-ovulation methods; declaration of abstinence for the duration of the trial; or withdrawal are not acceptable methods of contraception) d. vasectomised partner. To be considered not of child-bearing potential, females must be surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or post-menopausal (defined as no menses for 12 months in women not using hormonal contraception or hormone replacement therapy, confirmed by a follicle stimulating hormone [FSH] level in the postmenopausal range at Screening). 6) Free of clinically significant abnormal findings as determined by medical history, physical examination, vital signs, laboratory tests and ECG. 7) Is able to provide written informed consent. 8) Is willing and able to comply with study requirements (including diet and smoking restrictions), complete the pain evaluations, remain at the study site overnight, and return for follow-up 7 (± 2) days after surgery. **Exclusion Criteria** A subject will not be eligible for study entry if any of the following exclusion criteria are met: 1) Known hypersensitivity reactions or allergy (e.g. asthma, rhinitis, angioedema or urticaria) in response to nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen), acetylsalicylic acid (aspirin), ingredients of the study drug, or any other drugs used in the study, including anaesthetics and antibiotics that may be required on the day of surgery. 2) A history of active or previous peptic ulceration/ haemorrhage, gastrointestinal bleeding or perforation, heart failure, renal or hepatic failure, uncontrolled hypertension, asthma, nasal polyps, or chronic rhinitis. 3) Has complications from the tooth extraction or any other clinically significant medical history that, in the opinion of the investigator, would affect the subject's ability to comply or otherwise contraindicate study participation, including but not limited to the following: cardiac, respiratory, gastroenterological, neurological, psychological, immunological, haematological, oncological, or renal disease. 4) Has undergone another dental surgery within 60 days prior to the day of surgery.

	5) A positive urine drugs of abuse screen or alcohol breathalyser test at screening and during the study (with the exception of a positive drugs of abuse screen that is a consequence of permitted prescription medicines). 6) If female, has a positive pregnancy test at screening (serum) or on the day of surgery prior to surgery (urine), or is lactating. 7) Has known or suspected, (in the opinion of the investigator), history of alcoholism or drug abuse within 2 years of screening or evidence of tolerance or physical dependence before dosing with study drug. 8) Taking any concomitant medications that might confound assessments of pain relief, such as psychotropic drugs, antidepressants, sedative-hypnotics (other than those permitted for conscious sedation), or other analgesics taken within five times of their elimination half-lives. Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) are permitted if the subject has been on a stable dose for at least four weeks prior to Visit 1 (screening). 9) Is considered by the investigator, for any reason (including, but not limited to the risks described as precautions, warnings and contraindications in the current version of the investigator's brochure for 300 mg ibuprofen PR tablets), to be an unsuitable candidate to receive the study drug. 10) Has a history of chronic use (defined as daily use for > 2 weeks) of nonsteroidal anti-inflammatory (NSAIDs), opiates, or glucocorticoids (except inhaled nasal steroids and topical corticosteroids), for any condition within 6 months before dosing with study drug. 11) Has significant difficulties swallowing capsules or tablets or is unable to tolerate oral medication. 12) Previously participated in another clinical study of 300 mg ibuprofen PR tablets, or received any investigational drug, device, or therapy within 90 days before screening. 13) Enrolment of the Investigator, his / her family members, employees and other dependent persons. 14) Failure to satisfy the investigator of fitness to participate for any other reason.
Products to be Evaluated and Treatment Regimen:	**Test product:** • 300 mg ibuprofen PR tablets for oral administration **Reference products:** • 200 mg ibuprofen IR tablets for oral administration

	• Placebo (for blinding purposes, two types of placebo tablets will be made; one to look like the test product and one to look like the reference product) **Treatment regimens:** Eligible subjects meeting all study entry criteria will be randomised to receive 1 of the following treatments: • Treatment A: test product; 2×300 mg ibuprofen PR tablets, BID (total daily dose 1200 mg) • Treatment B: reference product; 2×200 mg ibuprofen IR tablets, TID (total daily dose 1200 mg) • Treatment C: matching placebo tablets
Methodology:	This is a single centre, randomised, double blind, double-dummy, parallel group-, multiple-dose, active and placebo controlled efficacy study to evaluate the efficacy and safety of ibuprofen 2×300 mg ibuprofen PR tablets in subjects with postoperative dental pain. Eligible subjects will complete all screening procedures within 28 days before the surgery and randomisation. At Screening, subjects will provide written informed consent to participate in the study before any protocol specified procedures or assessments are completed. On Day 1, subjects who continue to be eligible for study participation after completing screening procedures and assessments will undergo extraction of 2 or more third molars. At least 1 of the third molars must be a fully or partially bone impacted mandibular molar. If only 2 molars are removed, then they must be ipsilateral. All subjects will receive local anaesthesia (2% lidocaine with 1:100,000 epinephrine). Nitrous oxide will be allowed at the discretion of the investigator. Subjects who experience moderate to severe pain intensity (a score of ≥ 5 on a numeric rating scale [NRS] from 0-10 where 0 = no pain, 10 = worst pain ever) within 6 hours after surgery and who continue to meet all study entry criteria will be randomised in a 3:3:1 ratio to receive 2×300 mg ibuprofen PR tablets every 12 hours (Q12h), 2×200 mg ibuprofen IR tablets every 8 hours (Q8h), or placebo. The randomisation 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). Subjects will re-assess their baseline pain intensity using the NRS immediately before receiving study drug (pre-dose, Time 0) and their pain intensity (NRS) and pain relief (5-point categorical scale) at the following time points (pre-dose, if at one of the dosing timepoints of 0, 8, 12 and/or 16 hours): 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, if any. 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. The double stopwatch method will be used to record the time to perceptible pain relief and time to meaningful pain relief during the 8 hours following the first dose or until subject takes rescue medication. Subjects will complete a global evaluation of study drug 24 hours (+/- 5 minutes) after Time 0 or immediately before the first dose of rescue medication (whichever occurs first). Vital signs will be recorded after the subject has been in a sitting position for 3 minutes at the following times: before surgery, within 30 minutes before Time 0, 12 and 24 hours after Time 0, and/or immediately before the first dose of rescue medication. Adverse events (AEs) will be monitored and recorded from the time of signing of the informed consent form (ICF) until the Follow up- Visit (or Early Termination Visit). During the 24 hours following Time 0, subjects will complete efficacy and safety assessments. Subjects will remain at the study site overnight and will be discharged on Day 2. Paracetamol / acetaminophen (1000 mg) will be permitted as the initial rescue medication. Subjects will be encouraged to wait at least 60 minutes after receiving study drug before taking rescue medication. If acetaminophen rescue medication is not effective in relieving the subject's pain, 5 mg oxycodone rescue medication may be administered at the discretion of the investigator. Subjects are not permitted to take any concomitant medications that might confound assessments of pain relief, such as psychotropic drugs, antidepressants, sedative-hypnotics (other than those permitted for conscious sedation), or other analgesics taken within five times of their elimination half-lives (other than those used at the surgery). Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) are permitted if the subject has been on a stable dose for at least four weeks prior to Visit 1 (screening). Other restrictions include the following: alcohol use is prohibited from 24 hours before surgery until discharge on Day 2; nothing by mouth from midnight before surgery until 1 hour after surgery; clear liquids only are allowed starting 1 hour after surgery until 1 hour after dosing; 1 hour after dosing, the subject's diet may be advanced according to standard practice. Upon discharge from the study site, subjects may be prescribed pain medication for use at home according to the standard practice of the

	study site. On Day 8 (± 2 days), subjects will return to the study site for an abbreviated confirmatory physical assessment and AE assessments.
Statistical Evaluation:	**Analysis Populations** The analysis populations include the following: • The intent-to-treat (ITT) population will consist of all subjects who are treated with study drug and who have at least 1 pain relief assessment after Time 0. The ITT population is the primary population for the efficacy analysis. • The per protocol- (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 utilized to evaluate the sensitivity of the primary efficacy analysis. • The safety population will include all subjects who are treated with study drug. The safety population is the population for all safety assessments. **Subject Characteristics** Demographic and baseline characteristics (including date of birth, sex, race, weight, height, BMI and medical history) will be summarized for each treatment group and for the overall population using descriptive statistics. No formal statistical analyses will be performed. **Efficacy Analyses** The primary efficacy null hypothesis is that SPID12 for placebo is equal to SPID12 for ibuprofen 2×300 mg PR tablets. The primary analysis will be an ANCOVA (Analysis of Covariance) model that includes the main effect of treatment and the baseline pain score as a covariate 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. All other comparisons between the treatment regimens, including ibuprofen 2×200 mg IR tablets versus placebo, will be considered secondary. No P value adjustment will be made for multiple endpoints or multiple comparisons. Each efficacy endpoint will be summarized descriptively by treatment group. For continuous secondary endpoints such as pain intensity score, SPID at each scheduled time point, peak pain intensity, TOTPAR4, TOTPAR8, TOTPAR12, TOTPAR24, SPID4, SPID8, SPID24, SPRID4, SPRID8, SPRID12, and SPRID24, descriptive statistics (such as mean, standard deviation, median, minimum, and maximum) will be provided for each treatment regimen. Nominal P values from

