Study Title: A Randomized, Double Blind, Placebo-Controlled, Parallel Group, Dose-Response Study of Meloxicam Co-Crystal in The Treatment of Post-Surgical Dental Pain

Protocol Number: MECC-TBZ-2001

Document: Protocol Version 5.0

Dated: September 15, 2020

NCT04571515

MECC-TBZ-2001 CLINICAL STUDY PROTOCOL

Protocol Title	A Randomized, Double Blind, Placebo-Controlled, Parallel Group, Dose-Response Study of Meloxicam Co-Crystal in The Treatment of Post-Surgical Dental Pain.
Protocol Number	MECC-TBZ-2001
Product	Meloxicam [Co-crystal of Meloxicam: Salicylic acid (1:1)]
Study Type	Phase 2b
Version	Version 5.0 15 September 2020
Protocol Date	Original Date 28 March 2020 Revision Dates 11 May 2020 25 June 2020 11 September 2020 15 September 2020
Registry Name	ClinicalTrials.gov
IND Number	[redacted]
Legal/Filing Sponsor	Mylan Inc. 1000 Mylan Blvd, Canonsburg, Pennsylvania 15317, United States

DOCUMENT HISTORY

Document Version, Date	Summary of Changes with Rationale
Version 1.0 28 Mar 2020	N/A
Version 2.0 11 May 2020	[redacted] Exclude subjects <18 years of age. Addition of specific questioning of subjects regarding GI adverse events during the study and follow up period. Clarification of double dummy design for drug blinding.
Version 3.0 25 June 2020	[redacted] Exclude subjects taking strong inhibitors and inducers of CYP2C9.
Version 4.0 11 September 2020	Including the measurement of salicylic acid in the PK samples. [redacted] Include text confirming that the dental surgery and related anesthesia, sedation, and prophylactic antibiotics are not investigational and will occur regardless of research. [redacted] Include a vital signs assessment prior to surgery. Adapt the order of procedures that will not impact outcomes to fit with clinic preferred process.
Version 5.0 15 September 2020	Due to discontinuation of hydrocodone/acetaminophen 5/500 mg tablets, the rescue medication has been changed to 5/325 mg tablets.

PROTOCOL SYNOPSIS

Protocol Title	A Randomized, Double Blind, Placebo-Controlled, Parallel Group, Dose-Response Study of Meloxicam Co-Crystal in The Treatment of Post-Surgical Dental Pain.
Protocol Number	MECC-TBZ-2001
Study Sites	The study is planned to be conducted at 1 study site.
Study Period Planned	The study is planned to be conducted over a period of approximately 3 months.
Duration of Individual Treatment	The duration from screening to follow up is expected to be approximately 1.5 months. Subjects will be dosed with study drug on Day One.
End of Study	End of study is defined as last subject, last visit.
Background and Rationale	The effective treatment of pain is important to both patients and to wider society; inadequately controlled pain negatively affects quality of life and function, and in a post-surgical environment, it affects the functional recovery, the risk of post-surgical complications, and the risk of persistent postsurgical pain. Finding alternatives to opioids, can expand safe and effective options in pain management to meet this important public health need and help to reduce the public health burden from adverse outcomes related to prescribed opioids. Meloxicam is a member of the non-steroidal anti-inflammatory drugs (NSAIDs) group of medications that exhibit anti-inflammatory and analgesic activity in clinical studies. NSAIDs have demonstrated efficacy for the treatment of acute pain, however current oral formulations of meloxicam are not suitable for the treatment of acute pain due to a relatively slow absorption. In contrast, an IV formulation of meloxicam has recently demonstrated efficacy in models of acute pain. Meloxicam [Co-crystal of Meloxicam: Salicylic acid (1:1)] (hereafter MECC-SA) is being developed to provide a rapid absorption of meloxicam from an oral dose. This is the first assessment of efficacy of MECC-SA in subjects with acute pain; however, it is anticipated to provide analgesia to these subjects due to the rapid absorption demonstrated in Study [redacted] The efficacy dose-response profile of MECC-SA is currently unknown and the purpose of this study is to establish an understanding of the dose-response relationship for this formulation. The dental pain model is considered an ideal model of post-surgical acute pain as it has high assay sensitivity and is highly predictive of efficacy in later stage models. It is also ideal as the surgery, the anesthetic regimen, and perioperative

	care protocols can be standardized across patients. The dental surgical model has demonstrated the efficacy of analgesic medications across a range of different pharmacology, including NSAIDs and opioids and, more specifically, has demonstrated efficacy for an IV formulation of meloxicam.
Primary Objectives	To evaluate the efficacy and safety of MECC-SA in subjects following dental surgery and to establish the dose-response relationship.
Primary endpoints	Overall (summed) pain intensity difference (SPID) over 0-24 hours.
Secondary Objectives	N/A
Secondary Endpoints	Efficacy • Overall (summed) pain intensity difference (SPID) over 0-2 hours, 0-4 hours, 0-8 hours, 0-12 and 12-24 hours after initial dose of study drug. • Pain intensity difference (PID) over time. • Total pain relief (TOTPAR) over 0-2 hours, 0-4 hours, 0-8 hours, 0-12 hours, 12-24 hours, and 0-24 hours. • Time to perceptible relief (as measured by double-stopwatch technique) after first dose. • Time to meaningful pain relief (as measured by double-stopwatch technique) after first dose. • Proportion of subjects with overall pain reductions from baseline of ≥30% and ≥50% within 4 hours following the first dose. • Patient's global assessment (PGA) of pain control from 0-24 hours. • Elapsed time from the start of study medication to first rescue medication administration. • Proportion of subjects using rescue medication from 0-24 hours. • Number of times rescue medication used from 0-24 hours. Safety • Adverse Events. • Laboratory safety tests. • ECGs. • Vital signs. PK • Population PK parameters for meloxicam and salicylic acid (C_{max},

	$pAUC_{0-4}$ and $pAUC_{0-24}$).
Methodology	This will be a randomized, double-blind, placebo-controlled, parallel group, dose-response study, randomizing approximately 110 male or female subjects who have had dental surgery (removal of ≥2 third molars) performed. Subjects will receive study drug on Day 1. The study design is consistent with research design recommendations of the IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) group for trials involving subjects with short-duration acute pain. Subjects will attend screening at Visit 1, to occur within 30 days prior to the planned dental surgery. The subjects will have the operation performed on Day 1 using appropriate local anesthesia and sedation (performed using nitrous oxide and a local injection of lidocaine with epinephrine). Subjects will also receive prophylactic antibiotics post-surgically. Pain Intensity (PI) (using a 0-10-point numeric pain rating scale (NPRS) where 0 is no pain and 10 is the worst pain imaginable) will be assessed during the 5 hours following surgery. If the subject scores a NPRS ≥5 and a rating of moderate or severe pain on a 4-point categorical pain rating scale (i.e., none, mild, moderate, severe) during this time they will be eligible for randomization. A diary will be used to record the pain scores. Subjects will be randomized to receive either MECC-SA (10 mg QD, 15 mg QD, 10 mg BID or 15 mg BID) or placebo. Dosing of study medication must be within 15 minutes of the eligible pain score. PI scores (NPRS) will be measured at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 14, 16, 20 and 24 hours after the first dose of study medication, as well as immediately before any rescue medication and/or at the time of early termination. Pain relief assessment (using a 5-point scale - none = 0, slight = 1, moderate = 2, good or a lot = 3, and complete = 4) will be measured at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 14, 16, 20 and 24 hours after the first dose of study medication, as well as immediately before any rescue medication and/or at the time of early termination. A Patient Global Assessment (PGA) of pain control will be made at 24 hours post dose, rated on a 5-point scale, ranging from 0 to 4, where 0-poor, 1-fair, 2 good, 3-very good, or 4-excellent and/or at the time of early termination. The times to first perceptible relief and meaningful pain relief will be determined using the double-stopwatch technique. The time to onset of first perceptible relief (time that the first watch is stopped) is defined as the post dose time at which the subject first begins to feel pain relief. The time to meaningful pain relief (time that the second watch is stopped) is defined as the post dose time at which the subject begins to feel meaningful pain relief. Rescue medication of immediate release hydrocodone/acetaminophen will be allowed at any time, but subjects will be encouraged to wait until at least 1 hour post-dose if possible. A PI score assessment will be made immediately prior to

	any rescue medication. PK samples will be taken pre-dose and 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 14, 16, 20 and 24 hours after the first dose at Day 1. Subjects will be discharged from the clinic following the 24-hour assessments; if the subject requires a longer duration of in-patient assessment due to reasons associated with the surgery this is acceptable. A final follow up telephone call will occur approximately 5 days after the last dose of study drug administration. Safety will be assessed via recording of AEs, safety laboratory testing and pre- and post-dose 12-lead ECGs and vital signs. Adverse events of special interest will include those related to gastrointestinal (GI) AEs, particularly bleeds and those related to serious cardiovascular (CV) events. Unless consent is withdrawn, subjects who prematurely terminate study drug will have discharge procedures performed at that time or at an early termination (ET) visit scheduled as soon as possible.
Study Treatment	Treatments to be received during the study will include one of the following treatment arms: 1. MECC-SA 15 mg QD. 2. MECC-SA 10 mg QD. 3. MECC-SA 15 mg BID. 4. MECC-SA 10 mg BID. 5. Placebo BID. To maintain the blind due to differences in appearance between the tablets, subjects will receive in a double dummy design, two tablets when dosed (one that is representative of a 10 mg tablet and one that is representative of a 15 mg tablet). Due to the double dummy design, neither the subject, nor the Investigator will know what treatment a subject receives. To maintain the blind between QD and BID arms, subjects assigned to QD arms will receive placebo at the second dose. Per the clinic procedures, subjects will also be blindfolded during dosing.
Inclusion/ exclusion criteria	**Inclusion criteria** 1. Males and females ≥18 years of age. Females may be of either childbearing or non-childbearing potential. All females of childbearing potential must be using an acceptable, highly effective method of contraception and have a negative serum pregnancy test at screening. 2. Requirement for dental surgery for extraction of ≥2 x third molars, at least 1 of which involves partial or complete mandibular bony impaction. 3. Pain Intensity (PI) using a Numeric Pain Rating Scale (NPRS) ≥5 during

	the 5 hours following the end of surgery. 4. Rating of moderate or severe pain on a 4-point categorical pain rating scale (i.e., none, mild, moderate, severe) during the 5 hours following the end of surgery. 5. Able to understand and complete the study requirements (including literacy, to enable diary and questionnaire completion), provide written informed consent, and agree to abide by the study protocol and its restrictions. **Exclusion Criteria** 1. Previously dosed with MECC-SA. 2. Subject with known hypersensitivity to aspirin, NSAIDs or other medication used in the study. 3. Subjects with known hypersensitivity to items used in surgery. 4. Known active GI bleeding or a history of peptic ulcer disease. 5. Known active inflammatory bowel disease, e.g., Crohn's Disease or ulcerative colitis. 6. A history of bleeding disorders that may affect coagulation. 7. A clinically significant history of respiratory insufficiency, hypotension, bradycardia, migraine, frequent headaches, seizures, renal, hepatic, cardiovascular metabolic, neurologic or psychiatric disease in the opinion of the Investigator. 8. History of Hepatitis B or C or HIV infection. 9. History of alcohol or drug abuse within the last 5 years prior to the study. 10. History of myocardial infarction or coronary artery bypass graft surgery within the 12 months prior to the study. 11. Clinically significant abnormality on the 12-lead ECG at screening which in the judgment of the investigator would put the subject at potential risk if enrolled into the study (these subjects should not be re-screened). Clinically significant abnormalities may include but are not limited to the following: left bundle branch block, Wolff-Parkinson-White syndrome, clinically significant arrhythmias (e.g., ventricular tachycardia). 12. History of long QT syndrome or screening ECG with QTcF >470 milliseconds for female or >450 milliseconds for male subjects. 13. Current evidence of, or history within the 6 months prior to screening of unstable ischemic heart disease, NYHA Class II-IV right or left ventricular failure. 14. History of malignancy of any organ system treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or

	metastases. The only exceptions are previous in situ carcinoma of the cervix, localized basal cell carcinoma of the skin or localized squamous carcinoma of the skin if the subject has been treated and is considered cured. 15. Use of any investigational drug within 28 days, or 5 half-lives, prior to screening whichever is longer. 16. Use of medications with the potential to interact with MECC-SA (as indicated in the current Investigator's Brochure), or medications required during the study such as local anesthesia or sedatives, or medications with the potential to affect or confound pain status during the study. This includes (but not limited to) use of any of the following medications: • Strong CYP2C9 inhibitors or inducers within 28 days or 5 half-lives (whichever is longer) prior to the study. • Long-term opioid use (>30 consecutive days in the past year) and/or use of extended release opioids within 30 days of the dental extraction. • Antiepileptic drugs within 28 days prior to the study. • Tricyclic anti-depressants, monoamine oxidase inhibitors, or SNRIs within 28 days prior to the study. • Sedative or hypnotic drugs within 28 days prior to the study (other than the nitrous oxide used during the operation). • Use of "medical" or recreational marijuana within 28 days prior to the study. • Warfarin within 28 days prior to the study. • Apixaban within 28 days prior to the study. • Lithium within 28 days prior to the study. • Methotrexate within 28 days prior to the study. • Calcineurin inhibitors (e.g., cyclosporine and tacrolimus) within 28 days prior to the study. • Pemetrexed within 28 days prior to the study. • Combination of diuretic with ACE inhibitor or angiotensin receptor blocker within 28 days prior to the study. • Gabapentin or pregabalin within 28 days prior to the study. • Cholestyramine within 7 days prior to the study. • Meloxicam within 7 days prior to the surgery.