	ANCOVA models comparing the placebo group with other treatment groups, including terms for treatment and baseline pain will be provided for SPID, SPRID, and TOTPAR variables, but no formal statistical inferences will be drawn on the basis of these tests. For ordinal secondary endpoints, such as pain intensity difference at each scheduled time point, pain relief at each scheduled time point, peak pain relief, response to study drug, and global evaluation of study drug, descriptive summaries will be provided and will include the number and percentage of subjects within each category for each treatment group. Nominal P values from Fisher's exact tests (or chi-square- tests, as appropriate) comparing the placebo group with other treatment groups will be provided for peak pain relief and global evaluation of study drug, but no formal statistical inferences will be drawn on the basis of these tests. For each time to- event endpoint, Kaplan Meier methodology will be used to evaluate the treatment effect. Time to onset of analgesia (measured as time to perceptible pain relief confirmed by meaningful pain relief) will be based on data collected using the double stopwatch method. Time to onset of analgesia will be -right censored- at 8 hours for subjects who do not experience both perceptible pain relief and meaningful pain relief during the 8-hour interval after Time 0. For time to onset of analgesia, the comparison of interest will be the ibuprofen 2×300 mg PR group versus the ibuprofen 2×200 mg IR group. The summary tables will provide the number of subjects analysed, the number of subjects censored, estimates for the quartiles, and 95% confidence intervals (CIs) for the estimated median and the restricted mean estimate. P values from the Wilcoxon or log rank- tests (as appropriate) will also be used to compare placebo to the active treatments. For the responder analysis and the proportion of subjects using rescue medication, logistic regression models that adjust for baseline intensity and/or significant demographic variables, if appropriate, will be used to evaluate the treatment effect. Baseline values are defined as the last measurements taken before dosing with a study drug. 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. The primary analysis will use windowed worst observation carried forward (WOCF) methodology for subjects who use rescue medication. Any pain measurements taken during a period of time in which rescue medication is active (4 hours) will be replaced by the last pain measurement before the rescue medication was taken. A sensitivity analysis will also be performed, in which all pain assessments recorded after the first dose of rescue medication has been taken will be disregarded and the rules outlined above will be used for missing data. All data for assessments other than pain assessments will be analysed as collected; missing data due to premature termination or any other reason will be left as missing. **Safety Analysis** Data listings will be provided for protocol-specified safety data. The Medical Dictionary for Regulatory Activities (MedDRA) (Version 19.0 or higher) will be used to classify all AEs with respect to system organ class and preferred term. Adverse event summaries will include only TEAEs, which will be summarized for each treatment group. For vital sign measurements, descriptive statistics will be provided at each scheduled time point for each treatment group. Changes from Baseline for vital signs will be calculated for each subject, and descriptive statistics will be provided on changes in vital signs from Baseline for each treatment group at each scheduled time point after Baseline. No formal statistical tests will be performed.

1 BACKGROUND AND RATIONALE

1.1 Background for the Study and Rationale

Reckitt Benckiser (RB) is co-developing a new 300 mg ibuprofen prolonged release (PR) tablet with Strides Shasun Ltd. The product has been developed to meet consumer and patient needs to have access to longer acting over-the-counter analgesics. This PR formulation will reduce fluctuations in drug plasma concentrations and allow for a lower frequency of administration which is desirable in situations where pain duration is expected to be prolonged and require multiple doses of immediate release formulations. As a result, the product would be more consumer friendly, require less dosing and improve compliance with treatment.

The proposed therapeutic indications of the PR product are for the short-term symptomatic treatment of mild to moderate pain such as dysmenorrhea, rheumatic pain, muscular pain, pain of non-serious arthritic conditions and backache.

The proposed posology in adults over the age of 18 is:

Ibuprofen 300 mg PR tablets. Two tablets to be taken every 12 hours when required for pain relief. No more than 2 doses in 24 hours. The maximum daily dose is 1200 mg and there is no proposed indication in the paediatric population.

Therefore, the purpose of the proposed study is to provide supporting pivotal efficacy evidence for European, Russian, and Australian applications and not to support any application in the USA. This efficacy study will provide further evidence on the safety and efficacy of the product in addition to the data obtained in two bioequivalence studies BE/17/279 and BE/17/281.

1.2 Investigational Product

Ibuprofen [2-(4-isobutylphenyl) propionic acid] is a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and anti-pyretic properties[(2)]. It was initially available in 1969 as a prescription only medicine, indicated for rheumatoid arthritis, osteoarthritis and other chronic painful conditions such as ankylosing spondylitis. Following further research and the establishment of a reassuring safety profile, it was launched in 1983 as an over-the-counter (OTC) medication, marketed as Nurofen®.

Absorption of ibuprofen after oral administration is fairly rapid with peak serum concentrations occurring within 1 to 2 hours after administration. Ibuprofen is extensively bound to plasma proteins (99%) when administered at therapeutic levels and has a plasma half-life of about 2 hours. Excretion by the kidney is both rapid and complete, but only a small proportion of drug is excreted unchanged in urine, the majority being extensively metabolised in the liver to 2 major inactive metabolites. The pharmacokinetics of ibuprofen has been extensively reviewed by Davies[(3)].

1.3 Treatment Rationale

The treatment of the test product is in line with the proposed posology of the final product and the treatment of the active comparator is in line with the posology provided in the label of the product. The treatments will be administered orally, as this is the standard route of administration for these products.

The following are the treatment regimens of each product in the study:

- Treatment A: test product, 2x300 mg PR ibuprofen tablet, twice daily [total daily dose 1200 mg]
- Treatment B: reference product, 2x200 mg IR ibuprofen tablet, three times a day [total daily dose 1200 mg]
- Treatment C: matching placebo tablets for both the test and reference regimens

The active comparator (Treatment B) currently marketed in a number of geographies including a number of different European countries. It has therefore been chosen to fulfil requirements that when it is included in a marketing authorisation dossier as a comparator that it is licenced within the EU.

1.4 Study Population and Indication

The following study population will be invited to participate in this clinical trial:

Adult participants aged 18 to 50 requiring extraction of 2 or more third molars, at least 1 of which must be a fully or partially bone-impacted mandibular molar, (if only 2 molars are removed, then they must be ipsilateral), and who experience moderate to severe pain following surgery.

Such population is expected to present pain levels that will allow for assessing the magnitude of treatment effect in a low variability setting.

1.5 Non-Clinical Evidence

No non-clinical evidence is available for the PR tablet.

1.6 Clinical Evidence to Date

A total of 5 single and multiple-dose pharmacokinetic studies (139-15, BE-16-081, BE-16-295, BE-17-279, BE-17-281) have been performed with the test product. These studies demonstrated the oral bioavailability (BA) of the ibuprofen PR tablets (dosed at 2x300 mg) is comparable to Brufen® (Ibuprofen) IR Tablets (dosed at 3x200 mg) after a single dose and at steady state conditions. In terms of the release profile and absorption, C_{max} tends to be slightly higher in the IR formulation when compared with the PR formulation [21.96 ±3.87 µg/mL vs 14.51 ±3.1 µg/mL]. However the C_{max}, (Maximum Observed Plasma Concentration), T_{max}, (Time to Maximum Plasma Concentration) and $AUC_{0\text{-}Tmax}$ (Area Under the Plasma Concentration Curve) of the PR formulation suggest that's the onset of action should not be any slower than the IR reference when considering the minimum effective concentration of ibuprofen[4]. In terms of total exposure ($AUC_{0\text{-}\infty}$) the concentration profile is bioequivalent between the PR test product and the IR reference product [163.41 ±43.0 µg.h/mL vs 168.59 ±37.7 µg.h/mL]. A food effect is demonstrated when the test product is taken in the fed state, with an expected increase in the absorption rate.

In the 5 PK studies performed (over 200 subjects) only a limited number of mild, transient adverse events were reported.

Summary Outcomes:

- The Clinical data available for this reformulation (Ibuprofen 300 mg PR) suggests an adequate pharmacokinetic profile to achieve a sufficient therapeutic effect in the proposed study
- There are no safety concerns with the test product
- Ibuprofen 300 mg PR had an increased rate of absorption when administered with food.
- Ibuprofen 300 mg PR tablets had a comparable concentration profile to the comparator IR product and was bioequivalent based on $AUC_{0\text{-}\infty}$

1.7 Risks / Benefits

This study has been designed to confirm the therapeutic efficacy of ibuprofen 300 mg PR. Participants in this study are subjects aged 18-50 who require the extraction of 2 or more third molars, at least 1 of which must be a fully or partially bone impacted mandibular molar. Subjects will undergo dental surgery that is equivalent to that of the standard-of-care that would be expected for the above condition. They should be otherwise healthy and each subject will undergo a full health check as part of the enrolment into the study to confirm that they are healthy as defined in this protocol (see Section 4).

Participants randomised into the placebo arm would not be expected to derive any therapeutic benefit from the administration of the placebo tablets. The placebo arm is essential to the study

design as it ensures that any conclusion of non-inferiority from the trial is a reflection of the true properties of the treatments; that is, it demonstrates the assay sensitivity of the study. However, this obviously leaves the participants without adequate analgesia in the post-operative procedure and from an ethical perspective this is mitigated in the study design by the use of rescue medication that would be in line with standards of treatment. Although it is hypothesised that the investigational medicinal product (IMP) will provide adequate analgesia in the study, this cannot be guaranteed, and therefore the use of rescue medication also addresses the potential of reduced or lack of efficacy.

Ibuprofen is an established pharmaceutical ingredient and the adverse reactions associated with administration of 1200 mg/24 hour (OTC doses) are well known and documented[(2)(5)]. The adverse reactions most frequently occurring with a single dose being nausea, gastrointestinal upset, vomiting, diarrhoea, light headedness, dizziness and headache. Rarely, more serious reactions have been reported including GI bleeding, ulceration and perforations, hypertension and renal failure. When OTC doses of ibuprofen (200-400 mg/dose; 1200 mg/day) are taken for acute episodes of pain there is an extremely low risk of causing serious gastrointestinal events[(5)].

The specific 200mg Ibuprofen tablet to be used in this study as the active comparator (Treatment B) is marketed in the EU under the Nurofen brand and has an excellent safety profile.

It is not anticipated that the safety profile of ibuprofen will be altered after administration of multiple single doses of ibuprofen 300 mg PR in the context of this study. There are not expected to be any drug-drug interactions with the non-investigational medicinal products included within the study design. A washout period of at least 6 days is deemed to be sufficient prior to the Follow-up/Early Termination Visit to ensure adequate safety monitoring of the IMP.

The investigation site will have adequate set up, experience and safety measures that would be expected of a centre able to perform regular molar extractions. They will also have adequate experience in the safety monitoring of participants post dose that would be expected in a clinical trial setting. Therefore, it is considered that the risk related to study procedures are low and limited to common adverse events (AEs) related to the dental procedure, administration of routine anaesthetics, and discomfort from vital sign measurements. Any subject that experiences immediate complications during the surgery will be excluded from the study.

Therefore, the overall benefit-risk profile for the use of the investigational product as defined in this protocol is considered favourable.

1.8 Ethical Conduct of the Study

This study will be conducted in accordance with this protocol and the principles set out in the Declaration of Helsinki. It will comply with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

2 STUDY OBJECTIVES

Primary Objective:

- To evaluate the superiority of 2×300 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.

Key Secondary Objectives:

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

Additional Secondary Objectives:

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

3 STUDY DESIGN AND RATIONALE FOR DESIGN

This is a single centre randomised, double-blind, double dummy, parallel group, multiple-dose, active and placebo-controlled efficacy study to evaluate the efficacy and safety of 2×300 mg ibuprofen PR tablets in subjects with postoperative dental pain.

The dental pain model used in this study is a robust and well established postsurgical pain model that produces pain that is predictable in its character, duration, and intensity[(6)]. The model is widely accepted and has a proven record of assay sensitivity (i.e. separating active drugs from each other, as well as from placebo). The model is frequently used to evaluate NSAID type analgesics. Results from dental pain studies are accepted by the US Food and Drug Administration (FDA) and European authorities and have been widely extrapolated to other general pain conditions.

The decision to conduct the study in the United States was taken as suitably qualified and experienced test sites could not be found in Europe. The specific test site has been chosen to conduct the study as they have a proven history of quality and safety when conducting studies of this type.

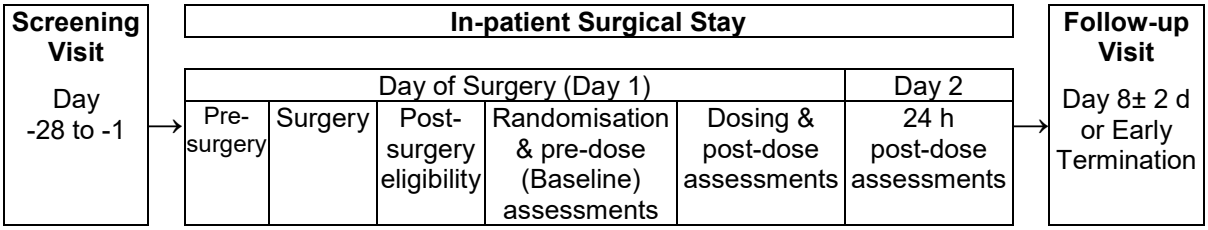
The placebo products have two purposes:

1. To mask the treatment identify for PR and IR arms
2. Act as a control arm

The dose of the test product is the proposed posology of the final product and the dose of the active comparator is the posology provided in the label of the product.

Eligible subjects will be randomised in a 3:3:1 ratio to receive 2×300 mg ibuprofen PR tablets Q12h, 2×200 mg ibuprofen IR tablets Q8h, or placebo. The randomisation 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 randomisation schedule will be prepared by a statistician not otherwise involved in the study. Randomisation will be performed using an interactive web response system (IWRS). 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.

Figure 3.1 Study Design Schematic



Note: Un-scheduled visits may occur at any point throughout the study

Table 3-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary Objective: To evaluate the superiority of 2×300 mg ibuprofen PR tablets compared with placebo in subjects experiencing acute dental pain after third molar extraction over 12 hours post initial dose.	**Primary Endpoint:** The primary efficacy endpoint is the summed pain intensity difference (SPID) over the 0 to 12 hours (SPID12) after Time 0 and will be used to compare the test product (2x300 mg PR ibuprofen) and the placebo product. The clinical relevance of the difference between placebo and PR ibuprofen over 12 hours after initial dose will be evaluated as confirmatory evidence (for the purposes of this study, a difference of 30% in PID scores over 12 hours after initial dose will be considered clinically relevant).
Secondary Efficacy Objectives: • To evaluate the analgesic performance of a total daily dose of 1200 mg of ibuprofen PR formulation compared to ibuprofen IR formulation over 24 hours post initial dose.	**Key Secondary Efficacy Endpoints:** • The summed pain intensity difference (SPID) over 0 to 24 hours (SPID24) will be used to compare the test product (2×300 mg ibuprofen PR tablets twice daily [BID]) and comparator product

• To evaluate the total analgesic effect, peak analgesic effect, onset and duration of action and the subject's overall assessment of the study medications.	(2×200 mg ibuprofen IR tablets three times a day [TID]). **Efficacy Endpoints:** • Summed pain intensity difference (SPID) over 0 to 4 hours (SPID4), over 0 to 8 hours (SPID8), over 0 to 12 hours (SPID12), and over 0 to 24 hours (SPID24) after Time 0 • 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 (a responder will be defined as a subject with ≥30% improvement in pain intensity without rescue medication during the first 8 hours) • NRS pain intensity difference (PID) at each scheduled time point after Time 0 • Pain intensity score at each scheduled time point • Pain relief score at each scheduled time point after Time 0 • Peak pain relief • Time to onset of analgesia (measured as time to perceptible pain relief confirmed by time to meaningful pain relief) using double stopwatch • 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 **Exploratory Endpoint:** • Patient's global evaluation of study drug
Safety Objective: To evaluate the safety and tolerability of 2×300 mg ibuprofen PR tablets.	**Safety Endpoints:** • Incidence of treatment-emergent adverse events (TEAEs) • Incidence of clinically relevant changes in vital sign measurements

Subjects in the PR group will take 2×300 mg ibuprofen PR tablets at Hours 0 and 12. Subjects in the IR group will take 2×200 mg ibuprofen IR tablets at Hours 0, 8, and 16. To maintain double-blinding, at each dosing timepoint (Hours 0, 8, 12, and 16) all subjects will take a total of 4 tablets (placebo-only or active plus placebo, depending on randomised treatment group).

Table 3-2 Treatment Regimens

	PR Group	IR Group	Placebo Group
Hour 0	2 PR, 2 placebo for IR	2 placebo for PR, 2 IR	2 placebo for PR, 2 placebo for IR
Hour 8	2 placebo for PR, 2 placebo for IR	2 placebo for PR, 2 IR	2 placebo for PR, 2 placebo for IR
Hour 12	2 PR, 2 placebo for IR	2 placebo for PR, 2 placebo for IR	2 placebo for PR, 2 placebo for IR
Hour 16	2 placebo for PR, 2 placebo for IR	2 placebo for PR, 2 IR	2 placebo for PR, 2 placebo for IR
Hour 24	final assessments	final assessments	final assessments

The study will enrol approximately 280 male and female subjects 18-50 years of age who experience moderate to severe pain intensity within 6 hours after dental surgery to remove 2 or more third molars. At least 1 of the third molars must be a fully or partially bone impacted mandibular molar. If only 2 molars are removed, they must be ipsilateral. Subjects must satisfy all eligibility criteria including providing informed consent and willingness to remain at the clinic overnight.

The study will be conducted in 1 study site in the United States.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Study Population

The study will enrol approximately 280 male and female subjects.

4.2 Inclusion Criteria

Only subjects to whom all of the following conditions apply will be included:

1. Is male or female ≥ 18 and ≤ 50 years of age.
2. Requires extraction of 2 or more third molars. At least 1 of the third molars must be a fully or partially bone-impacted mandibular molar. If only 2 molars are removed, then they must be ipsilateral.
3. Experiences moderate to severe pain intensity within 6 hours after surgery, as measured by a numeric rating scale (NRS) score of ≥ 5 on a 0-10 scale.
4. Has a body weight ≥ 45 kg and a body mass index (BMI) ≤ 35 kg/m^2.
5. Female subjects of child-bearing potential must be willing to use a highly effective method of contraception throughout the study. A highly effective method of birth control is defined as one which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly, such as the following:
    a. surgical sterilisation
    b. contraceptive implants or injectables
    c. combined oral contraceptives
    d. some IUDs (intrauterine devices)
    e. true sexual abstinence, when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence such as calendar, ovulation, symptothermal, or post-ovulation methods; declaration of abstinence for the duration of the trial; or withdrawal are not acceptable methods of contraception), or
    f. vasectomised partner.

    To be considered not of child-bearing potential, females must be surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or post-menopausal (defined as no menses for 12 months in women not using hormonal contraception or hormone replacement therapy, confirmed by a follicle stimulating hormone [FSH] level in the postmenopausal range at Screening).
6. Free of clinically significant abnormal findings as determined by medical history, physical examination, vital signs, laboratory tests and ECG.
7. Is able to provide written informed consent.
8. Is willing and able to comply with study requirements (including diet and smoking restrictions), complete the pain evaluations, remain at the study site overnight, and return for follow-up 7 (± 2) days after surgery.