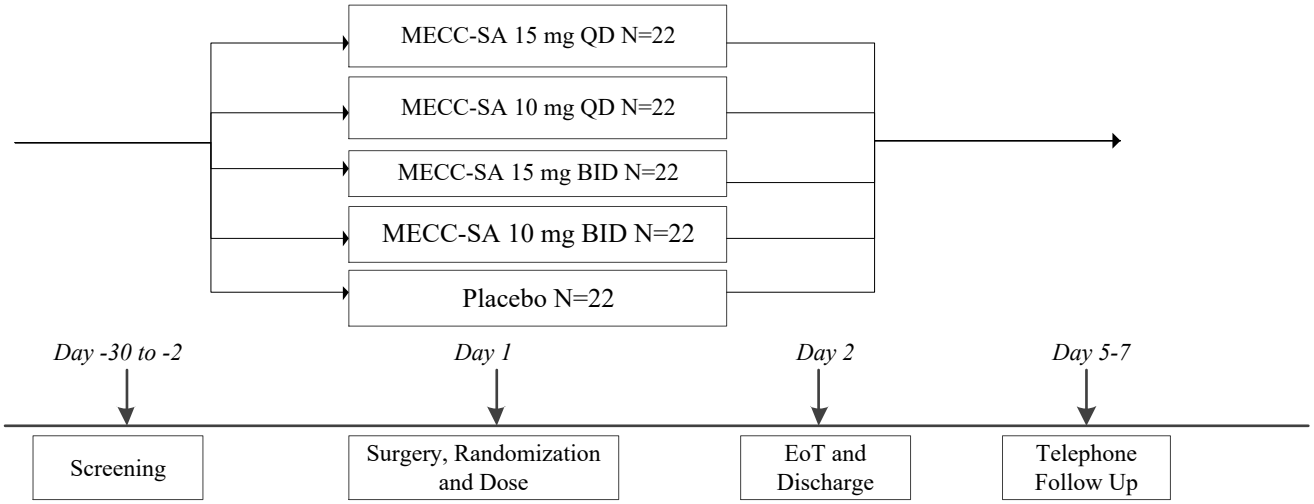
	• Aspirin within 7 days prior to the surgery. • Analgesics (including opioids, acetaminophen and NSAIDs) within 24 hours prior to the surgery. 17. Inability to refrain from any of the following medications pre-, intra-, or post-surgery: • Systemically administered corticosteroids. • Epidural or spinal anesthetics. • General anesthesia. • Analgesia other than those pre-specified for breakthrough pain relief. 18. BMI >35 kg/m^2. 19. Pregnant or nursing females or females intending to become pregnant during the course of the study. 20. Serum creatinine >1.5 x Upper Limit of Normal. 21. Serum ALT, AST, or bilirubin >2 x Upper Limit of Normal. 22. Clinically significant abnormal laboratory test(s) at screening deemed exclusionary by the Investigator. 23. Signs or symptoms of an infection or a fever that would increase the risk of surgery. 24. Other acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
Planned Number of Subjects	N=110 subjects (N=22/treatment arm) to give approximately N=100 evaluable subjects for the primary endpoint (N=20/treatment arm).
Statistical Methods	The primary efficacy endpoint is the overall (summed) pain intensity difference over 0-24 hours (SPID 0-24). [redacted]

	[redacted] [redacted] To analyze the primary endpoint, a 3-parameter E_{max} model will be fitted to the SPID 0-24 standardized means (observed mean for each dose and placebo divided by the pooled standard deviation) for placebo and 10 mg QD, 15 mg QD, 10 mg BID and 15 mg BID MECC-SA. Standardized effect sizes will be estimated from the E_{max} model together with their 95% confidence intervals and p-values. Baseline pain intensity score (PI) will be used as a covariate in the E_{max} model. The numerical dose values will be 10, 15, 20, 30 and 0 for 10 mg QD, 15 mg QD, 10 mg BID, 15 mg BID and placebo respectively. Additional models may be explored utilizing a Multiple Comparison Procedure – Modeling (MCP-Mod) approach. If the E_{max} model fails to converge, and no other suitable models are identified using MCP-Mod, an Analysis of covariance (ANCOVA) will be used to assess the difference between treatment groups for SPID 0-24. The ANCOVA model will include treatment and study site as fixed effects and baseline PI score as a covariate. The difference between MECC-SA and placebo will be estimated from the least squares means (LS means) along with the 95% confidence interval (CI) and associated 2-sided p-values. In addition, the standardized effect sizes for each dose will be calculated by dividing the differences in LS means for each dose and placebo by the pooled standard deviation. PK parameters for meloxicam and salicylic acid (C_{max}, $pAUC_{0-4}$, $pAUC_{0-24}$) will also be calculated.

STUDY DIAGRAM AND STUDY SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to the Study Conduct Section (6) for detailed information on each procedure and assessment required for compliance with the protocol.

Figure 1: Study Diagram



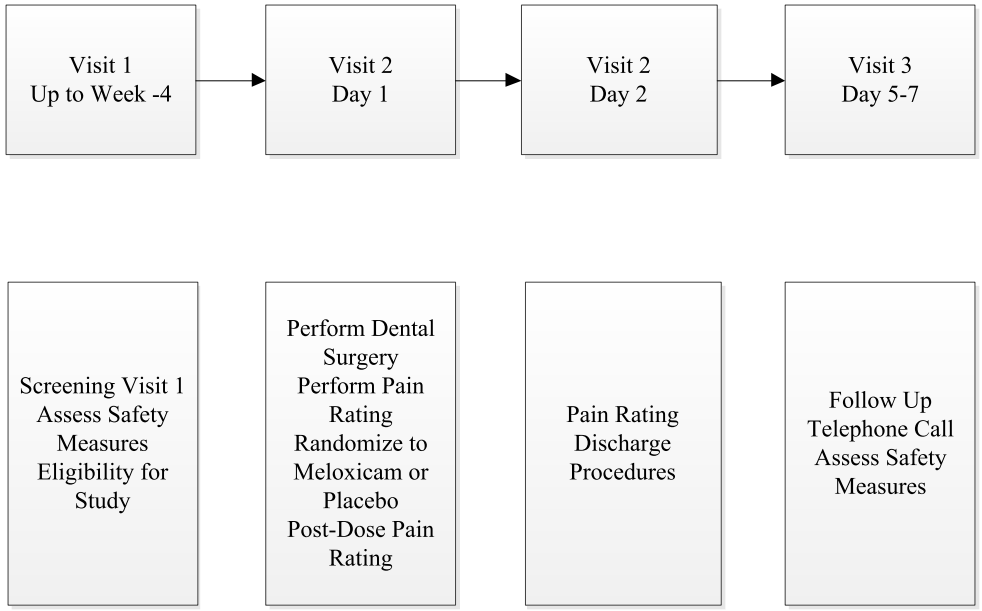

Visit 1
Up to Week -4
Visit 2
Day 1
Visit 2
Day 2
Visit 3
Day 5-7
Screening Visit 1
Assess Safety Measures
Eligibility for Study
Perform Dental Surgery
Perform Pain Rating
Randomize to Meloxicam or Placebo
Post-Dose Pain Rating
Pain Rating
Discharge Procedures
Follow Up Telephone Call
Assess Safety Measures

Table 1: Study Schedule

VISIT	1 (Screen)	2 (In-clinic)	2 (In-clinic)	Follow up Telephone Call
DAY	-30 to -2	1	2	5-7
Written informed consent	X			
IVRS/IWRS registration	X			
Demography and medical history	X			
Review concomitant medications	X	X	X	X
General physical examination[1]	X		X[15]	
Height	X			
Weight	X			
Temperature		X[2]		
Vital Signs (supine/semi-recumbent blood pressure, pulse rate)	X	X[3]	X[15]	
12-lead ECG (supine/semi-recumbent)	X	X[4]	X[15]	
Serum or urine pregnancy test[5]	X	X[2]	X[15]	
Urinalysis[6]	X		X[15]	
Urine drug screen	X	X[2]		
Blood safety labs (hematology, chemistry) including FSH (V1)[7]	X		X[15]	
PK Sample[8]		X	X	
Diary training		X[2]		
Review AEs[9]	X	X	X	X
Inclusion/exclusion criteria	X	X		
Dispense diary for pain assessment recordings		X		
Subject records AEs at home	X			X
Subject records AEs in the clinic		X	X	
Perform dental surgery		X		
Pain Assessments (Pain Intensity, Categorical Pain Rating) (prior to randomization)		X[10]		
Randomize to study via IVRS/IWRS		X		
Dispense study drug		X[11]		
Administer study drug (within 15 minutes of eligible pain assessments)		X[12]		
Administer study drug (12 hours after first dose)		X		
Pain Intensity Assessments (post-randomization)		X[13]	X[13]	
Pain Relief Assessments (post-randomization)		X[13]	X	
Patient Global Assessment of Pain Control			X[14]	
Record Rescue Medication Use		X	X	X

[1] Including respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurological systems, lymph nodes, skin, extremities, head, ears, eyes, nose, and thyroid gland.

[2] Prior to surgery.

[3] Vital signs (blood pressure and pulse rate) are taken prior to surgery, pre-dose and 24 hours post-dose performed after ECG measurements taken at the same nominal time.

[4] 12-lead ECG will be performed both pre-dose and 24 hours post-dose as single measures.

[5] Serum pregnancy test at screening, urine at other visits.

[6] Urinalysis for blood, protein, nitrites, leukocyte esterase, pH, glucose and ketones. If positive for blood, protein, nitrites or leukocytes esterase a sample for microscopy/culture should be analyzed by the central laboratory.

[7] FSH to be measured in females who have been amenorrheic for at least 2 years, to confirm non-child bearing potential.

[8] PK sample taken pre-dose and 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 14, 16, 20 and 24 hours after the first dose of study medication.

[9] All AEs will be recorded from time of consent until the telephone follow up/End of Study (EOS) Visit. The Investigator is also responsible for notifying the sponsor if they become aware of any AE after the study period has ended and it is considered related to the study medication. When assessing AEs, the subject will be specifically asked regarding the presence of any GI symptoms.

[10] Pain assessments (Pain Intensity and Categorical Pain Rating) performed for up to 5 hours post completion of surgery. Subjects with NPRS ≥5 and a rating of moderate or severe pain on a 4-point categorical pain rating scale (i.e., none, mild, moderate, severe) during this time they will be eligible for randomization.

[11] Drug is dispensed at ‘time zero’ and 12 hours later.

[12] Dosing of study medication must be within 15 minutes of the eligible pain assessments.

[13] Post-dose pain assessments made at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 14, 16, 20 and 24 hours after the first dose of study medication, and immediately before any dose of rescue medication. Assessments will also be made immediately following the time of first relief and time of meaningful relief.

[14] Patient’s Global Assessment of Pain Control measured at 24 hours post-dose, or at time of early termination if applicable.

[15] Procedures performed after the final pain assessment (24 hours post-dose).

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Table 2: List of Commonly Used Abbreviations

AE	Adverse event
ACE	Angiotensin Converting Enzyme
ALT	Alanine transaminase
ANOVA	Analysis of variance
AST	Aspartate transaminase
AUC	Area Under the Curve
BID	Twice Daily
BMI	Body Mass Index
BP	Blood Pressure
bpm	Beats per minute
cm	Centimeter
C_{max}	Maximum plasma concentration
CRF	Case Report Form
COX	Cyclooxygenase
CRO	Contract Research Organization
CV	Cardiovascular
CV	Coefficient of Variation
ECG	Electrocardiogram
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
GM	Geometric Mean
HIV	Human Immunodeficiency Virus
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
kg	Kilogram
LOCF	Last Observation Carried Forward
LS mean	Least Squares mean
MAR	Missing At Random
mFAS	Modified Full Analysis Set
MI	Missing imputation

mg	Milligram
NYHA	New York Heart Association
INN	International Non-proprietary Name
ITT	Intent To Treat
IVRS/IWRS	Interactive Voice Response System/ Interactive Web Response System
MECC-SA	Meloxicam [Co-crystal of Meloxicam: Salicylic acid (1:1)]
mL	Milliliter
mmHg	Millimeter of mercury
MMRM	Mixed Model Repeated Measures
MNAR	Missing Not At Random
ms	Millisecond
NSAID	Non-Steroidal Anti-Inflammatory Drug
NPRS	Numeric Pain Rating Scale
pAUC	Partial Area Under the Curve
PGA	Patient Global Assessment
PI	Pain Intensity
PK	Pharmacokinetic
PPAS	Per Protocol Analysis Set
PR	Pulse Rate
prn	*pro re nata*
QC	Quality Control
QD	Once Daily
QTc	QT corrected
QTcF	QT corrected (Fredericia's correction)
RoW	Rest of World
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SID	Subject Identification
SOP	Standard Operating Procedure
SPID	Summed Pain Intensity Difference
T½	Half life
T_{max}	Time of maximum concentration
TOTPAR	Total pain relief
US	United States
WoCBP	Women of Childbearing Potential

1 INTRODUCTION

1.1 Indication

Acute, post-operative pain.

1.2 Background and Rationale

The effective treatment of pain is important to both patients and to wider society; inadequately controlled pain negatively affects quality of life and function, and in a post-surgical environment, it affects the functional recovery, the risk of post-surgical complications, and the risk of persistent post-surgical pain [1].