4.3 Exclusion Criteria

A subject will not be eligible for study entry if any of the following exclusion criteria are met:

1. Known hypersensitivity reactions or allergy (e.g., asthma, rhinitis, angioedema or urticaria) in response to nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen), acetylsalicylic acid (aspirin), ingredients of the study drug, or any other drugs used in the study, including anaesthetics and antibiotics that may be required on the day of surgery.
2. A history of active or previous peptic ulceration/ haemorrhage, gastrointestinal bleeding or perforation, heart failure, renal or hepatic failure, uncontrolled hypertension, asthma, nasal polyps, or chronic rhinitis.
3. Has complications from the tooth extraction or any other clinically significant medical history that, in the opinion of the investigator, would affect the subject's ability to comply or otherwise contraindicate study participation, including but not limited to the following: cardiac, respiratory, gastroenterological, neurological, psychological, immunological, haematological, oncological, or renal disease.
4. Has undergone another dental surgery within 60 days prior to the day of surgery.
5. A positive urine drugs of abuse screen or alcohol breathalyser test at screening and during the study (with the exception of a positive drugs of abuse screen that is a consequence of permitted prescription medicines).
6. If female, has a positive pregnancy test at screening (serum) or on the day of surgery prior to surgery (urine), or is lactating.
7. Has known or suspected, (in the opinion of the investigator), history of alcoholism or drug abuse within 2 years of screening or evidence of tolerance or physical dependence before dosing with study drug.
8. Taking any concomitant medications that might confound assessments of pain relief, such as psychotropic drugs, antidepressants, sedative-hypnotics (other than those permitted for conscious sedation), or other analgesics taken within five times of their elimination half-lives. Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) are permitted if the subject has been on a stable dose for at least four weeks prior to Visit 1 (screening).
9. Is considered by the investigator, for any reason (including, but not limited to the risks described as precautions, warnings and contraindications in the current version of the investigator's brochure [IB] for 300 mg ibuprofen PR tablets), to be an unsuitable candidate to receive the study drug.
10. Has a history of chronic use (defined as daily use for > 2 weeks) of nonsteroidal anti-inflammatory (NSAIDs), opiates, or glucocorticoids (except inhaled nasal steroids and topical corticosteroids), for any condition within 6 months before dosing with study drug.
11. Has significant difficulties swallowing capsules or tablets or is unable to tolerate oral medication.

12. Previously participated in another clinical study of 300 mg ibuprofen PR tablets, or received any investigational drug, device, or therapy within 90 days before screening.
13. Enrolment of the Investigator, his / her family members, employees and other dependent persons.
14. Failure to satisfy the investigator of fitness to participate for any other reason.

4.4 Subjects of Reproductive Potential

Woman of childbearing potential must use a highly effective contraceptive method for the entire duration of study participation.

A highly effective method of birth control is defined as one which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly, such as the following:

- Surgical sterilisation
- Established use of oral, injected or implanted hormonal methods of contraception
- Some intrauterine devices (IUDs) or intrauterine systems (IUSs)
- Male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). [For female subjects on the study, the vasectomised male partner should be the sole partner for that subject]
- True abstinence which is in line with the preferred and usual lifestyle of the subject. Periodic abstinence such as calendar, ovulation, symptothermal, or post-ovulation methods; declaration of abstinence for the duration of the trial; and withdrawal are not acceptable methods of contraception.

4.5 Discontinuation / Withdrawal and Replacement of Subjects

The Investigator may withdraw the subject from the study at any time. Reasons for removing a subject from the study include, but are not limited to:

- AEs that in the judgement of the Investigator may cause severe or permanent harm (significant clinical deterioration is an AE)
- Violation of the study protocol
- In the Investigator's judgement, it is in the subject's best interest
- Subject declines further study participation
- If applicable, randomisation code is broken

If subjects choose to prematurely stop the study prior to the scheduled discharge at Hour 24, safety and tolerability assessments must be performed prior to discharge, and, if possible, efficacy assessments should be performed.

If subjects choose to prematurely stop the study after clinic discharge but prior to the follow-up visit, at least 2 documented attempts should be made to contact the subjects for follow-up assessments which will include the assessments described for the follow-up visit (Section 7.4).

5 STUDY TREATMENT

5.1 Investigational Products

Active Test Product

Ibuprofen PR tablets 300 mg, single oral dose of 600 mg. A yellow to pale yellow coloured, film coated, caplet shaped tablet, debossed as 'N12' on one side and plain on the other side.

Table 5-1 Active Test Product

Name of Ingredient	Quantity/Tablet(mg)	Function	Reference
Ibuprofen	300.00	Active	Ph.Eur.
Silicon dioxide	3.00	Glidant/Anti-adherent	Ph.Eur.
Hypromellose K4M Premium	62.50	Rate Controlling Polymer	Ph.Eur.
Hypromellose K100 LV	32.50	Rate Controlling Polymer	Ph.Eur.
Silicified Microcrystalline cellulose 50	100.00	Filler/Binder	NF
Silicified Microcrystalline cellulose 90	50.00	Filler/Binder	NF
Croscarmellose sodium	17.50	Disintegrant	Ph.Eur.
Glycine	25.00	Release Modifier	Ph.Eur
Silicon dioxide	3.00	Glidant/Anti-adherent	Ph.Eur.
Stearic acid	6.00	Lubricant	Ph.Eur.
Total weight of core tablet	**599.50 mg**		
Film coating and Polishing			
Opadry Yellow 15B520019	7.50	Coating agent	In House
Purified water[#]	q.s.	Coating vehicle	Ph.Eur.
Carnauba Wax	0.025	Polishing Agent	Ph.Eur
Total weight	**607.025 mg**		

[#] Removed during the process.

Placebo for Test Product

A yellow to pale yellow coloured, film coated, caplet shaped tablet, debossed as 'N12' on one side and plain on the other side.

Table 5-2 Placebo for Test Product

Ingredient	mg/tablet	Function	Reference Standard
Core			
Hypromellose K4M Premium	125.10	Rate Controlling Polymer	Ph. Eur.
Hypromellose K100 Premium LV	65.05	Rate Controlling Polymer	Ph. Eur.
Silicified Microcrystalline Cellulose 50	200.17	Filler/ Binder	NF
Silicified Microcrystalline Cellulose 90	100.08	Filler/ Binder	NF
Croscarmellose Sodium	35.03	Disintegrant	Ph. Eur.
Glycine	50.04	Release Modifier	Ph. Eur.
Silica, Colloidal Hydrated	12.02	Glidant/ Anti-adherent	Ph. Eur.
Stearic Acid	12.01	Lubricant	Ph. Eur.
Coating and Polishing			
Opadry Yellow 15B520019	7.50	Coating Agent	In house
Carnauba Wax	0.025	Polishing Agent	Ph. Eur.
Processing agent			
Purified Water	q.s.*	Coating Vehicle	Ph. Eur.
Total	**607.025**		

* Does not remain in final product except traces. Removed during the coating process.

Comparator Product

Nurofen Ibuprofen acid tablets 200 mg, single oral dose of 400 mg. A white to off white, biconvex, round, sugar coated tablet.

Table 5-3 Comparator Product

Name of Ingredient	Unit Formula (mg/tablet)	Function	Reference to Standards
Active Ingredient			
Ibuprofen	200.0	Active ingredient	Ph.Eur.
Other Ingredients			
Croscarmellose Sodium	30.0	Disintegrating agent	Ph.Eur.
Sodium Lauryl Sulphate	0.5	Tablet lubricant	Ph.Eur.
Sodium Citrate	43.5	Bulk filler	Ph.Eur.
Stearic Acid	2.0	Tablet lubricant	Ph.Eur.
Colloidal Anhydrous Silica	1.0	Granule flow aid	Ph.Eur.
Tablet Core Weight	277.0		
Sugar Coat Ingredients			
Carmellose Sodium	0.7	Sugar coat binder	Ph.Eur.
Talc	33.0	Sugar coat bulking agent	Ph.Eur.
Acacia Spray Dried	0.6	Sugar coat binder	Ph.Eur.
Sucrose	116.1	Sugar coat	Ph.Eur.
Titanium Dioxide	1.4	Colour	Ph.Eur.
Macrogol 6000	0.2	Tablet polish	Ph.Eur.
Purified Water	ND	Sugar syrup solvent	Ph.Eur.
Coated Tablet Weight	429.0		

Placebo for Comparator Product

A white to off white, biconvex, round, sugar coated tablet.

Table 5-4 Placebo for Comparator Product

Ingredient	Quantity (%w/w)	Function	Reference Standard
Core			
Mannitol	46.81	Filler	Ph. Eur
Microcrystalline Cellulose	16.14	Filler	USP/NF
Magnesium Stearate	1.61	Lubricant	Ph. Eur.
Sugar coating			

Carmellose Sodium	0.16	Sugar coat binder	Ph. Eur
Talc	7.69	Sugar coat bulking agent	Ph. Eur
Acacia Spray Dried	0.14	Sugar coat binder	Ph. Eur
Sucrose	27.06	Sugar coat	Ph. Eur
Titanium Dioxide	0.33	Colour	Ph. Eur
Macrogol 6000	0.05	Tablet polish	Ph. Eur
Purified Water*	ND	Sugar syrup solvent	Ph. Eur

Test Product and Placebo for Test Product will be manufactured and packed (primary pack) to Good Manufacturing Practice (GMP) standards by Strides Shasun Limited, R.S No 32-34 PIMS Road, Periyakalpet, Kalapet, Pondicherry, 605014, India and shipped to Investigational Materials Supplies Unit (IMSU), RB, Dansom Lane, Hull, HU8 7DS.

Nurofen Ibuprofen acid (Comparator) and the Placebo for Comparator tablets will be manufactured to GMP standards by Reckitt Benckiser, Thane Road, Nottingham, NG90 2DB, UK. Both active and placebo tablets will be unprinted for blinding purpose.

Both the products (Comparator and Placebo) will be primary packed at Sharp Clinical Services, Elvicta Business Park, Crichowell, NP8 1DF, UK and shipped to Investigational Materials Supplies Unit (IMSU), RB, Dansom Lane, Hull, HU8 7DS.

The Test Product, Placebo for Test Product, Comparator Product and the Placebo for Comparator product will be assembled to GMP standards by the IMSU, RB, Dansom Lane, Hull HU8 7DS, and bulk certified by RB Research and Development Qualified Person. All the products will be shipped directly from IMSU to the study site.

5.2 Non-Investigational Products

In preparation for the surgery, subjects will receive local anaesthesia (2% lidocaine with 1:100,000 epinephrine). Nitrous oxide will be allowed at the discretion of the investigator.

5.3 Permitted Therapies

After randomisation and administration of study drug, paracetamol / acetaminophen (1000 mg) will be permitted as the initial rescue medication. Subjects will be encouraged to wait at least 60 minutes after receiving study drug before taking rescue medication. If acetaminophen rescue medication is not effective in relieving the subject's pain, 5 mg oxycodone rescue medication may be administered at the discretion of the investigator.

At the investigators discretion repeat doses of rescue medication may also be administered as required.

The Investigator or designees will record all medication taken by the subject at the screening visit in the subject's electronic Case Report Form (eCRF). Any medication taken by the subject

from the time of giving informed consent through to the end of the subject's participation in the study (last assessment) will be recorded on the concomitant medication page in the eCRF.

Upon discharge from the study site, subjects may be prescribed pain medication for use at home according to the standard practice of the study site.

5.4 Treatment Compliance

For the duration of each assessment the subject will remain at the study site under the supervision of the Investigator or designees. The Investigator or designees will provide supervised drug administration along with clear instructions and support to the subject to facilitate the best possible compliance with study requirements. Any non-compliance during the study will be observed and recorded by study site staff as a protocol deviation.

5.5 Packaging and Labelling and Supply / Resupply

For each subject one pack will be provided containing all required tablets for each dosing timepoint. Each tablet will be held in a blister within the pack. The pack will clearly show which tablets are to be taken at which timepoint.

All packs regardless of treatment regimen will be the same except for a kit number and will therefore not identify the treatment.

The IMP will be labelled in accordance with EudraLex Volume 4 Good Manufacturing Practice (GMP) Guidelines, Annex 13 - Manufacture of Investigational Medicinal Products, parts 26 to 33 (Labelling) and in accordance with directive 2003/94/EC as amended and including any other applicable national/state legislation. The IMP will be labelled in English

All IMP will be packed and labelled to GMP by the Investigational Material Supplies Unit (IMSU), Reckitt Benckiser Healthcare (UK) Ltd, Dansom Lane, Hull, HU8 7DS, UK. IMP will be shipped from the IMSU to the study site.

5.6 Storage Conditions

The Investigator or designated individual will keep all IMP(s) in a pharmacy or a secure storage facility, accessible only to those individuals authorised by the Investigator to dispense the medication.

The Investigator or designated individual will maintain an inventory. This will include the description and quantity of IMP(s) received during the course of this study, as well as a record of the materials that are dispensed and returned (how much, to whom and when). This inventory ("Drug Dispensing Log") will be subject to review by the study monitor during monitoring visits.

The Investigator agrees not to supply IMP(s) to any person except study personnel and patients enrolled in this study.

The IMP should be stored between 8-25 °C and is not to be refrigerated or frozen.

Temperatures must be constantly monitored and readings logged in a temperature log on working days.

The temperature in the secure storage facility will be recorded using a minimum/maximum thermometer. If the temperature falls outside the specified range of 8-25 °C, the Sponsor should be notified immediately and appropriate action should be agreed and documented. The temperature log will be reviewed by the study monitor at each monitoring visit.

5.7 Blinding

This study 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, colour and weight.

All subjects will receive 4 tablets at each dosing timepoint. At each timepoint each subject will receive 2 tablets that may be either PR or the placebo made to look like PR and 2 tablets that may be IR or the placebo made to look like IR. See Table 3-2 Treatment Regimens. This includes those in the placebo arm who will receive 2 placebo tablets designed to look like PR and 2 placebo tablets designed to look like IR at all dose timepoints.

All subject packs will be designed and labelled to ensure blinding is maintained.

Subjects, investigators and site staff will all be blind to the treatments.

Unblinding will only occur after database lock or in the case of emergency unblinding, see Section 5.8.

5.8 Emergency Unblinding Procedures

Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment.

For emergency unblinding, study personnel will use the IWRS. If treatment assignment is unblinded for an individual subject, study personnel will be notified of that subject's treatment assignment without unblinding the treatment assignments for the remaining subjects in the study. Thus, the overall study blind will not be compromised. If a subject's treatment assignment is unblinded, he/she may or may not be asked to withdraw from the study. The investigator should make this decision after consultation with the medical monitor.

5.9 Drug Accountability

The Investigator will keep all study medication (including rescue medication) in a pharmacy or a secure storage facility, accessible only to those individuals authorised by the Investigator to dispense the medication.

The Investigator or designated individual will maintain an inventory. This will include the description and quantity of study drug received during the course of the study, as well as a record of the materials that are dispensed and returned (how much, to whom and when). This inventory will be subject to review by the study monitor during monitoring visits.

The Investigator agrees not to supply study drug to any person except study personnel and subjects in this study.

5.10 Return and Destruction

The Investigator agrees to conduct a drug-supply inventory, to record the results of this inventory ("IMP Removal from Site" form) and to ensure all original IMP containers whether empty or containing IMP are sent to RB's representative at the end of the study.

RBs representative will then arrange for the appropriate and timely destruction of all containers and unused IMP upon confirmation from RB following provision of a full reconciliation by Premier (on finalisation of the study report).

6 STUDY PROCEDURES BY VARIABLE

6.1 Informed Consent

Prior to conducting any study-related activities, written informed consent must be obtained from the subject (Section 12.2).

6.2 Randomisation

Eligible subjects will be randomised in a 3:3:1 ratio to receive 2×300 mg ibuprofen PR tablets Q12h, 2x200 mg ibuprofen IR tablets Q8h, or placebo using permuted blocks of fixed size. The randomisation 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 randomisation schedule will be prepared by a statistician not otherwise involved in the study. Randomisation will be performed using an interactive web response system. 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.

6.3 Drug Administration

Subjects will be dosed under clinic supervision to ensure compliance. Prior to dosing, each subject will be instructed by the Investigator or clinic staff on how to take the medication.

6.4 Demographics

Demographic information will be recorded including gender, date of birth and race.

6.5 Medical History and Concomitant Medication

Relevant medical history, including history of current disease and information regarding underlying diseases will be recorded. The duration of surgery and all concomitant medication taken will be recorded as well as permitted therapies (see Section 5.3).

6.6 Physical Examination

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).

Height, weight, and BMI will be assessed at Screening.

6.7 Laboratory Tests

The following fasting clinical laboratory tests will be performed at Screening.

Hematology:	hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count (or estimate), white blood cell count including differential
Serum Chemistry:	albumin, total bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, glucose, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase, uric acid, urea, inorganic phosphorous, cholesterol (total and High Density Lipoprotein (HDL)), triglycerides, gamma glutamyl transferase
Coagulation:	prothrombin time, partial thromboplastin time, fibrinogen
Urinalysis:	pH, specific gravity, blood, glucose, protein, ketones, leucocyte esterase, nitrites (in the event that the dipstick test is positive, red blood cells, white blood cells, epithelial cells, crystals, bacteria and casts will be examined microscopically)
Virology:	hepatitis B, hepatitis C, HIV

The following laboratory tests will also be performed:

- Alcohol breathalyzer test will be performed before surgery on Day 1.

- Urine drug screen samples will be collected at Screening and before surgery on Day 1 to test for amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine (PCP), and tetrahydrocannabinol (THC).
- For female subjects of childbearing potential, a blood sample for the serum pregnancy test will be collected at Screening and a urine pregnancy test sample will be collected before surgery on Day 1.

Blood and urine samples for hematology, serum chemistry, and urinalysis will be prepared using standard procedures and will be sent to a central laboratory for analyses.

6.8 Electrocardiograms

A 12-lead electrocardiogram will be performed at Screening.

6.9 Vital Signs

Vital signs will be recorded after the subject has been in a sitting position for 3 minutes. Vital sign assessments will include blood pressure, heart rate, respiratory rate, and body temperature. Clinically significant abnormalities in vital signs should be recorded as AEs.

6.10 Blood Sampling

Blood sampling will be performed according to the site's standard practices, as described in the study manual or other site documentation.

6.11 Oral Radiography

Oral radiographs (X-rays) will be taken at Screening (radiographs taken within 1 year before Screening will be acceptable and do not need to be repeated).

6.12 Pain Intensity

Subjects will rate their pain intensity using a numeric rating scale (NRS) from 0-10 where 0 = no pain and 10 = worst pain ever at the timepoints mentioned on Table 7-1.