Opioids have been used to treat many forms of pain in the USA, sometimes unnecessarily or inappropriately, leading to extensive misuse of these powerful medications and culminating in the current health crisis. It is estimated that 115 Americans die every day from opioid induced overdoses and that in 2015 alone, the cost to the US economy of the opioid epidemic was $504 billion [2], with a drug overdose rate in 2015 of 16.3 per 100,000 [3], increasing to 21.7 per 100,000 in 2017 [4]. Clearly the misuse of opioids has a huge impact both on individual patients and their families but also on the wider society. The Centers for Disease Control have also determined through a meta-analysis that opioid therapy prescribed to treat acute pain is associated with a greater likelihood of long-term opioid use [5]. Therefore, reducing opioid use or replacing opioids with alternative drugs would be advisable. Advice from groups such as Washington State Agency Medical Directors' Group is that post-surgical use of opioids should be avoided where possible with alternative drugs offered as analgesia or minimized [6].

Alternatives to opioids can expand safe and effective options in pain management to meet this important public health need and help to reduce the public health burden from adverse outcomes related to prescribed opioids.

Meloxicam is a member of the non-steroidal anti-inflammatory drugs (NSAIDs) group of medications that exhibit anti-inflammatory, anti-pyretic and analgesic activity in clinical studies. Non-steroidal anti-inflammatory drugs have demonstrated efficacy for the treatment of chronic inflammatory conditions such as rheumatoid arthritis, osteoarthritis [7] and acute pain [8]; [9]. NSAIDs are currently recommended by the American College of Rheumatology for the treatment of osteoarthritis [10] and have indications for the treatment of rheumatoid arthritis (RA); however, most recent treatment guidelines for RA have focused on disease modification rather than analgesia [11]; [12]. NSAIDs are considered generally safe for short-term use with the following exceptions: patients with NSAID-exacerbated respiratory disease, patients with prior myocardial infarction who are receiving antithrombotic therapy, patients with asthma, and patients with a history of renal disease [13].

The apparent primary mechanism of action of meloxicam, and of other NSAIDs, is the reduction of prostaglandin (PG) production through its inhibitory activity against

cyclo-oxygenase (COX-1 and COX-2) [14]. Meloxicam is currently approved in oral formulations in USA as a treatment for chronic diseases: osteoarthritis, rheumatoid arthritis, and juvenile rheumatoid arthritis pauciarticular and polyarticular course (at the 7.5 mg dose only in children that weigh ≥60 kg). An IV formulation of meloxicam is currently approved in USA for the management of moderate-severe pain.

Meloxicam is available in tablet form; (MOBIC® [Boehringer Ingelheim] and various generic forms and QMIIZ® orally disintegrating tablets [Tersera Therapeutics]) and in capsule form (VIVLODEX® [Iroko Pharmaceuticals]). MOBIC is approved at doses of 7.5 and 15 mg once per day and VIVLODEX is approved at doses of 5 and 10 mg once per day. Meloxicam has been extensively studied in humans as MOBIC and VIVLODEX in chronic pain indications, including osteoarthritis and rheumatoid arthritis. Meloxicam has also recently been approved by US FDA in an intravenous formulation as ANJESO® (Baudax Bio, Inc) at a dose of 30 mg for the management of moderate-severe pain.

Based on the demonstration that meloxicam is effective for the treatment of chronic pain such as osteoarthritis at doses of ≥7.5 mg/day and that this effect is mediated by inhibition of cyclooxygenase, a concentration of approximately 1090 ng/mL, which is similar to the steady state concentration of 7.5 mg meloxicam, would be considered sufficient for mediating an analgesic response [15]. E*x vivo* assays performed on samples taken from subjects receiving 7.5 mg meloxicam have demonstrated an 83% inhibition of COX-2 [15].

Gastrointestinal (GI) AEs were the most frequently reported AEs in all treatment groups across MOBIC trials, reflective of the safety profile of meloxicam. The most commonly reported AEs in both short-term and long-term studies of MOBIC in osteoarthritis are summarized in Table 3.

Table 3: Adverse Events (%) Occurring in ≥2% of MOBIC Patients in 4 to 6 Weeks and 6 Month Active-Controlled Osteoarthritis Trials

	4 to 6 Weeks Controlled Trials		6 Month Controlled Trials	
	MOBIC 7.5 mg Daily	**MOBIC 15 mg Daily**	**MOBIC 7.5 mg Daily**	**MOBIC 15 mg Daily**
No. of Patients	8955	256	169	306
Gastrointestinal	11.8	18.0	26.6	24.2
Abdominal pain	2.7	2.3	4.7	2.9
Constipation	0.8	1.2	1.8	2.6
Diarrhea	1.9	2.7	5.9	2.6
Dyspepsia	3.8	7.4	8.9	9.5
Flatulence	0.5	0.4	3.0	2.6
Nausea	2.4	4.7	4.7	7.2
Vomiting	0.6	0.8	1.8	2.6
Body as a Whole				
Accident household	0.0	0.0	0.6	2.9
Edema (a)	0.6	2.0	2.4	1.6
Pain	0.9	2.0	3.6	5.2
Central and Peripheral Nervous System				

	4 to 6 Weeks Controlled Trials		6 Month Controlled Trials	
	MOBIC 7.5 mg Daily	MOBIC 15 mg Daily	MOBIC 7.5 mg Daily	MOBIC 15 mg Daily
Dizziness	1.1	1.6	2.4	2.6
Headache	2.4	2.7	3.6	2.6
Hematologic				
Anemia	0.1	0.0	4.1	2.9
Musculoskeletal				
Arthralgia	0.5	0.0	5.3	1.3
Back pain	0.5	0.4	3.0	0.7
Psychiatric				
Insomnia	0.4	0.0	3.6	1.6
Respiratory				
Coughing	0.2	0.8	2.4	1.0
Upper respiratory tract infection	0.2	0.0	8.3	7.5
Skin				
Pruritus	0.4	1.2	2.4	0.0
Rash (b)	0.3	1.2	3.0	1.3
Urinary				
Micturition frequency	0.1	0.4	2.4	1.3
Urinary tract infection	0.3	0.4	4.7	6.9

a. WHO preferred terms edema, edema dependent, edema peripheral, and edema legs combined

b. WHO preferred terms rash, rash erythematous, and rash maculo-papular combined

Higher doses of MOBIC (22.5 mg and greater) have been associated with an increased risk of serious GI events, [redacted]

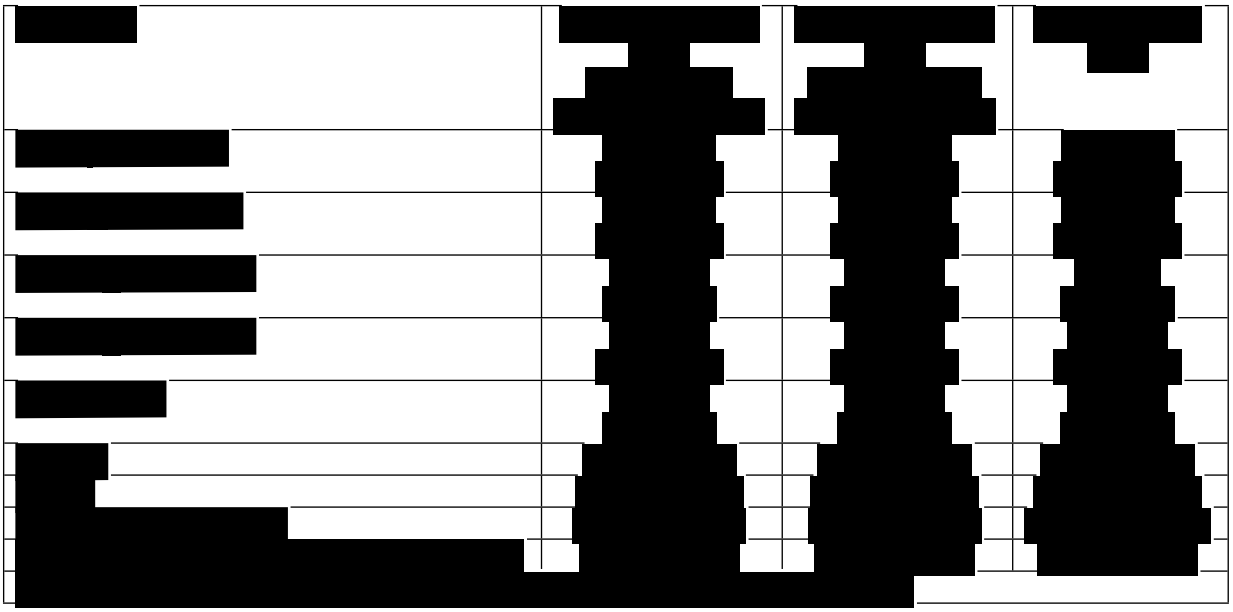
MECC-SA contains salicylic acid as a co-former, this is at a low dose (up to 11.6 mg for BID dosing of MECC-SA 15 mg) which is anticipated to have negligible physiological effects. However, it is acknowledged that salicylic acid (and acetylsalicylic acid) at higher doses can cause adverse effects, such as local gastrointestinal effects such as ulceration of the GI tract, particularly when administered with other NSAIDs. As the potential for local GI toxicity for salicylic acid is not known all GI symptoms should be assessed and documented.

As discussed in the most recent specific Cochrane Review of meloxicam [16] and the general review of NSAIDs for the treatment of acute pain [8], current oral formulations of meloxicam (e.g., MOBIC and VIVLODEX) are not indicated for, nor are they suitable for, the treatment of acute pain due to the delayed absorption of the product.

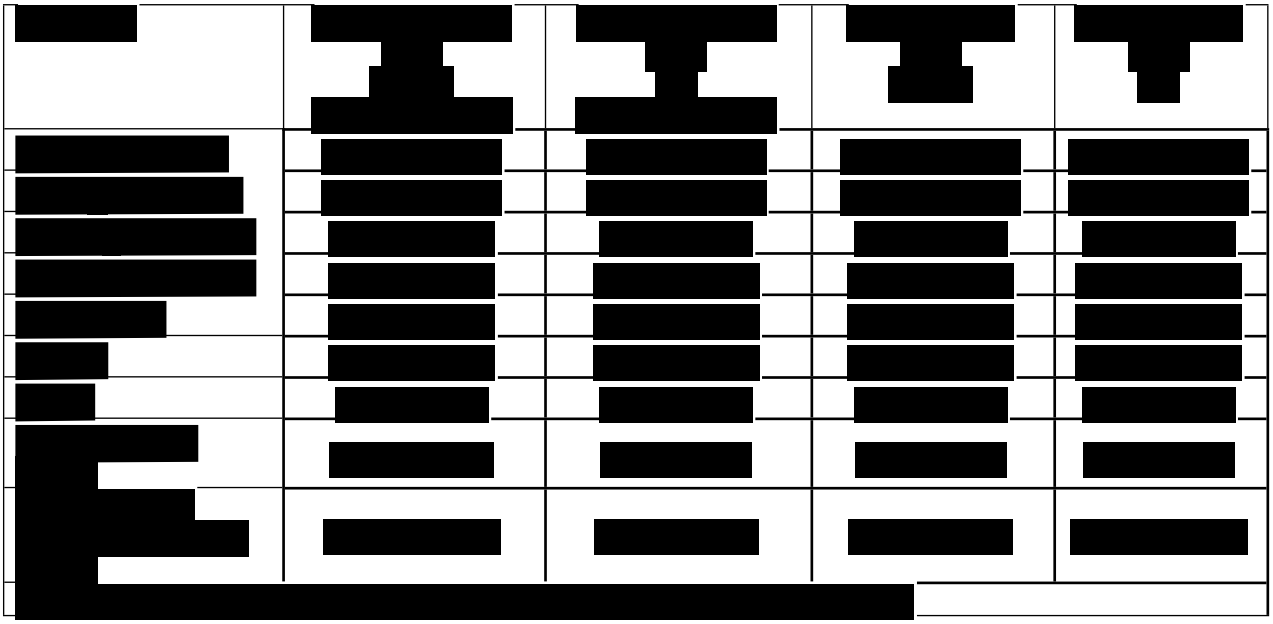
Meloxicam however, has demonstrated efficacy in a number of clinical studies using intramuscular (IM) and intravenous (IV) formulations, including short-term studies in dental extraction [17]; [18] and post-bunionectomy surgery [19]; [20]. Furthermore, some data are suggestive that IM meloxicam has a more rapid onset than oral meloxicam in rheumatoid arthritis pain [21] and sciatica [22].

MECC-SA is being developed to provide a rapid absorption of meloxicam from an oral dose.

[redacted]

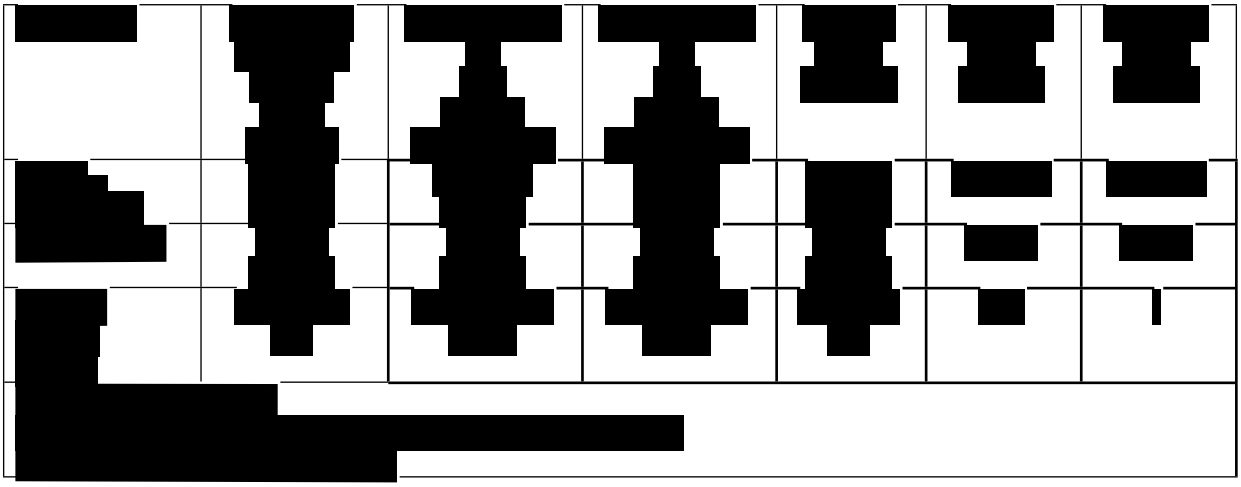


[redacted]



especially as ANJESO (IV meloxicam) 30 mg has a reported C_{max} of 7972.5 ng/mL and an AUC_{inf} of 121437.6 ng.hr/mL.