6.13 Stopwatch Assessment

Two stopwatches will be started immediately after the subject has swallowed the study drug with 8 ounces of water. Each subject will be instructed, "Stop the first stopwatch when you first feel any pain relief whatsoever. This does not mean you feel completely better, although you might, but when you first feel any relief in the pain you have now" (perceptible pain relief). The subject will also be instructed, "Stop the second stopwatch when you feel the pain relief is meaningful to you" (meaningful pain relief). If the subject does not press the stopwatches within 8 hours after Time 0 the subject will discontinue use of the stopwatches.

6.14 Pain Relief Scale

Subjects will rate their pain relief relative to Time 0 using a 5-point categorical scale. Subjects will be asked “How much relief have you had since your starting pain?” with response choices of none = 0, a little = 1, some = 2, a lot = 3, and complete = 4. At each assessment time point, the pain intensity NRS 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.

6.15 Subject’s Global Evaluation of Study Drug

For the global evaluation of study drug, the subject will be asked “How effective do you think the study drug is as a treatment for pain?” with response choices of 0 = poor, 1 = fair, 2 = good, 3 = very good, or 4 = excellent. Subjects will complete the global evaluation of study drug 24 hours after Time 0 or immediately before the first dose of rescue medication (whichever occurs first).

6.16 Adverse Events

During the study the Investigator will ask the subject: “Are you experiencing any symptoms or complaints?” at the baseline visit, and “Have you had any symptoms or complaints since the last time you were asked?” during the study. In addition, spontaneously reported AEs are collected.

The observation period for an individual subject will start after giving informed consent and will finish at the last visit (follow-up visit) for the given individual subject. All AEs that arise during the observation period will be recorded and an assessment of the AE will be performed as per Section 8.2 by a medically qualified Investigator. If a subject has an AE that is still ongoing at the last visit, an attempt will be made by the Investigator to follow this up as per Section 8.4.

If an untoward medical occurrence happens after the subject has signed the consent form but before administration of the IMP, it should be reported as an adverse event, including those associated with study procedures.

7 STUDY PROCEDURES BY VISIT

7.1 Study Flow Chart / Table of Study Procedures and Assessments

Table 7-1 Schedule of Assessments

	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.

i Subjects will complete a global evaluation of study drug 24 hours after Time 0 or immediately before the first dose of rescue medication (whichever occurs first).

j Adverse events will be monitored and recorded from the time of signing of the informed consent form until the Follow-up Visit (or Early Termination Visit).

k If an unscheduled visit occurs the Investigator should follow the activities detailed in Section 7.5.

7.2 Screening Visit (Day -28 to Day -1)

- Written informed consent
- Assign a screening number
- Inclusion/exclusion criteria
- Demographics
- Medical history
- Complete physical examination (excluding the genitourinary examination)
- Vital signs
- Electrocardiogram
- Height, weight, and BMI
- Clinical laboratory tests (haematology, chemistry, urinalysis)
- Serum pregnancy test for female subjects of childbearing potential
- Urine drug screen
- Oral radiography (oral radiographs taken within 1 year before Screening will be acceptable and do not need to be repeated)
- Review study restrictions with subject
- Schedule surgery

7.3 Day of Surgery (Day 1)

7.3.1 Pre-Surgery

- Inclusion/exclusion criteria review
- Medical history review
- Vital signs
- Urine pregnancy test for female subjects of childbearing potential
- Urine drug screen
- Alcohol breathalyzer test
- Concomitant medications

- Adverse events

7.3.2 Surgery

- Subjects who continue to be eligible for study participation after completing screening procedures and assessments will undergo extraction of 2 or more third molars. At least 1 of the third molars must be a fully or partially bone impacted mandibular molar. If only 2 molars are removed, then they must be ipsilateral.
- All subjects will receive local anesthesia (2% lidocaine with 1:100,000 epinephrine).
- Nitrous oxide will be allowed at the discretion of the investigator.

7.3.3 Post-surgery Eligibility Assessments and Randomisation

- Vital signs
- Concomitant medications
- Adverse events
- Pain intensity NRS
- Subjects who experience moderate to severe pain intensity (NRS score of ≥ 5) within 6 hours after surgery and who continue to meet all study entry criteria will be randomised

7.3.4 Dosing and Post-dose Assessments (Hour 0 through Hour 24)

- Subjects will re-assess their baseline pain intensity using the NRS immediately before receiving IMP (pre-dose, Time 0)
- Administer IMP at the timepoints in Table 3-2
- Subjects will assess their pain intensity (NRS) and pain relief (5 point categorical scale) at the following time points (pre-dose, if at one of the dosing timepoints of 0, 8, 12 or 16 hours): 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, if any. 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.
- Subjects will use the double stopwatch method to record the time to perceptible pain relief and time to meaningful pain relief during the 8 hours following the first dose or until subject takes rescue medication
- Subjects will complete a global evaluation of study drug 24 hours after Time 0 or immediately before the first dose of rescue medication (whichever occurs first)
- Vital signs will be recorded after the subject has been in a sitting position for 3 minutes at the following times: before surgery, within 30 minutes before Time 0, 12 and 24 hours after Time 0, and/or immediately before the first dose of rescue medication

- Concomitant medications
- Adverse events
- Subjects will remain at the study site overnight and will be discharged on Day 2.
- Upon discharge from the study site, dispense/prescribe pain medication.
- Schedule follow-up visit

7.4 Follow-up Visit (Day 8 ± 2 days) or Early Termination

- Abbreviated confirmatory physical assessment, including an examination of the subject's mouth and neck
- Vital signs
- Concomitant medications
- Collect unused pain medications
- Record any post discharge adverse events

7.5 Unscheduled Visits

If unscheduled visits occur, the Investigator must record the reason for unscheduled visit, including any AEs, concomitant therapy changes, withdrawal (if deemed appropriate) and any clinical assessments deemed appropriate for the clinical care of the subject. Unscheduled visits should not alter the timing of the routine study schedule.

7.6 Study Restrictions

7.6.1 Prohibited Therapies

Subjects are not permitted to take any concomitant medications that might confound assessments of pain relief, such as psychotropic drugs, antidepressants, sedative-hypnotics (other than those permitted for conscious sedation), or other analgesics taken within five times of their elimination half-lives (other than those used at the surgery). Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) are permitted if the subject has been on a stable dose for at least four weeks prior to Visit 1 (screening).

7.6.2 General and Dietary Restrictions

Other restrictions include the following: alcohol use is prohibited from 24 hours before surgery until discharge on Day 2; nothing by mouth from midnight before surgery until 1 hour after surgery; clear liquids only are allowed starting 1 hour after surgery until 1 hour after dosing; 1 hour after dosing, the subject's diet may be advanced according to standard practice.

8 SAFETY REPORTING

8.1 Adverse Event Definitions

An Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study procedure. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. [ICH E6 1.2].

Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is classified as any untoward medical occurrence that:

- results in death
- is life-threatening
- requires in-patient hospitalization or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity or
- is a congenital anomaly/birth defect

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious.

[ICH E2A] Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Note: If the event is related to the investigational product and is both serious and unexpected, it is classified as a suspected unexpected serious adverse reaction (SUSAR). In case of double-blinded studies, unblinding is needed in order to determine a SUSAR.

8.2 Assessment of Adverse Events

All AEs that arise after the subject has given informed consent will be recorded in the subject's source documents and electronic case report forms (eCRFs). AEs can be reported spontaneously by the subject or in response to non-leading questioning or observation by the Investigator or be a significant laboratory abnormality.

All adverse events (AE) and all serious adverse events (SAEs) are collected, fully investigated and documented.

As the study will be conducted on subjects who have been through removal of impacted third molars, it is expected that they will present post-surgical symptoms, for example: swelling and bruising. For the purposes of this study, when at normal/expected magnitude, such occurrences will not be reported as AEs as they are expected and, therefore, are not “untoward” as in the AE standard definition.

SAEs should be followed until resolution or stabilisation. Participants with ongoing SAEs at study termination will be further followed up until recovery or until stabilisation of the disease after termination.

For each AE a causality assessment of the event to the study drug must be performed. The relationship to IMP must be determined by the Investigator (if medically qualified) or by a medically qualified Co-Investigator.

Table 8-1 AE Relationship Descriptions

Relationship	Description
Unassessable/ Unclassifiable	Insufficient information to be able to make an assessment
Conditional/ Unclassified	Insufficient information to make an assessment at present (causality is conditional on additional information)
Unrelated	No possibility that the AE was caused by the IMP
Unlikely	Slight, but remote, chance that the AE was caused by the IMP, but the balance of judgement is that it was most likely not due to the IMP
Possible	Reasonable suspicion that the AE was caused by the IMP
Probable	Most likely that the AE was caused by the IMP
Certain	The AE was definitely caused by the IMP

For each AE a severity description should be given.

Table 8-2 AE Severity Descriptions

Severity	Description
Mild	The AE does not limit usual activities; the subject may experience slight discomfort

Severity	Description
Moderate	The AE results in some limitation of usual activities; the subject may experience significant discomfort
Severe	The AE results in an inability to carry out usual activities; the subject may experience intolerable discomfort or pain

Expectedness for each AE will be determined based on the information in Section 6.9 of the Investigator's Brochure.

All AEs will be coded by the Sponsor using the most up-to-date version of MedDRA.

8.3 Reporting of Adverse Events

In the event of a Serious Adverse Event (SAE), the Investigator must report the event using the SAE form to the Sponsor Global Vigilance Group (GVG), by contacting GVG by email: gvg@rb.com while copying in the contract research organisation (CRO) and Sponsor Project/Study Managers within 24 hours of knowledge of the event.

The out of hours emergency phone number is +44 (0)1482 326151.