Acknowledging that a BID dosing regime is planned in this study, and based on the fasted data from Study , predicted exposure for BID dosing of MECC-SA are summarized in Table 6.



[redacted]

1.3 Investigational Product

MECC-SA is being developed to provide a rapid absorption of meloxicam from an oral dose.

The meloxicam component of the co-crystal formulation is considered to be the primary active component of the product.

Salicylic acid is used as the co-former in the MECC-SA tablets. Considering that meloxicam is a BCS Class II compound, the rate-limiting step for meloxicam absorption is solubility. The intended use of salicylic acid in MECC-SA is to increase the rate of absorption of meloxicam by increasing its solubility and dissolution. The dose of salicylic acid (5.8 mg and 11.6 mg considering QD and BID dosing of MECC-SA 15 mg, respectively) used in MECC-SA formulation is considered as a subtherapeutic dose (approved oral clinical doses of acetylsalicylic acid are in the range of 50- 325 mg/day) with negligible physiological effects. Whilst the side effect profile of acetylsalicylic acid is well known, including local effects on the GI tract, it is acknowledged that the local side effects of its metabolite (via hydrolysis in the GI tract, liver and plasma) salicylic acid when given orally are unknown, although a fraction of acetylsalicylic acid is metabolized to salicylic acid in the GI tract prior to absorption. Considering the low dose of salicylic acid in the formulation, MECC-SA is not considered a new fixed combination drug.

Based upon the available data, it can be considered that salicylic acid that is incorporated into MECC-SA is (1) at sub-therapeutic levels with negligible physiological effects and (2) enhances the effectiveness of meloxicam by increasing its solubility and dissolution thereby increasing its rate of absorption. Therefore, the product would not be considered a new fixed-combination drug.

The efficacy dose response profile of MECC-SA is currently unknown, and the purpose of this study is to establish an understanding of the dose response relationship for this formulation.

1.4 Ethics and Benefit-Risk Considerations

As discussed in Section 1.2, meloxicam has been extensively studied and subsequently prescribed for the treatment of chronic pain associated with osteoarthritis and rheumatoid arthritis but oral forms of meloxicam have not been used to treat acute pain due to slow absorption of the drug. A rapidly absorbing form of meloxicam should demonstrate efficacy in the treatment of acute pain and if the drug has a similar overall exposure (and lower than that of IV meloxicam) to that of other oral meloxicam products the safety profile should be similar.

This is the first assessment of efficacy of MECC-SA in subjects with acute pain, however it is anticipated to provide analgesia to these subjects due to the rapid absorption demonstrated in study [redacted] It is estimated that a 15 mg dose of MECC-SA would exceed 1090 ng/mL within 30-45 minutes of dosing, therefore acute analgesia could be anticipated at or around this time. Assuming linearity of exposure for meloxicam, a 10 mg dose of MECC-SA would exceed 1090 ng/mL at around 1.25 hours. It can therefore be anticipated that a 10 mg dose would achieve acute analgesia, however it may not be as efficacious as 15 mg.

As some studies of ANJESO [19]; [20] might indicate some loss of efficacy prior to 24 hours whereby the confidence intervals for the IV meloxicam and placebo overlap at later timepoints, the inclusion of BID doses of MECC-SA will assess whether BID dosing provides a better duration of action than QD dosing. [redacted] The administration of MECC-SA 15 mg BID should therefore be well tolerated.

As MECC-SA will be administered under controlled conditions in a clinic-based study, the risks and benefits to individual subjects can be carefully assessed; rescue medication will be available to subjects (whether taking active or placebo) if the pain associated with the surgical procedure is too great post-dose.

The use of placebo in the study is appropriate to ensure that any change from baseline in pain assessments related to the study drug can be adjusted for the 'placebo-response' that is common in pain studies. All subjects will be allowed to use rescue medication if the pain associated with the surgical procedure is too great post-dose.

Complete information for MECC-SA may be found in the Single Reference Safety Document, which for this study is the MECC-SA Investigator's Brochure.

2 OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objectives

To evaluate the efficacy and safety of MECC-SA in subjects following dental surgery and to establish the dose response relationship.

2.2 Endpoints

2.2.1 Primary Endpoint

- Overall (summed) pain intensity difference (SPID) over 0-24 hours.

2.2.2 Secondary Endpoints

Efficacy

- Overall (summed) pain intensity difference (SPID) over 0-2 hours, 0-4 hours, 0-8 hours, 0-12 hours and 12-24 hours after initial dose of study drug.
- Pain intensity difference (PID) over time.
- Total pain relief (TOTPAR) over 0-2 hours, 0-4 hours, 0-8 hours, 0-12 hours, 12-24 hours, and 0-24 hours.
- Time to perceptible relief (as measured by double-stopwatch technique) after first dose.
- Time to meaningful pain relief (as measured by double-stopwatch technique) after first dose.
- Proportion of subjects with overall pain reductions from baseline of ≥30% and ≥50% within 4 hours following the first dose.
- Patient's global assessment (PGA) of pain control from 0-24 hours.
- Elapsed time from the start of study medication to first rescue medication administration.
- Proportion of subjects using rescue medication from 0-24 hours.
- Number of times rescue medication used from 0-24 hours.

Safety

- Adverse Events.
- Laboratory safety tests.
- ECGs.

- Vital signs.

PK

- Population PK parameters for meloxicam and salicylic acid (C_{max}, $pAUC_{0-4}$ and $pAUC_{0-24}$).

3 STUDY DESIGN

3.1 Overall Design

This will be a randomized, double-blind, placebo-controlled, parallel group, dose-ranging study, randomizing approximately 110 male or female subjects that have had third molar dental surgery. Subjects will receive a dose of study drug on Day 1 after surgery and a further dose approximately 12 hours later.

3.2 Rationale for Study Design

The study design is consistent with research design recommendations of the IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) group for trials involving subjects with short-duration acute pain [23].

The dental surgical pain model has been in widespread use for over 50 years, is well characterized, and is frequently used to investigate the pharmacodynamic properties of analgesic molecules (onset/offset, dose response, and potency). Efficacy in the dental model is highly predictive of efficacy in later stage models and has a high assay sensitivity [24]. The model is also ideal as the surgery, the anesthetic regimen, and perioperative care protocols can be standardized across patients.

The dental surgical pain model has demonstrated the efficacy of analgesic medications across a range of different pharmacology, including NSAIDs and opioids [24] and specifically has demonstrated efficacy for an IV formulation of meloxicam [18] recently approved as ANJESO.

This study will specifically identify if MECC-SA has efficacy in a model of acute post-operative pain and will enable the identification of the most appropriate dose and regime of MECC-SA to continue in development.

3.3 End of Study Definition

End of study is defined as last subject, last visit.

4 STUDY POPULATION

4.1 Study Population

Approximately 110 subjects will be randomized to give approximately N=100 evaluable subjects for the primary endpoint (N=20/treatment arm).

Screening to end of study for each subject will be approximately 1.5 months in duration.

4.2 Inclusion and Exclusion Criteria

4.2.1 Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriate medically qualified member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Males and females ≥18 years of age. Females may be of either childbearing or non-childbearing potential. All females of childbearing potential must be using an acceptable, highly effective method of contraception and have a negative serum pregnancy test at screening.
2. Requirement for dental surgery for extraction of ≥2 x third molars, at least 1 of which involves partial or complete mandibular bony impaction.
3. Pain Intensity (PI) using a Numeric Pain Rating Scale (NPRS) ≥5 during the 5 hours following the end of surgery.
4. Rating of moderate or severe pain on a 4-point categorical pain rating scale (i.e., none, mild, moderate, severe) during the 5 hours following the end of surgery.
5. Able to understand and complete the study requirements (including literacy, to enable diary and questionnaire completion), provide written informed consent, and agree to abide by the study protocol and its restrictions.

4.2.2 Exclusion Criteria

Subject candidates must not be enrolled in the study if they meet any of the following criteria:

1. Previously dosed with MECC-SA.
2. Subject with known hypersensitivity to aspirin, NSAIDs or other medication used in the study.
3. Subjects with known hypersensitivity to items used in surgery.
4. Active GI bleeding or a history of peptic ulcer disease.
5. Active inflammatory bowel disease, e.g., Crohn's Disease or ulcerative colitis.
6. A history of bleeding disorders that may affect coagulation.
7. Significant history of respiratory insufficiency, hypotension, bradycardia, migraine, frequent headaches, seizures, renal, hepatic, cardiovascular metabolic, neurologic or psychiatric disease, in the opinion of the Investigator.
8. History of Hepatitis B or C or HIV infection.
9. History of alcohol or drug abuse within the last 5 years prior to the study.

10. History of myocardial infarction or coronary artery bypass graft surgery within the 12 months prior to the study.

11. Clinically significant abnormality on the 12-lead ECG at screening which in the judgment of the investigator would put the subject at potential risk if enrolled into the study (these subjects should not be re-screened). Clinically significant abnormalities may include but are not limited to the following: left bundle branch block, Wolff-Parkinson-White syndrome, clinically significant arrhythmias (e.g., ventricular tachycardia).

12. History of long QT syndrome or screening ECG with QTcF >470 milliseconds for female or >450 milliseconds for male subjects.

13. Current evidence of, or history within the 6 months prior to screening of unstable ischemic heart disease, NYHA Class II-IV right or left ventricular failure.

14. History of malignancy of any organ system treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases. The only exceptions are previous in situ carcinoma of the cervix, localized basal cell carcinoma of the skin or localized squamous carcinoma of the skin if the subject has been treated and is considered cured.

15. Use of any investigational drug within 28 days, or 5 half-lives, prior to screening whichever is longer.

16. Use of medications with the potential to interact with MECC-SA (as indicated in the current Investigator's Brochure), or medications required during the study such as local anesthesia or sedatives, or medications with the potential to affect or confound pain status during the study. This includes (but not limited to) use of any of the following medications:

    - Strong CYP2C9 inhibitors or inducers within 28 days or 5 half-lives (whichever is longer) prior to the study.
    - Long term opioid use (>30 consecutive days in the past year) and/or use of extended release opioids within 30 days of the dental extraction.
    - Antiepileptic drugs within 28 days prior to the study.
    - Tricyclic anti-depressants, monoamine oxidase inhibitors, or SNRIs within 28 days prior to the study.
    - Sedative or hypnotic drugs within 28 days prior to the study (other than the nitrous oxide used during the operation).
    - Use of "medical" or recreational marijuana within 28 days prior to the study.
    - Warfarin within 28 days prior to the study.
    - Apixaban within 28 days prior to the study.
    - Lithium within 28 days prior to the study.
    - Methotrexate within 28 days prior to the study.

- Calcineurin inhibitors (e.g., cyclosporine and tacrolimus) within 28 days prior to the study.
- Pemetrexed within 28 days prior to the study.
- Combination of diuretic with ACE inhibitor or angiotensin receptor blocker within 28 days prior to the study.
- Gabapentin or pregabalin within 28 days prior to the study.
- Cholestyramine within 7 days prior to the study.
- Meloxicam within 7 days prior to the surgery.
- Aspirin within 7 days prior to the surgery.
- Analgesics (including opioids, acetaminophen and NSAIDs) within 24 hours prior to the surgery.

17. Inability to refrain from any of the following medications pre-, intra-, or post-surgery:
    - Systemically administered corticosteroids.
    - Epidural or spinal anesthetics.
    - General anesthesia.
    - Analgesia other than those pre-specified for breakthrough pain relief.
18. BMI >35 kg/m^2.
19. Pregnant or nursing females or females intending to become pregnant during the course of the study.
20. Serum creatinine >1.5 x Upper Limit of Normal.
21. Serum ALT, AST, or bilirubin >2 x Upper Limit of Normal.
22. Clinically significant abnormal laboratory test(s) at screening deemed exclusionary by the Investigator.
23. Signs or symptoms of an infection or a fever that would increase the risk of surgery.
24. Other acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

4.2.3 Criteria for Study Drug Termination, Withdrawal From the Study and Study Termination

Subjects may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study center.

Every effort should be made to retain subjects in the study. When available, a reason for not completing the study will be recorded in the case report form (CRF).

If, a subject discontinues from the study prematurely, due to any reason as provided in the below withdrawal criteria, the site should request the subjects' consent for being followed-up during further study visits to perform safety and efficacy assessments as per Table 1.

Subjects must be withdrawn from the study prior to randomization under the following circumstances:

- The subject withdraws consent.
- The subject has a positive pregnancy test at Visit 2 (Day 1) or at any preceding point prior to this following Screening (Visit 1).
- Despite education/reinforcement, the subject shows persistent inadequate compliance with required study visits/procedures, potentially compromising safety monitoring while on study drug based on investigator's discretion.
- The subject takes prohibited treatment presenting a safety concern to dosing with study drug.
- If it is in the subject's best interest based on decision of the Principal Investigator or Sub-Investigator e.g., due to occurrence of an AE and/or other findings considered to present a safety concern prior to dosing with study drug. Specifically, the following would mandate withdrawal:
    - The subject experiences a GI bleed or significant CV event prior to Visit 2 (Day 1).
    - The subject has significant abnormalities observed (after appropriate repeat assessments to confirm the findings) on 12 lead ECGs such as left bundle branch block, Wolff-Parkinson-White syndrome, clinically significant arrhythmias (e.g., ventricular tachycardia) or QTcF >500 msec.

A subject may be required to terminate study drug for reasons including the following:

- The subject withdraws consent.
- For female subjects, diagnosis of pregnancy or stated intention to become pregnant. All efforts should be made by the site to obtain consent from the pregnant women, so that they are followed until delivery or termination.

- Despite education/reinforcement, the subject shows persistent inadequate compliance with required study visits/procedures, potentially compromising safety monitoring while on study drug based on investigator's discretion.
- The subject takes prohibited treatment presenting a safety concern to continued dosing with study drug.
- The subject requires more than 6 tablets/day (equivalent to 30 mg hydrocodone and 1950 mg acetaminophen) rescue medication.
- At the investigator's discretion (it is recommended that the investigator discusses with medical monitor prior to decision), if it is in the subject's best interest due to occurrence of an AE and/or other findings considered to present a safety concern to continued dosing with study drug and warrants treatment withdrawal. Specifically, the following would mandate withdrawal:
    - The subject experiences a GI bleed or significant CV event.
    - The subject has significant abnormalities observed (after appropriate repeat assessments to confirm the findings) on 12-lead ECGs such as left bundle branch block, Wolff-Parkinson-White syndrome, clinically significant arrhythmias (e.g., ventricular tachycardia) or QTcF >500 msec.
- If the blind is broken for a subject by the Investigator.

The Principal Investigator and/or Mylan reserves the right to terminate the study for any reason.

The study will be terminated early if there are significant subject safety concerns that are indicative of a change to the risk: benefit profile for the overall study population. In this case the IRB will be informed accordingly.

Subjects who prematurely terminate the study will have discharge procedures performed prior to leaving the clinic or an Early Termination (ET) visit scheduled as soon as possible.

4.3 Replacement Policy

Subjects who are withdrawn from the study will not be replaced.

4.4 Lifestyle Guidelines

Subjects are to observe the following restrictions during the study.

4.4.1 Meals and Dietary Restrictions

In order to avoid interference with sedation and operative procedures subjects should fast from midnight prior to the surgery.

Subjects will be allowed to eat food after 2 hours post-first dose.

Subjects should not consume any water or other drinks for 2 hours prior to the surgery.

Subjects may consume water and other drinks *ad libitum* following completion of the surgery.

Subjects will be given snacks and meals at appropriate times (after the fasting period) during confinement in the clinic.

4.4.2 Alcohol and Tobacco

At all study visits, subjects will be required to:

- Abstain from alcohol for at least 24 hours prior to admission for the surgery at Visit 2 (Day 1) and continue abstaining from alcohol until after discharge on Visit 2 (Day 2).
- Abstain from smoking or vaping (or other tobacco based products) following admission for the surgery at Visit 2 (Day 1) and continue abstaining from smoking or vaping until after discharge on Visit 2 (Day 2).

4.5 Contraception

4.5.1 Females - Non-Childbearing Potential

Female subjects of non-childbearing potential must meet at least one of the following criteria:

1. Postmenopausal females, defined as females, who have been amenorrheic for at least 2 years and confirmed via serum FSH.
2. Females who have a documented hysterectomy and/or bilateral oophorectomy.

All other females will be considered to be of childbearing potential.

4.5.2 Females - Childbearing Potential

Female subjects of childbearing potential must use an acceptable, highly effective method of contraception starting 28 days prior to dosing and continuing at least 28 days following the last treatment, such methods include at least one of the following:

- Abstinence (periodic abstinence is not acceptable)
- Tubal ligation
- Intrauterine device or intrauterine system
- Barrier method, like condom, with spermicide
- Male partner who has had a vasectomy for at least 6 months. Male partners with vasectomies of <6 months are NOT considered protected
- Hormonal contraceptives (oral, injected, transdermal, or implanted) with the exception of low dose gestagens, i.e., only containing lynestrenol or norethisterone, since they do not inhibit ovulation and are therefore not considered as highly effective. The subject must remain on the hormonal contraceptive throughout the

study and must have been on a stable regimen of hormonal contraceptives for an adequate period prior to the study to ensure effectiveness (e.g., 3 months)

4.6 Pregnancy Testing

A serum pregnancy test will be performed on all female subjects at Screening. Urine pregnancy testing will be performed on all females of childbearing potential at subsequent visits as described in the schedule of activities (results will be reviewed and must be negative prior to dosing). In the event of a positive test, the subject will be withdrawn from the study (or will not enter the study if during screening).

Any pregnancy occurring after randomization to study drug will be followed up and reported to the sponsor as per Section 10.5.

5 STUDY DRUG

5.1 Investigational Drug

MECC-SA will be provided as 10 and 15 mg tablets.

- 15 mg tablets (and matching placebo) [redacted]
- 10 mg tablets (and matching placebo) [redacted]

Placebo is a tablet identical to the corresponding dose of active study drug.

To maintain the blind, subjects will take in a double dummy design, two tablets (one that is representative of a 10 mg tablet and one that is representative of a 15 mg tablet) of study drug or placebo will be administered on one day, Visit 2 (Day 1). Due to the double dummy design, neither the subject, nor the Investigator will know what treatment a subject receives. To maintain the blind, regarding QD and BID dosing, subjects assigned to QD treatment arms will receive placebo at the second dose. Additionally, per the clinic procedures, subjects will be blindfolded during dosing.

Study drugs will be administered following randomization and approximately 12 hours following the first dose.

5.1.1 Administration of Study Drugs

Study drug (two tablets containing MECC-SA or matching placebo) will be administered in a double dummy design at the clinic at each dosing time.

Subjects should take the study drugs with about 240 mL of water at ambient temperature in each period under the supervision of trained study personnel.

This activity will be followed by mouth and hand check of the subjects to assess compliance to dosing.

Study drugs must be swallowed whole and must not be chewed, crushed or divided.

In the event of any significant dosing errors, the Medical Monitor, or Mylan study contact should be contacted immediately.

5.2 Drug Inventory

Mylan will supply:

- MECC-SA and matching placebo.

The Investigator site will supply:

- Medication required for sedation and anesthesia during the surgery.
- Rescue medication for pain relief following randomization, hydrocodone/acetaminophen (5/325 mg).
- All materials associated with the surgical procedure.

5.3 Study Medication Complaints

In the event the subject has a complaint/concern during study participation regarding the study supplied study medication, they should contact the site.

In the event of a complaint/concern regarding any study medication provided by Mylan for this study, as a minimum the following information should be sent by the site via e-mail to [redacted]

- Study number
- Principal Investigator name
- Subject ID
- Date of occurrence of incident/complaint
- Description of incident/complaint (facts)
- Confirmation if the complaint caused or resulted in a SAE? If “Yes”, confirmation that the SAE has been reported

Additional information and potentially the return of study medication may be requested by Mylan in order to investigate the complaint.

5.4 Storage, Disposition of Unused Study Drug and Drug Accountability

The Investigator, or an approved representative, e.g., pharmacist, will ensure that all investigational products are stored in a secured area under recommended storage conditions and in accordance with applicable regulatory requirements while at the investigator site.

Study drug should be stored in accordance with the drug label. Storage conditions stated in the Investigator’s Brochure may be superseded by the label storage.

Temperature of storage facilities should be monitored and recorded on a daily basis using validated devices that record maximum and minimum temperatures. Should the storage facility experience any excursion of temperature outside of the labelled storage condition this must be reported immediately to Mylan or designee. At sites where daily monitoring and recording is not possible at weekends, then on the next working day after the weekend the temperature record (e.g., max/min thermometers) should be checked immediately for any temperature excursions. Devices used for temperature monitoring should be regularly calibrated. Affected material must be placed into quarantine until the impact of the excursion has been assessed and confirmed by Mylan.

The investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of the study drug. If Mylan supply drug accountability forms these must be used. Alternatively, Mylan may approve use of standard institution forms. In either case, the forms must identify the study drug, including batch or code numbers, and account for its disposition on a subject-by-subject basis, including specific dates and quantities. The forms must be signed by the individual who dispensed the drug, and copies must be provided to Mylan or designee.

At the end of the study, Mylan will provide instructions as to disposition of any unused investigational product. If Mylan authorizes destruction at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Mylan. Destruction must be adequately documented.

5.5 Randomization

Assignment of Subject Identification (SID) number, randomization number and study medication, as well as site drug inventory control will be managed by an automated Interactive Voice/Web Response system (IVRS/IWRS). A manual containing complete instructions for internet or telephone access and use will be provided to each site prior to study start. At their first clinic visit, the IVRS/IWRS will assign a SID. Each SID will be unique and serve as the primary subject identifier throughout all phases of the study. The SID must appear on all CRF pages, source documents, laboratory data, ECG and diary data. Subjects qualifying to enter the study drug treatment phase, will be assigned an additional "randomization number" by the IVRS/IWRS at randomization. Subjects will be allocated to treatment within blocks for the given allocation ratio.

At Visit 2 (Day 1) eligible subjects will be randomized to receive MECC-SA (10 mg QD, 15 mg QD, 10 mg BID or 15 mg BID) or matching placebo in a 1:1:1:1:1 ratio through the IVRS/IWRS.

5.6 Breaking the Blind

Emergency subject unblinding will be managed by an automated IVRS/IWRS.

A manual containing complete instructions for internet or telephone access and use will be provided to each site prior to study start.

Subject unblinding should be discouraged unless knowing the treatment received by the subject would change the way an AE is treated.

5.7 Rescue Medication For Relief of Pain

Any use of rescue medication while the subject is in the clinic will be recorded, including the dose and time of administration.

5.7.1 Pre-Dose

If a subject requires the use of rescue medication prior to administration of study drug, the subject will not be eligible for randomization.

5.7.2 Post-Dose

Rescue medication of immediate release hydrocodone/acetaminophen (5/325 mg) will be allowed to treat breakthrough pain, subjects will be encouraged to refrain from rescue medication until at least 1-hour post-dose. A dose of rescue medication will be allowed as needed up to once every two hours. A maximum of 6 tablets (equivalent to 30 mg hydrocodone and 1950 mg acetaminophen) will be allowed; if a subject requires greater than this the subject should be withdrawn from the study.

Pain Intensity will be measured immediately before any rescue medication is administered.

5.8 Concomitant Medications

All concomitant medications taken during the study (from signing informed consent to post-study follow-up) must be recorded with indication, daily dose, and start and stop dates of administration in the CRF. All subjects will be questioned about concomitant medication at each clinic visit and at follow up.

Medications taken prior to dosing with study medication will be documented as a prior medication. Medications taken after dosing with study medication will be documented as concomitant medications.

Subjects will abstain from all prohibited medications as described in the exclusion criteria section of this protocol (Section 4.2.2). Use of prohibited medication during the study will be deemed a protocol deviation and such subjects will be assessed by Mylan or designee regarding potential need to early terminate study drug (e.g., for safety reasons – see Section 4.2.3).

5.9 Recommended Procedure in a Subject Experiencing Adverse Effects Secondary to Excessive Pharmacological Effects of Study Drug

Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting and epigastric pain, which are generally reversible with supportive care.

Gastrointestinal bleeding can occur. Severe poisoning may result in hypertension, acute renal failure, hepatic dysfunction, respiratory depression, coma, convulsions, cardiovascular collapse and cardiac arrest. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAID and may occur following an overdose.

Subjects should be managed with symptomatic and supportive care following an NSAID overdose or symptoms suggestive of excessive pharmacological effect. Accelerated removal of meloxicam by 4 g oral doses of cholestyramine given three times a day has been demonstrated in a clinical trial [25].

5.10 Treatment Compliance

Subjects will be dosed in the clinic on Visit 2 (Day 1) of the study, a visual check of the subject's mouth and hands will be made to ensure compliance of dosing.

6 STUDY CONDUCT

Subjects eligible for study recruitment will have the nature, purpose, and risks of the study explained to them by the investigator. They will be provided with a written copy of the informed consent form (ICF) for the study and given sufficient time to consider the study's implications before deciding to participate. Subjects agreeing to participate in the study will sign the ICF and be given a duplicate copy before undergoing any screening or pre-screening (if required) procedures. A unique SID will be issued at the time of consent by IVRS/IWRS system.

Once a subject enrolls in this trial the site will make every effort to retain the subject for the planned duration of the trial. Clinical trial site staff are responsible for developing and implementing support and retention plans. Elements of this plan may include the following.

- Thorough explanation of the complete clinical trial visit schedule and procedural requirements during the informed consent process and re-emphasis at each clinic visit.
- A simple explanation of the key data and key time points that are critical for the trial's successful analysis, and the importance of all the treatment groups to the overall success of the trial.
- Discussion at screening, and subsequent regular review of possible barriers to clinic visit attendance and full study participation and compliance.
- Collection of contact information at screening (address, phone numbers, email), which is regularly reviewed at subsequent clinic visits.
- Use of appropriate and timely study visit reminders.
- Immediate and multifaceted follow-up on missed clinic visits.

In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the

subject so that they can appropriately be withdrawn from the study. All contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, then and only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up." For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the CRF. Regardless of site plans to support and retain subjects within the trial, subjects may voluntarily withdraw from the trial for any reason and at any time.

For a subject that completes the study and all procedures it is anticipated that the duration of study would be approximately 1.5 months.

For details and timings of assessments, refer to Section 7.