This emergency phone number will be confirmed to the Investigator at the Study Initiation Visit.

All SAE Forms must be provided via email. Any inconsistencies in the information received from the Investigator will be clarified using the Adverse Event Data Clarification Form. The Investigator must retain a copy of all the SAE forms in the Investigator Site File.

The Investigator must inform their Institutional Review Board (IRB) of all SAEs occurring in the study within 7 days for fatal or life-threatening SAEs and 15 days for all other SAEs as per Sponsor instructions and as described in the Safety Management Plan.

The Investigator should not break the randomisation code except when it is necessary to do so in order to ensure the subject receives appropriate medical care.

SAEs and non-serious AEs will be reported to the appropriate regulatory authorities by the Sponsor in accordance with the authorities' requirements. The Sponsor is responsible for expedited reporting of all SUSARs/ SAEs to relevant authorities and IECs/IRBs as required by regulations. If the event requires expedited reporting, a CIOMS (Council for International Organizations of Medical Sciences) form will be produced and GVG will take actions as per the study specific Safety Management Plan.

8.4 Follow-up of Adverse Events

All SAEs and all AEs that have not resolved by the end of the study will be followed up by the Investigator until resolution or until the Investigator believes there will be no further change, whichever is the earlier. This may involve the subject making additional visits to the site.

If a subject has unresolved AEs requiring follow-up, investigators must attempt to contact subjects by telephone or other means.

8.5 Overdose, Abuse, Misuse and Medication Errors

The Sponsor defines “overdose” as the administration of a quantity of an investigational IMP given per administration or cumulatively, which is above the maximum recommended dose according to the authorised product information.

The Sponsor defines “abuse” as the persistent or sporadic, intentional excessive use of an IMP, which is intended to produce harmful physical or psychological effects e.g. intentional overdose to experience psychological effects.

The Sponsor defines “misuse” as situations where the IMP is intentionally and inappropriately used not in accordance with the authorised product information.

Overdoses, abuse, misuse are reportable to the Sponsor irrespective of the presence of an associated AE / SAE. The overdose, abuse, misuse and any associated AE / SAE will be captured on an AE CRF (Case Report Form) page / SAE form.

Due to the full inpatient nature of this study, in which medication doses will be supervised by site staff, cases of overdose, abuse or misuse are not expected to occur.

Medication errors are any unintentional errors in dispensing or administration of the IMP which relates to:

- Taking / being administered an incorrect IMP
- Taking / being administered a drug by the wrong route of administration e.g. swallowing a suppository
- The accidental administration of the IMP to a person who is not a subject within the study

Medication errors are reportable to the Sponsor irrespective of the presence of an associated AE / SAE. Medication errors with or without an associated AE / SAE will be captured on the AE CRF page / SAE form.

8.6 Pregnancy

Pregnancy both in a female subject or the female partner of a male subject is considered a collectable event and will be recorded as an AE in all cases. It will be qualified as an SAE only if it fulfils SAE criteria.

Due to the full inpatient nature of this study, pregnancy cases are not expected to occur during the study.

9 STATISTICAL CONSIDERATIONS

This section presents a summary of the planned statistical analyses. A statistical analysis plan (SAP) that describes the details of the analyses to be conducted will be written prior to database lock.

Summary statistics for continuous variables will typically include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, summary statistics will typically include the number and percentage of subjects in each category. All data will be presented in listings.

Baseline values are defined as the last measurements taken before dosing with study drug.

9.1 Determination of Sample Size

The sample size determination is based on the primary efficacy variable, SPID12. According to Farrar 2001[(1)], 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[(7)], 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 2×300-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 randomised into each of the PR and IR groups. Thus 280 subjects will be enrolled into the study.

9.2 Interim Analysis

No interim analysis is planned.

9.3 Analysis Datasets

The analysis populations include the following:

- The intent-to-treat (ITT) population will consist of all subjects who are treated with study drug and who have at least 1 pain relief assessment after Time 0. The ITT population is the primary population for the efficacy analysis.
- The per-protocol (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 utilized to evaluate the sensitivity of the primary efficacy analysis.
- The safety population will include all subjects who are treated with study drug. The safety population is the population for all safety assessments.

9.4 Subject Disposition and Characteristics

The numbers of subjects randomised, completing, and withdrawing, along with reasons for withdrawal, will be tabulated overall and by treatment group. The number of subjects in each analysis population will be reported. Demographic and baseline characteristics (including date of birth, sex, race, weight, height, BMI, medical history, and surgery duration) will be summarized for each treatment group and for the overall population using descriptive statistics. No formal statistical analyses will be performed.

9.5 Efficacy Analyses

The comparison of primary interest is between PR ibuprofen and placebo. In addition, the comparison between IR ibuprofen and placebo will be presented with p-values to demonstrate study sensitivity. Point estimates and 95% confidence intervals will be used to evaluate the clinical relevance of any differences between the PR and IR formulations. All treatment differences will be presented with 95% confidence intervals. No P value adjustment will be made for multiple endpoints or multiple comparisons. In the event of model assumptions for normality being violated, non-parametric methods will be used.

Each efficacy endpoint will be summarized descriptively by treatment group.

9.5.1 Primary Endpoint(s)

The primary endpoint, summed pain intensity difference (SPID) over 0 to 12 hours (SPID12), will be used to compare the test product (2×300 mg ibuprofen PR tablets) against the placebo product.

9.5.1.1 Primary Analysis

The primary efficacy null hypothesis is that SPID12 for placebo is equal to SPID12 for ibuprofen 2×300 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.

9.5.1.2 Secondary Analysis

The clinical relevance of the difference between placebo and PR ibuprofen over 12 hours after initial dose will be evaluated.

9.5.2 Secondary Endpoints

- The summed pain intensity difference (SPID) over 0 to 24 hours (SPID24) will be used to compare the test product (2×300 mg ibuprofen PR tablets twice daily [BID]) and comparator product (2×200 mg ibuprofen IR tablets three times a day [TID]).
- Summed pain intensity difference (SPID) over 0 to 4 hours (SPID4), over 0 to 8 hours (SPID8), and over 0 to 12 hours (SPID12) after Time 0
- 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 (a responder will be defined as a subject with ≥30% improvement in pain intensity without rescue medication during the first 8 hours)
- Numeric rating scale (NRS) pain intensity difference (PID) at each scheduled time point after Time 0
- Pain intensity score at each scheduled time point
- Pain relief score at each scheduled time point after Time 0
- Peak pain relief
- Time to onset of analgesia (measured as time to perceptible pain relief confirmed by time to meaningful pain relief) using double stopwatch
- 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

9.5.2.1 Secondary Endpoint Analyses

For continuous secondary endpoints such as pain intensity score, SPID at each scheduled time point, peak pain intensity, TOTPAR4, TOTPAR8, TOTPAR12, TOTPAR24, SPID4, SPID8, SPID24, SPRID4, SPRID8, SPRID12, and SPRID24, descriptive statistics (such as mean, standard deviation, median, minimum, and maximum) will be provided for each treatment regimen. P values from ANCOVA models comparing the placebo group with other treatment groups, including terms for treatment and a covariate for baseline pain will be provided for SPID, SPRID, and TOTPAR variables, but no formal statistical inferences will be drawn on the basis of these tests. In the event that normality assumptions are violated for a parameter, non-parametric analysis methods will be used.

For ordinal secondary endpoints, such as pain intensity difference at each scheduled time point, pain relief at each scheduled time point, peak pain relief, and global evaluation of study drug, descriptive summaries will be provided and will include the number and percentage of subjects within each category for each treatment group. Nominal P values from Fisher's exact tests (or chi-square tests, as appropriate) comparing the placebo group with other treatment

groups will be provided for peak pain relief and global evaluation of study drug, but no formal statistical inferences will be drawn on the basis of these tests.

For each time-to-event endpoint, Kaplan-Meier methodology will be used to evaluate the treatment effect. Time to onset of analgesia (measured as time to perceptible pain relief confirmed by meaningful pain relief) will be based on data collected using the double stopwatch method. Time to onset of analgesia will be right-censored at 8 hours for subjects who do not experience both perceptible pain relief and meaningful pain relief during the 8-hour interval after Time 0. The summary tables will provide the number of subjects analysed, the number of subjects censored, estimates for the quartiles, and 95% confidence intervals (CIs) for the estimated median and the restricted mean estimate. P values comparing placebo to active treatment from Wilcoxon or log-rank tests (as appropriate) will also be used to examine treatment effect.

For time to onset of analgesia, the comparison of interest will be the ibuprofen 2×300 mg PR group versus the ibuprofen 2×200 mg IR group. The summary table for this comparison will provide the number of subjects analysed, the number of subjects censored, estimates for the quartiles, and 95% confidence intervals (CIs) for the estimated median and the restricted mean estimate.

For the proportion of subjects who are responders and the proportion of subjects using rescue medication, logistic regression models that adjust for baseline intensity and/or significant demographic variables, if appropriate, will be used to evaluate the treatment effect.

For the responder analysis, subjects will be censored at 8 hours and for the use of rescue medication/time to first rescue subjects will be censored at 24 hours.

9.6 Safety Analyses

9.6.1 Safety Endpoint(s)

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

9.6.1.1 Safety Endpoint Analyses

Data listings will be provided for protocol-specified safety data. The Medical Dictionary for Regulatory Activities (MedDRA) (Version 19.0 or higher) will be used to classify all AEs with respect to system organ class and preferred term. Adverse event summaries will include only TEAEs, which will be summarized for each treatment group.