6.1 Screening Procedures

Each prospective subject must agree to participate in screening procedures by signing the most recent ICF before any screening procedure is initiated. The Principal Investigator or Medical Sub-Investigator will review the inclusion and exclusion criteria to confirm eligibility of each subject prior to enrollment.

6.1.1 Screening (Visit 1)

Subjects will commence screening procedures within 30 days prior to the planned surgical procedure and subsequent randomization, to confirm that they meet the selection criteria for the study. If the time between screening procedures and potential randomization exceeds 30 days as a result of unexpected delays, then the subject will need to be discussed with Mylan or designee to consider potential for re-screening (if re-screening is agreed, the subject will need to be re consented and assigned a new SID via IVRS/IWRS). Re-screening for other reasons may be possible following discussion with the Mylan or designee. If re-screening occurs this will be clearly documented within the site file.

At Screening (Visit 1), the following will be completed; procedures can be performed in a different order, but informed consent must be obtained prior to any procedures and the 12-lead ECG must be performed prior to vital signs or obtaining blood samples.

- Written informed consent.
- IVRS/IWRS registration.
- Complete medical history, demographics.
- Complete history of all prescription or non-prescription drugs, dietary supplements taken within 28 days prior to consent. History of alcohol or illicit drug use.
- Record 12-lead ECG – supine or semi-recumbent.
- Record vital signs – supine or semi-recumbent blood pressure (BP) and pulse rate (PR).

- Measure height and weight.
- Serum pregnancy test for all female subjects.
- Blood will be collected for safety laboratory tests. Laboratory tests at screening include confirmation of non-childbearing potential in any female who has been amenorrheic for at least 2 years, via serum FSH.
- Urinalysis (for blood, protein etc.). Sample to be tested for microscopy/culture if positive for blood, protein, nitrites or leukocyte esterase.
- Urine drug screen.
- General physical examination, including respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurological systems, lymph nodes, skin, extremities, head, ears, eyes, nose, and thyroid gland.
- Check study inclusion/exclusion criteria.
- Review AEs (AEs are to be recorded starting from signature of consent).
- Schedule Visit 2 (Day 1) and remind the subject of lifestyle and study drug and concomitant medication requirements for visits.
    - Subjects should be reminded to fast from midnight prior to the surgery.

Subjects may be discharged from the clinic following completion of all assessments.

6.2 Treatment Phase

6.2.1 Visit 2 (Day 1)

The following procedures will be completed; procedures can be performed in a different order as long as they are performed at the correct nominal time and would not impact on other tests, e.g., 12-lead ECGs that are taken at the same nominal time as vital signs or blood samples are taken prior to those other procedures:

6.2.1.1 Pre-Dose Procedures

- Check the subject has fasted from midnight.
- Review AEs.
- Review concomitant medications.
- Record vital signs – supine or semi-recumbent blood pressure (BP) and pulse rate (PR).
- Perform urine drug screen.
- Urine pregnancy test (if female of childbearing potential).
- Check study inclusion/exclusion criteria.

- Record body temperature.
- Diary training.
- Perform dental surgery, using appropriate local anesthesia and sedation (performed using nitrous oxide and a local injection of lidocaine with epinephrine). Subjects will also receive prophylactic antibiotics post-surgery.
- Pain assessments (Pain Intensity (0-10-point numeric pain rating scale – NPRS) and Categorical Pain Rating (4-point scale – none, mild, moderate, severe)) will be made during the 5 hours post-surgery until a baseline pain assessment is achieved.
    - Subjects with NPRS ≥5 and a rating of moderate or severe pain on a 4-point categorical pain rating scale (i.e., none, mild, moderate, severe) during this time they will be eligible for randomization.
- Randomization using IVRS/IWRS.
    - To occur such that dosing occurs within 15 minutes of the eligible pain scores.
- 12-lead ECG – supine or semi-recumbent taken prior to dosing.
- Vital signs (BP and PR) – supine or semi-recumbent taken prior to dosing.
- Blood for a PK sample taken prior to dosing.

6.2.1.2 Dosing and Post-Dose Procedures

- Administer first dose of study drug (two tablets to maintain the blind).
    - Within 15 minutes of the baseline pain scores.
- Administer second dose of study drug (two tablets to maintain the blind).
    - Approximately 12 hours after the first dose.
- Pain Intensity (0-10-point NPRS) measured at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 14, and 16 hours after the first dose of study medication and immediately before any rescue medication and/or at the time of early termination. Assessments will also be made immediately following the time of first relief and time of meaningful relief.
    - Pain scores should be made at the nominal time in the event of more than one procedure taking place at the same nominal time.
- Pain Relief Assessments (5-point scale - none = 0, slight = 1, moderate = 2, good or a lot = 3, and complete = 4) measured at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 14, and 16 hours after the first dose of study medication and immediately before any rescue medication and/or at the time of early termination. Assessments will also be made immediately following the time of first relief and time of meaningful relief.

- Pain scores should be made at the nominal time in the event of more than one procedure taking place at the same nominal time.

- Time of first perceptible relief is recorded (double-stopwatch method) – time the first stopwatch is stopped.
  - Defined as post-dose time at which the subject first begins to feel pain relief.
- Time of meaningful relief is recorded (double-stopwatch method) – time the second stopwatch is stopped.
  - Defined as the post-dose time at which the subject begins to feel meaningful pain relief.
- PK sample taken at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 14, and 16 hours after the first dose of study medication.
  - Where PK samples and pain assessments occur at the same time, the pain assessment should be made prior to the PK sample.
- Adverse events should be assessed throughout the day.
  - When assessing AEs, the subject will be specifically asked regarding the presence of any GI symptoms.
- Any use of rescue medication should be recorded throughout the day.
  - Rescue medication will be allowed at any time, but subjects will be encouraged to wait until at least 1-hour post-dose if possible.

6.2.2 Visit 2 (Day 2)

- Adverse events should be assessed throughout the day.
  - When assessing AEs, the subject will be specifically asked regarding the presence of any GI symptoms.
- Any use of rescue medication should be recorded throughout the day.
- Pain Intensity (0-10-point NPRS) measured at 20 and 24 hours after the first dose (Day 1) of study medication and immediately before any rescue medication.
  - Pain scores should be made at the nominal time in the event of more than one procedure taking place at the same nominal time.
- Pain Relief Assessments (5-point scale - none = 0, slight = 1, moderate = 2, good or a lot = 3, and complete = 4) measured at 20 and 24 hours after the first dose of study medication and immediately before any rescue medication and/or at the time of early termination.

- Patient Global Assessment (PGA) of pain control will be made at 24 hours after the first dose.
- PK sample taken at 20 and 24 hours after the first dose of study medication.

6.2.2.1 Discharge Procedures

- General physical examination, including respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurological systems, lymph nodes, skin, extremities, head, ears, eyes, nose, and thyroid gland.
- Record 12-lead ECG – supine or semi-recumbent.
- Record vital signs – supine or semi-recumbent BP and PR.
- Urine pregnancy test (if female of childbearing potential).
- Urinalysis (dipstick for blood, protein etc.). Sample to be sent for microscopy/culture if positive for blood, protein, nitrites or leukocyte esterase.
- Blood will be collected for safety laboratory tests.
- Review concomitant medications.
- Adverse Event assessment.
    - When assessing AEs, the subject will be specifically asked regarding the presence of any GI symptoms.
- Discharge subject from the clinic.
    - Provide appropriate post-discharge pain medications, per standard of care.
    - If a subject requires a longer duration of in-patient assessment due to reasons associated with the operation this is acceptable.

6.2.3 Early Termination (ET) visit

Subjects may request termination of study drug or withdrawal from the study at any time, or be required to withdraw or terminate study drug by the investigator or sponsor for reasons as per Section 4.2.3. If study drug is terminated or the subject withdraws or is withdrawn, the reason for termination/withdrawal should be established and recorded. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document the outcome of subject contact attempt, if possible. The investigator will contact Mylan or designee in the event that a subject fails to complete the study or violates the protocol.

If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be

collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Unless consent is withdrawn, subjects who prematurely terminate study drug will be asked to conduct the procedures detailed below prior to leaving the clinic or return to the clinic for an ET visit and will have this scheduled as soon as possible after their last dose of study drug.

At the Early Termination (ET) visit (or discharge from the clinic) the following procedures will be completed:

- General physical examination, including respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurological systems, lymph nodes, skin, extremities, head, ears, eyes, nose, and thyroid gland.
- Record 12-lead ECG – supine or semi-recumbent.
- Record vital signs – supine or semi-recumbent BP and PR.
- Urine pregnancy test (if female of childbearing potential).
- Urinalysis (dipstick for blood, protein etc.). Sample to be sent for microscopy/culture if positive for blood, protein, nitrites or leukocyte esterase.
- Blood will be collected for safety laboratory tests.
- Review concomitant medications.
- Adverse Event assessment.
    - When assessing AEs, the subject will be specifically asked regarding the presence of any GI symptoms.

Subjects may be discharged from the clinic at the discretion of the investigator following completion of all ET assessments.

Subjects who decide to discontinue from treatment and agree to remain in the study, are required to adhere to the study protocol, thus perform all activities and as per the scheduled study visits for completion of all assessments and procedures as outlined in Table 1.

6.3 End of Study (EOS) Visit

The End of Study (EOS) Visit will be performed by telephone on Day 5-7 of the study.

Procedures will be completed in the following order:

- Review concomitant medications.
- Adverse Event assessment.
    - When assessing AEs, the subject will be specifically asked regarding the presence of any GI symptoms.
- Review rescue medication used.

Subjects will be reminded that AEs should be reported to the study staff up to 30 days after the last dose of study medication.

7 TREATMENT PROCEDURES AND ASSESSMENT CRITERIA

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator or designated representative will take all steps necessary to ensure the safety and well-being of the subject. When a protocol required test cannot be performed the investigator or designated representative will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The Mylan study team will be informed of these incidents in a timely fashion.

Activities specific to this protocol are summarized in Table 1 and expanded upon further below.

7.1 Dental Surgery

The dental surgery and related anesthesia, sedation, and prophylactic antibiotics are not investigational and will occur regardless of research.

The dental surgery (extraction of ≥2 x third molars, at least 1 of which involves partial or complete mandibular bony impaction) will be performed on Visit 2 (Day 1).

The procedure will be performed using appropriate local anesthesia and sedation (performed using nitrous oxide and a local injection of lidocaine with epinephrine). Subjects will also receive prophylactic antibiotics post surgically.

7.2 Efficacy Assessment

7.2.1 Pain Intensity (NPRS)

Pain Intensity (PI) (using a 0-10 point numeric pain rating scale (NPRS) where 0 is no pain and 10 is the worst pain imaginable) [26] will be assessed during the 5 hours following surgery. If the subject scores a NPRS ≥5 (and moderate or severe pain on the categorical scale) within 5 hours following surgery, they will be eligible for randomization.

Assessments will be made following surgery until a baseline pain is achieved.

Assessments will be made at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 14, 16, 20, and 24 hours after the first dose of study medication, and immediately before any rescue medication and/or at the time of early termination.

Assessments will also be made immediately following the time of first relief and time of first meaningful relief.

The PI will be recorded in a diary.

7.2.2 Categorical Pain Rating

A pain rating using a 4-point categorical rating scale (none, mild, moderate, severe) will be used to assess eligibility for randomization. If the subject records moderate or severe (and a NPRS ≥5) within 5 hours following surgery, they will be eligible for randomization.

Assessments will be made following surgery until a baseline pain is achieved.

The categorical pain rating will be recorded in a diary.

7.2.3 Pain Relief Assessment

A pain relief assessment will be made using a using a 5-point scale - none = 0, slight = 1, moderate = 2, good or a lot = 3, and complete = 4.

Assessments will be made at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 14, 16, 20, and 24 hours after the first dose of study medication, and immediately before any rescue medication and/or at the time of early termination.

Assessments will also be made immediately following the time of first relief and time of first meaningful relief.

The pain relief assessment will be recorded in a diary.

7.2.4 Patient Global Assessment (PGA)

A Patient Global Assessment (PGA) of pain control will be rated on a 5-point scale, ranging from 0 to 4, where 0-poor, 1-fair, 2 good, 3-very good, or 4-excellent.

Assessments will be made at 24 hours after the first dose of study medication or at time of early termination if applicable.

The PGA will be recorded in a diary.

7.2.5 Time to First Perceptible Pain Relief

Time to first perceptible pain relief will be assessed using a double stopwatch approach.

The time to onset of first perceptible pain relief (time that the first watch stopped) is defined as the post-dose time at which the subject first begins to feel pain relief.

7.2.6 Time to Meaningful Pain Relief

Time to meaningful pain relief will be assessed using a double stopwatch approach.

The time to onset of meaningful pain relief (time that the second watch stopped) is defined as the post-dose time at which the subject first begins to feel meaningful pain relief.

7.2.7 Rescue Medication Use

Rescue medication of immediate release hydrocodone/acetaminophen will be allowed at any time, but subjects will be encouraged to wait until at least 1-hour post-dose if possible. A PI score assessment will be made immediately prior to any rescue medication.

The time and dose of any rescue medication taken by a subject will be recorded in the CRF.

7.3 Safety Assessment

7.3.1 Adverse Event Assessment

If a subject reports any symptoms before drug administration, they will be evaluated by medical staff and necessary measurements will be performed. The Principal Investigator or Medical Sub-Investigator will be notified before dosing to determine the course of action.

Findings from screening procedures, e.g., laboratory tests or physical examinations will be recorded as medical history. Clinically significant worsening from the screening procedures will be recorded as adverse events.

Subjects will be routinely queried in regard to the presence or absence of AEs using open ended questions. When assessing AEs, the subject will be specifically asked regarding the presence of any GI symptoms. The clinic will provide documentation of any adverse events in the subject's CRF. The AE source documentation will minimally include the following information: date and time of assessment, the outcome of the response, and identification of the clinic staff member collecting the information.

7.3.2 Laboratory Safety

The following safety laboratory tests (Table 7) will be performed at Screening (Visit 1) and Visit 2 (Day 2).

Table 7: Laboratory Safety Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	Urea and Creatinine Glucose (non-fasting) Calcium Sodium Potassium Chloride Total CO_2 (Bicarbonate) AST, ALT Total Bilirubin Direct/Indirect bilirubin Alkaline phosphatase Uric acid Albumin Total protein CRP	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Microscopy/culture[a]	Serum FSH[b] Serum/urine hCG[c] Breath/blood alcohol test[d] Urine drug screen[e]

a. Only if urinalysis is positive for blood, protein, nitrites or leukocyte esterase.

b. Females who are amenorrheic for at least 2 years at Screening.

c. Serum hCG for all female subjects at Screening and urine hCG for females of childbearing potential at other visits.

d. At the Investigator's discretion an alcohol test may be performed. Where necessary blood or breath alcohol tests can be performed.

e. Urine drug screen to include the following as a minimum cocaine, cannabinoids, opiates, buprenorphine, benzodiazepines and amphetamines.

Hematology and chemistry will be analyzed by a local laboratory. Urinalysis will be conducted at the laboratory and if urine is positive for blood, protein, nitrites, or leukocyte esterase, will be analyzed via microscopy/culture by a laboratory.

Additionally a urine drug test will be performed at Screening (Visit 1) and on admission at Visit 2 (Day 1). If a subject has a positive test for amphetamines but is prescribed medication such as to treat ADHD, they would still be acceptable at the Investigator's discretion.

Blood volumes to be collected and blood and urine sample handling instructions will be per the local laboratory's standard procedures. The Investigator will provide collection materials for packaging and shipment of samples to the laboratory.

Any clinically significant findings in laboratory safety data should be recorded as an AE. Determination of clinical significance and seriousness will be based on the Investigator's medical judgment.

7.3.3 Vital Signs - Blood Pressure and Pulse Rate

Blood pressure (BP) and pulse rate (PR) will be measured at Screening (Visit 1), Visit 2 (Day 1), and Visit 2 (Day 2) at times specified in Table 1 and Section 6. Additional collection times, or changes to collection times of blood pressure and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

Supine or semi-recumbent BP will be measured with the subject's arm supported at the level of the heart and recorded to the nearest mmHg after 5 minutes of rest. Where possible, the same arm (preferably the dominant arm) will be used throughout the study.

The same size blood pressure cuff, which has been properly sized and calibrated, will be used to measure blood pressure each time. The use of automated devices for measuring BP and PR are acceptable, although, when done manually, PR will be measured in the brachial/radial artery for at least 30 seconds. Any clinically significant changes in BP and PR should be recorded as an AE. Determination of clinical significance and seriousness will be based on the Investigator's medical judgment.

7.3.4 12-lead ECG

In this study, 12-lead ECGs will be recorded using clinic ECG devices. ECGs should be collected at measured at Screening (Visit 1), Visit 2 (Day 1), and Visit 2 (Day 2) at times specified in Table 1 and Section 6. All 12-lead ECGs will be single recordings.

All scheduled ECGs should be performed after the subject has rested quietly for at least 5 minutes in a supine or semi-recumbent position. Pre-dose ECGs should be performed prior to commencing blood sampling or vital signs assessments.

To ensure safety of the subjects, a medically qualified individual at the site will assess ECG recordings and make any comparisons to baseline measurements.

At screening, the QTcF must be ≤470 msec for female or ≤450 msec for male subjects, and the ECG must show no clinically significant rate or rhythm abnormalities for the subject to be eligible (See Section 4.2.2).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. Any clinically significant ECG abnormalities measured at screening should be assessed for their effects on subject eligibility of the study and recorded in medical history. ECG parameters will not be recorded in the CRFs, but any clinically significant changes between the screening and subsequent ECGs should be recorded as an AE. Determination of clinical significance and seriousness will be based on the Investigator's medical judgment.

7.3.5 General Physical Examination

A full general physical examination will consist of an examination of the abdomen, cardiovascular system, lungs, lymph nodes, musculoskeletal and neurological systems, skin, extremities, head, ears, eyes, nose, and thyroid gland by trained medical personnel at the site. A full physical examination will be performed at Screening (Visit 1) and Visit 2 (Day 2).

Height and weight will be assessed at Screening (Visit 1).

Physical examination results will not be recorded in the CRFs, but any clinical significant finding at Screening (Visit 1) should be recorded under medical history and changes between Screening (Visit 1) and subsequent examinations should be recorded as an AE. Determination of clinical significance and seriousness will be based on the investigator's medical judgment.

7.3.6 Blood Volume

Total blood sampling volume for an individual subject is approximately 103.5 mL. Additional blood samples may be taken for safety assessments, provided the total volume taken during the study does not exceed 500 mL during any period of 30 consecutive days, and the ethics committee/IRB is notified of the blood collection.

Table 8: Blood Volume

Sample Type	Sample Volume (mL)	Number of Sampling Times		Total Volume (mL)
		Screening	Study Period	
Safety Labs	21 (Screen) 10.5 (Discharge)	1	1	31.5
PK	4	0	18	72
TOTAL				**103.5**

7.4 Pharmacokinetics

7.4.1 Plasma for Analysis of Meloxicam

Blood samples will be collected at the following times, with the date and time of each sample being recorded in the CRF:

- Pre-dose and 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 14, 16, 20, and 24 hours after the first dose of study medication.

All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (e.g., within 6 minutes of a 60-minute sample) for samples prior to ≤8 hours from dosing and ±1 hour for samples ≥12 hours from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and CRF.

PK sample handling instructions will be provided to the Investigator prior to initiation of the study.

Samples will be analyzed using validated analytical methods in compliance with Mylan standard operating procedures.

As part of understanding the pharmacokinetics of the study drug, samples may be used for metabolite identification and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical report.

7.4.2 Shipment of Pharmacokinetic Samples

The shipment details and assay lab contact information will be provided to the investigator site prior to initiation of the study.

7.5 Restrictions

Study restrictions include all items listed in the Lifestyle Guidelines (Section 4.4) and the concomitant medications as described in the exclusion criteria section of this protocol (Section 4.2.2) and will be prohibited throughout the duration of the study. If concomitant medications change during the study, a discussion between the Principal Investigator or a Medical Sub-Investigator along with Mylan should occur, and a decision to continue or discontinue the subject will be made based on the medication's pharmacology and pharmacokinetics.

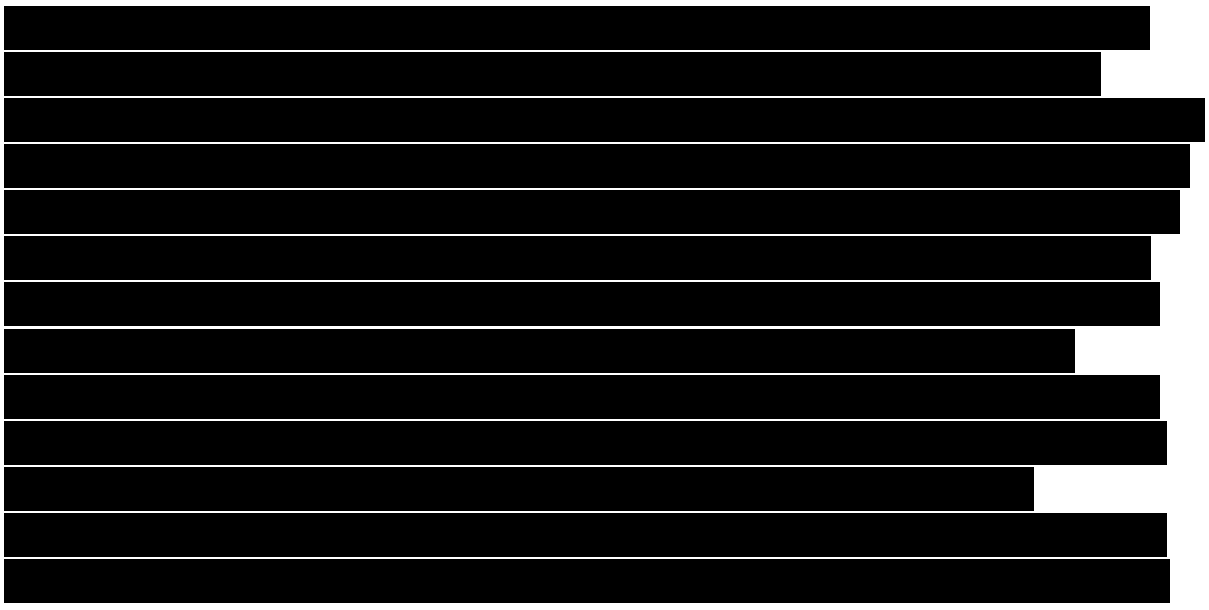
8 STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated and maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

8.1 Sample Size Determination

N=110 subjects (N=22/treatment arm) to give approximately N=100 evaluable subjects for the primary endpoint (N=20/treatment arm). This is on the basis of an approximately 10% dropout rate.

In order to derive the required sample size for the primary endpoint, simulations were performed according to the method described below:



[redacted]

The numerical dose values were 10, 15, 20, 30 and 0 for 10 mg QD, 15 mg QD, 10 mg BID, 15 mg BID and placebo respectively.

[redacted]

[redacted]

[redacted]

8.2 Populations for Analyses

8.2.1 Safety Analysis Set

The safety analysis set (SS) will include all subjects who received at least one dose of study drug. Data will be summarized according to the treatment a subject actually received.

8.2.2 Intent To Treat Analysis Set

The ITT analysis set includes all randomized subjects who received study drug, including subjects who discontinued study treatment or received protocol allowed rescue medication.

8.2.3 Per Protocol Analysis Set

The per protocol analysis set (PP) will include all subjects in the ITT who had no major protocol violation that would impact on the primary efficacy endpoint. Significant protocol deviations are defined in Section 9.4 and will be further defined in the SAP. The list of major protocol deviations will be finalized prior to database lock and unblinding as part of the final blinded data review (BDR). Data will be summarized and analyzed according to the treatment a subject actually received at randomization.

8.2.4 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set (PK) will include all subjects who receive a dose of study medication and who provide at least one post dose concentration sample for the Population PK analysis.

8.3 Statistical Analyses

8.3.1 Definition of the Primary Efficacy Endpoint(s)

The primary efficacy endpoint is the overall (summed) pain intensity difference (SPID) over 0-24 hours.

8.3.2 Primary Analysis of Primary Endpoint

The primary analysis of the primary efficacy endpoint will be based on the intention-to-treat (ITT) population.

The primary efficacy endpoint is the overall (summed) pain intensity difference over 0-24 hours (SPID 0-24).

A 3-parameter E_{max} model will be fitted to the SPID 0-24 standardized means (observed mean for each dose and placebo divided by the pooled standard deviation) for placebo and 5 mg, 10 mg and 15 mg MECC-SA. Standardized effect sizes will be estimated from the E_{max} model together with their 95% confidence intervals and p-values. Baseline pain intensity score (PI) will be used as a covariate in the E_{max} model.

The numerical dose values will be 10, 15, 20, 30 and 0 for 10 mg QD, 15 mg QD, 10 mg BID, 15 mg BID and placebo respectively.

Additional models may be explored utilizing a Multiple Comparison Procedure – Modeling (MCP-Mod) approach [27].

If the E_{max} model fails to converge, and no other suitable models are identified using MCP-Mod, an Analysis of covariance (ANCOVA) will be used to assess the difference between treatment groups for SPID 0-24. The ANCOVA model will include treatment and study site as fixed effects and baseline PI score as a covariate. The difference between MECC-SA and placebo will be estimated from the least squares means (LS means) along with the 95% confidence interval (CI) and associated 2-sided p-values. In addition, the standardized effect sizes for each dose will be calculated by dividing the differences in LS means for each dose and placebo by the pooled standard deviation.

Impact of Protocol Allowed Rescue Medication Use

For the primary analysis of the primary efficacy endpoint a 2-hour windowed last observation carried forward (W2LOCF) approach will be used whereby the PI score obtained before a given rescue medication will be carried forward to replace the PI scores collected at each observation timepoint within 2 hours following the rescue dose.

8.3.3 Secondary/Sensitivity Analysis of Primary Endpoint

Analyses for the primary endpoint will be repeated for the PP (8.2.3).

As a sensitivity analysis of the W2LOCF approach, a W4LOCF will also be used whereby the PI score obtained before a given rescue medication will be carried forward to replace the

PI scores collected at each observation within 4 hours following the rescue dose. The analysis will be conducted in both the ITT and the PP analysis sets.

8.3.4 Missing Data

The amount of missing data is expected to be minimal given the short duration of the study.

- Missing pain assessments for subjects who discontinued early due to lack of efficacy, an AE, or intolerance to study drug will be imputed using a baseline observation carried forward (BOCF) approach.
- Missing pain assessments due to other reasons for discontinuing will be imputed using a last observation carried forward (LOCF) approach.
- In addition to the BOCF/LOCF approaches outlined above, missing data may be imputed using appropriate multiple imputation (MI) methods. Further information will be provided in the SAP.
- Intermittent missing pain assessments between two non-missing scores will be imputed using linear interpolation.

The impact on the computation of the primary efficacy endpoint and the methods for handling missing data may be assessed in secondary/sensitivity analyses and any pre-planned analyses will be fully described in the SAP. As this is a Phase 2 study, additional post-hoc analyses may be carried out in order to more fully understand the data.