For vital sign measurements, descriptive statistics will be provided at each scheduled time point for each treatment group. Changes from Baseline for vital signs will be calculated for each subject, and descriptive statistics will be provided on changes in vital signs from Baseline for each treatment group at each scheduled time point after Baseline. No formal statistical tests will be performed.

9.7 Handling of Missing Data and Drop-outs

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.

The primary analysis will use windowed worst observation carried forward (WOCF) methodology for subjects who use rescue medication. Any pain measurements taken during a period of time in which rescue medication is active (4 hours) will be replaced by the last pain measurement before the rescue medication was taken. A sensitivity analysis will also be performed, in which all pain assessments recorded after the first dose of rescue medication has been taken will be disregarded and the rules outlined above will be used for missing data.

All data for assessments other than pain assessments will be analysed as collected; missing data due to premature termination or any other reason will be left as missing. In the event of a notable difference between treatment groups in the number of subjects using rescue medication, other sensitivity analyses may be performed. These will be detailed in the Statistical Analysis Plan (SAP).

9.8 Changes to the Original Statistical Plan

If there are any deviations to the proposed statistical analysis as described in this protocol these will either be documented in the final SAP or in a protocol amendment prior to database lock with the rationale and impact of the changes addressed.

10 DATA HANDLING AND RECORD KEEPING

10.1 Case Report Forms (CRFs)

Data will be recorded in an electronic Case Report Form (eCRF). For each enrolled study subject an eCRF is maintained. The Investigator or designees is responsible for the quality of the data record in the eCRF. eCRFs must be kept current to reflect subject status at each phase during the course of study. Subjects must not be identified in the eCRF by name or initials.

In the eCRF subjects will be identified by a subject number in combination with date of birth only, i.e., not by their name or initials. eCRF entries must be completed by appropriately trained site staff only. A log of trained and authorised staff able to complete the eCRF will be kept.

10.2 Specification of Source Documents

Source data must be available at the site to document the existence of the study subjects. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject. The investigator and study monitor will identify the data that will be recorded directly on the eCRF and for this data the eCRF will be considered the source document (i.e., no prior written or electronic record of the data). The study monitor will document this at the screening and it will also be documented in the Data Management Plan.

Source documents will include notes taken at the site and will include data such as demographic data, participation in study and ICF, medical history, SAEs, AEs and concomitant medication, results of examinations and assessments.

Where source data are in the form of a computer printout (e.g. medical records, laboratory data) they will be signed and dated by the investigator or designated person, confirming that the print out is a true and faithful record of the data for that subject. These print-outs will be filed in the study files.

The Investigator agrees to provide direct access to source data for study-related monitoring, audits, IRB review, and regulatory inspection(s). Direct access to source data requires that the subject gives written, documented consent to this.

10.3 Data Management

The data management group at Premier Research will be responsible for data management and eCRF activities.

Full details regarding data management will be described within the Data Management Plan.

10.4 Reporting of Protocol Deviations

Site staff should make the study monitor aware of any deviation from the protocol as soon as possible after occurrence. Waivers for inclusion / exclusion criteria are not allowed.

10.5 Retention of Essential Documentation

The Investigator should retain all essential documents (as defined in ICH E6 or according to other national and international regulations) until at least 5 years after the completion of the study (defined as last subject last visit in the study). These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

Subject files and other source data must be kept for the maximum period of time permitted by the Clinical Unit. The Investigator must notify the Sponsor of the retention period if this is shorter than described above.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Monitoring

The Sponsor will organise regular monitoring visits to be performed at intervals agreed with the Investigator. The anticipated monitoring frequency will be stated in the Monitoring Plan. Monitoring will also involve, as appropriate, correspondence and telephone contacts.

On-site monitoring includes source data verification (SDV) which is the procedure whereby the data contained in the eCRFs are compared with the primary source data and thereby verified as accurate. It will be performed in such a way as to preserve subject confidentiality, taking into account all ethical and legislative requirements.

The Investigator, or a designated member of the Investigator's staff, must be available at some time during the monitoring visit to review the data and resolve any queries and to allow direct access to the subject's records for SDV).

SDV will include as a minimum verification for all subjects, subject identity (date of birth, sex, initials and subject number), record of entry into the study and signature of the informed consent. In addition, details of SAEs in the subject's notes will be verified. Details included in the subject's notes as a minimum:

- Study number, brief description or title of study
- Date that the subject gave written consent
- All visit dates
- All SAEs
- All concomitant medications

At a site visit the eCRFs should be complete and available in order that the accuracy of their completion may be checked. Each completed eCRF for each subject must be signed electronically by the Investigator, to verify the data and statements submitted. Similarly, all alterations on paper records must be initialled and dated by the Investigator or a designated person, explained as necessary, with the original mistake left legible.

11.2 Audits and Inspections

For the purpose of ensuring compliance with the protocol, ICH GCP and applicable regulatory requirements, clinical studies sponsored by RB may be subject to an independent audit at the study site which will be conducted by personnel from an appropriate Quality Assurance Unit. Full consultation with the Investigator will be made prior to and during such audit, which will be conducted according to Quality Assurance Unit Standard Operating Procedures.

As soon as the Investigator is notified of a planned inspection by a Regulatory Authority, he / she must inform the Sponsor promptly and allow the Sponsor to participate in the inspection as permitted by applicable regulations and local laws.

11.3 Sponsor Policy on Fraud in Clinical Studies

In accordance with GCP, it is the Sponsor's policy to always follow-up suspected cases of fraud.

12 ETHICAL AND REGULATORY ASPECTS

12.1 Ethics Review and Regulatory Authority Approval

Written approval to conduct the study by an independent and appropriately constituted IRB must be obtained and a copy provided to the Sponsor before any protocol-related procedures that do not form part of the subject's normal clinical treatment are performed. The approval letter must contain:

- Name and address of the IRB.
- Date of meeting.
- Sufficient information to identify the version of the Protocol and subject information/informed consent.
- Sufficient information to identify the version of other documents reviewed.

The investigator must also provide the Sponsor with a list of IRB members that includes each member's name and profession.

Any amendments to the Protocol must be submitted to the IRB for approval unless where necessary to eliminate apparent immediate hazards to study subjects, and any administrative changes must be notified.

This study will be submitted to the applicable Regulatory Authorities. The study will only be undertaken when regulatory authorisation has been obtained by the Sponsor.

The Sponsor will notify the Regulatory Authority within 90 days of the end of the study (within 15 days if the study is terminated prematurely).

Premier Research will notify the IRB within 90 days of the end of the study (within 15 days if the study is terminated prematurely).

12.2 Subject Information and Consent

Informed consent should be obtained by means of a patient information sheet and ICF, prepared in accordance with ICH E6 (R2) section 4.8.10 and the applicable local regulations, written in a non-technical language. All subjects will be provided with oral and written

information describing the nature and duration of the study and the procedures to be performed. The subject will be asked to sign and date an ICF prior to any study-specific procedures being performed. No subject can enter the study before his/her informed consent has been obtained. A sample subject ICF used in the study will be included in the clinical study report for this protocol.

As part of administering the informed consent document, the Investigator must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician. The subject should understand the study, patient information sheet, and ICF before signing and dating the ICF. The Investigator or person obtaining consent must also sign and date the form. Each subject will be given a copy of the signed informed consent and written information.

12.3 Early / Premature Termination of the Study

In the unlikely event that this study generates an excessive frequency of adverse events, subjects' termination or suspension may be requested by the sponsor or the IRB or the Regulatory Authority.

The sponsor retains the right to terminate the study for non-safety reasons by giving an appropriate period of notice to all involved parties as per contractual agreements.

Any decisions to terminate or suspend the study will be notified in writing to the Investigator or designees, the IRB, Regulatory Authority and the clinicaltrials.gov database.

If the study is terminated early, study subjects who have attended screening will be informed that they are no longer required and if they have any questions, they should consult the study site staff. For subjects who have completed the study they will not be informed that the clinical study has been terminated. All data collected up to the point of study termination will be used in an abbreviated Clinical Investigation Report.

13 COMPENSATION, INDEMNITY AND INSURANCE

13.1 Clinical Study Agreement

Before the study commences, a contract between the Sponsor and Premier Research, who contracts with the Investigator, will be signed in which financial aspects of the study (including financial disclosure) as well as responsibilities and obligations are described.

13.2 Compensation

The Sponsor and the CRO carry insurance to pay compensation for injury, accident, ill health and death caused by participation in this study without regard to proof of negligence in

accordance with the current local regulations and requirements. Details on finance and insurance will be provided in a separate agreement between the investigator and the sponsor.

13.3 Indemnity

The Sponsor will provide appropriate indemnity for the Investigator and staff who conduct part or all of this study, upon request. The request must be received before the first subject is recruited.

13.4 Insurance

If required and in accordance with applicable regulatory and legal requirements, the Sponsor will take out appropriate insurance policies on behalf of the Investigator and staff who conduct part or all of this study and/or on behalf of the subjects participating in the study.

14 REPORTING, PUBLICATION AND PRESENTATION

A clinical study report will be prepared according to ICH E3 (Structure and Content of Clinical Study Reports) as part of the Sponsor's commitment to Good Clinical Practice. The report will be a record of the total study conduct and findings and will be subject to approval by the Investigator who will sign the final report.

The study data will be owned by the Sponsor. The Sponsor retains the right to publish the data independently of the Investigator. The Sponsor agrees that before it publishes the results, it will provide the Investigator with at least 30 days for full review prior to submission of the manuscript to the publisher. The Investigator must submit any proposed manuscript to the Sponsor for approval prior to submission for publication.

15 REFERENCES

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