8.3.5 Sub-Group Analyses

Subgroup analyses may be specified in the SAP. As this is a Phase 2 study, additional post-hoc analyses may be carried out in order to more fully understand the data.

8.3.6 Definition and Analysis of the Secondary Endpoints

All hypotheses will be tested at a two-sided significance level of 0.05. Nominal p-values will be presented for all secondary endpoints without adjustment for multiple comparisons (since this is a Phase 2 study).

8.3.6.1 Secondary SPID Endpoints and TOTPAR

The SPID endpoints for the time intervals 0-2, 0-4, 0-8, 0-12 and 12-24 hours will be analyzed using the E_{max}/ANCOVA model used for the analysis of the primary endpoint.

The TOTPAR endpoints for the time intervals 0-2, 0-4, 0-8, 0-12, 12-24 and 0-24 hours will be analyzed using the E_{max}/ANCOVA model used for the analysis of the primary endpoint.

8.3.6.2 Pain Intensity Differences (PID) Over Time

PID scores over time will be analyzed using a longitudinal mixed model for repeated measures (MMRM) with fixed effects for treatment, study site, time, treatment by time interaction and baseline PI score. Subject will be fitted as a random effect. Variance

estimation will be based on an unstructured covariance matrix. Missing data will be assumed to be Missing At Random (MAR). Least squares means (LS means) will be plotted by time to show the pain-relieving efficacy of both MECC-SA and placebo over 24 hours.

8.3.6.3 Time to Event Endpoints

The following analysis methods apply to the time-to-event endpoints listed:

- Time to perceptible pain relief (PPR).
- Time to meaningful pain relief (MPR).
- Elapsed time from the start of study medication to first rescue medication administration.

Time to event endpoints will be analyzed and plotted using Kaplan-Meier methodology and differences between MECC-SA and placebo evaluated using the log-rank test. The median time to event will be calculated and presented.

8.3.6.4 Responder Endpoints

The following analysis methods apply to the responder endpoints listed:

- Proportion of subjects with overall pain reductions from baseline of ≥30% and ≥50% within 4 hours following the first dose based on the PI scores. Both these analyses will be presented for both methods of handling rescue medication use (W2LOCF and W4LOCF approaches).
- Proportion of subjects using rescue medication during 0-24 hours.
- Patient's Global Assessment (PGA) of pain control for 0-24 hours after the initial dose scored on the 5-point scale will be dichotomized and the percentage of subjects reporting a PGA score of 2 (good) or better defined as a responder.

The number and percentage of responders in each treatment group will be summarized. A comparison between MECC-SA and placebo will be evaluated with the odds ratio (OR) and corresponding 95% confidence interval from a logistic regression model with treatment group and baseline PI as a covariate.

8.3.6.5 Frequency of Rescue Medication Use

The frequency of rescue medication use will be summarized and graphically presented for the 0-24 hours period after the first dose of study treatment.

8.3.7 Pharmacokinetics

For all pharmacokinetic data analyses, the PK population will be used.

Samples for PK determination of drug concentrations of meloxicam and salicylic acid, in plasma will be determined by a bioanalytical laboratory using validated bioanalytical

methods. Details of the validated bioanalytical method used will be provided in a separate bioanalytical report.

The plasma concentration data for meloxicam and salicylic acid will be listed, summarized on the basis of time intervals, and plotted using a scatter plot with time relative to the preceding meloxicam dosing time. Summary statistics (mean, standard deviation, minimum, maximum, number of subjects, and coefficient of variation) will be calculated for plasma concentrations for each time interval and by treatment group.

Population PK (PPK) analysis of meloxicam and salicylic acid concentrations will be performed using modeling. The PPK analysis will be conducted and reported separately. Details of the PPK model building will be described in a separate PPK analysis plan.

If the dose-response relationship cannot be established in this study (for example, no doses are effective, or all doses are equally effective) then exploratory exposure-response analysis may be conducted using individual predictions of exposure from the PPK analysis in this study. Outcomes from this analysis will be reported separately, if conducted.

8.3.8 Safety Analyses

Analysis of all safety data will be performed on the Safety Population and will be presented by the treatment received.

8.3.8.1 Adverse Events

Adverse events will be coded using the latest version of Medical Dictionary for Regulatory Authorities (MedDRA). The occurrence of AEs and SAEs will be summarized in terms of incidence, as well as in terms of total number of AEs. Analysis of AEs in terms of incidence by severity and by relatedness will also be provided.

Prior and concomitant medications will be coded using the latest version of WHO Drug Dictionary and will be summarized. Medical history will be listed by subject and coded using the latest version of MedDRA and will be summarized.

8.3.8.2 Vital Signs

Blood Pressure and pulse rate will be listed and descriptively summarized (N, mean, standard deviation, minimum and maximum) by treatment group and visit. Baseline (defined as the pre-dose value collected on Visit 2 (Day 1) and changes from baseline will be similarly summarized.

8.3.8.3 ECG Analyses

ECG data; QT, QTc (Fridericia's), heart rate (HR), QRS duration, PR and RR interval will be listed.

Baseline (defined as the pre-dose value collected on Visit 2 (Day 1) and change from baseline for QT, QTcF, HR, QRS, RR and PR will be summarized using descriptive statistics (N, mean, standard deviation, minimum and maximum) by treatment and study week.

For QTcF a classification of absolute values and increases from baseline will be performed. The number of subjects with maximum absolute QTcF <450 msec, 450 msec ≤QTcF <480 msec, 480 msec ≤QTcF <500 msec and QTcF values ≥500 msec will be tabulated by treatment and visit. The number of subjects with maximum increase from baseline QTcF <30 msec, 30 msec ≤QTcF <60 msec and QTcF ≥60 msec will be tabulated by treatment and visit.

8.3.8.4 Laboratory Data

Descriptive summaries of observed values and change from baseline (defined as the samples collected on Screening (Visit 1)) will be presented for clinical laboratory evaluations (Serum chemistry and hematology) by treatment group. Assessments of laboratory variables according to clinical relevance will be tabulated by visit and treatment group for each clinical laboratory parameter in frequency tables. Additionally, for each laboratory parameter, shifts in value from baseline to all post-baseline visits will be presented by treatment group in shift tables.

The assessment of categorical urinalysis variables will be tabulated by visit for each urine parameter by treatment group in frequency tables. Additionally, for each of the urine parameters, shifts in assessments from baseline to all post-baseline visits will be presented for each treatment group in shift tables.

8.3.9 Planned Interim Analyses

Not Applicable.

9 ADMINISTRATIVE PROCEDURES

9.1 Source Documentation Forms

All clinical data will be recorded by the clinical staff on raw data sheets and/or recorded electronically using validated software. If computerized systems are used to create, modify, maintain, archive, retrieve or transmit source data, they must comply with the applicable regulatory regulations and/or guidance.

The nature and location of all source documents will be documented separately. Source data may be directly captured from devices, transferred from 3rd parties (e.g., laboratory data) or entered manually into CRF/database.

9.2 Access to Data/Source Documentation

The Investigator or designated representative will permit full access to data and source documentation for the purpose of clinical monitoring, audits, IRB/IEC review and regulatory inspections.

9.3 Final Clinical Study Report and Case Report Forms (CRFs)

A written clinical study report will be provided in accordance with the International Conference on Harmonization (ICH) E-3 guidelines including Annex I (Synopsis) documenting the clinical execution of the study. This report will include a description of any protocol deviations. The final report will also include reasons for withdrawals and any necessary treatment(s). The report will also include tables presenting demographics (separate summary tables for enrolled and completed subjects), and AEs recorded during the study. In addition, the clinical study report will include a Quality Assurance statement, documenting that the report has been reviewed for completeness, accuracy, and compliance with the protocol and applicable local and federal regulations. For final clinical reporting purposes only, AEs deemed “definite”, “probable” or “possible” will be included in the treatment-related summaries/listings.

Case Report Forms (CRFs) containing data transcribed from subject source documents (as appropriate) and copies of other source documents will be supplied by the clinical site. The Principal Investigator must sign each subject’s CRF after completion of data entry, signifying that the data entered in the CRF is complete and accurate. Electronic CRFs may be provided.

9.4 Adherence to Protocol

Except for an emergency situation in which proper care for the protection, safety and well-being of the study subjects requires medical treatment, the study will be conducted as described in the approved protocol (and amendments, if applicable), GCP and applicable SOPs. In addition, the study will be conducted in accordance with the applicable regulatory requirements of the country where the study is being conducted as well as the country where the study will be submitted. Any deviation(s) from the protocol will be recorded and presented in the final report.

For the purposes of assessing protocol deviations, procedures conducted ±10% of the nominal timepoint will not be considered a protocol deviation.

The following protocol deviations are defined as major and would be considered to have an impact on the analysis of efficacy data:

- Subject did not meet efficacy-defined inclusion criteria (e.g., inclusion criteria 3 and 4)
- Subject did not meet exclusion criteria which may potentially impact the primary efficacy endpoint (to be reviewed and assessed on a case-by-case basis)

- Subject who is not 100% compliant with study medication
- Subject received an excluded concomitant treatment or medication that may impact the primary efficacy endpoint (e.g., a concomitant NSAID or other analgesic that is not pre-specified for rescue medication)

Additional criteria may be specified in the SAP.

9.5 Data Handling and Record Retention

All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected.

A CRF is required to be completed for each subject receiving study medication. The CRF is property of the sponsor and the Investigator must review all CRFs prior to submission to the sponsor.

The CRF may be considered as the source document. The investigator must seek prospective agreement to the sponsor in writing to use the CRF as source document prior the start of the study. In addition, items directly recorded in the CRF must be documented that they will be considered as source.

All records pertaining to the receipt and return of study supplies (particularly study medication) and copies of final case report forms, worksheets, and other pertinent source documents must be retained in accordance with ICH-GCP and the applicable regulatory requirements of the country where the study is being conducted as well as the country where the study will be submitted.

The investigator must obtain in writing the sponsor’s agreement to dispose of any records, even if the retention period has been reached.

9.6 Confidentiality

Information furnished to Clinical Investigators and IRBs/Ethics Committees will be maintained in confidence by the Clinical Investigator and IRB/Ethics Committee. By signing this protocol, the Investigator affirms to the Sponsor that he/she will maintain, in confidence, information furnished to the IRB/Ethics Committee relevant to this study under appropriate understanding of confidentiality with such IRB/Ethics Committee.

By signing the protocol, the Investigator agrees that within local regulatory restrictions and institutional and ethical considerations, the Sponsor may consult and/or copy source documents (e.g., laboratory/X-ray reports, ECG tracings, workbooks, medical records) in order to verify CRF data.

9.7 Ethics and Regulatory Authorities

Guidelines will be followed with regard to the treatment of human subjects in the study, in accordance with the requirements of the Declaration of Helsinki and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH-E6) in addition to the regulatory requirements of the country where the study is being conducted as well as the country where the study will be submitted.

9.7.1 Institutional Review Board/Ethics Committee

The Investigator is responsible for obtaining initial and continuing review (at intervals not more than once per year) of the study by an IRB/Ethics Committee, or in accordance with applicable government regulations of the country where the study is being conducted as well as the country where the study will be submitted. This study will not enroll any subjects until the IRB/Ethics Committee provides written approval of the protocol and the informed consent to the investigator. In addition, a copy of the IRB/Ethics Committee approval documents must be provided to the sponsor prior to enrolling any subjects into the study.

9.7.2 Regulatory Authority

This clinical study protocol, title and a list of investigational sites, IEC(s)/IRB(s) approvals, as well as other relevant documentation will be submitted to the local Regulatory Authorities for review and approval prior to trial start. Upon completion, the Regulatory Authorities will be notified the study has ended. The study will only be undertaken in compliance with the local regulatory requirements.

9.8 Informed Consent

A properly executed, written informed consent in compliance with current GCP guidelines and ICH guidelines shall be obtained from each volunteer prior to entering the study. A copy of the informed consent document(s) to be used will be submitted by the Investigator to an independent institutional review board (e.g., IRB or ethics committee) and the Sponsor and/or its agent for review and approval prior to the start of the study. The Investigator shall provide a copy of the signed and dated informed consent to the subject, and a signed and dated copy shall be maintained in the volunteer's medical record.

9.9 Disclosure and Publication of Clinical Study Data

The disclosure and publication of clinical study data will be detailed in the clinical trial agreement with the Investigators.

9.10 End of Trial

The end of trial is considered to be the date of last subject last visit or the date of early termination of the study whichever is the later.

10 ADVERSE EVENTS AND SAFETY REPORTING

The adverse event collection period begins at signing of informed consent and continues until the telephone End of Study (EOS) Visit. Adverse events occurring during this period need to be reported to the sponsor according to Section 10.3. The Investigator is also responsible for notifying the sponsor if he/she becomes aware of any adverse event after the study period has ended and it is considered related to the study medication (i.e., an adverse drug reaction). Once an AE is detected, it should be followed until its resolution or until it is judged by the principal investigator to be stable or permanent.

10.1 Definitions

Adverse Event

An ***adverse event*** (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory or physical findings, symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product whether or not considered related to the medicinal product.

Clinically significant changes from baseline in laboratory assessments, vital signs, and physical examination are to be recorded as adverse events. Clinically significant abnormalities include:

- a result associated with accompanying signs/symptoms
- a result that requires additional diagnostic testing or medical/surgical intervention
- a result that leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy
- a result considered to be an adverse event by the investigator or sponsor

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

- An abnormal safety assessment (e.g., laboratory, vital signs, ECG) associated with a clinical diagnosis that has been recorded as an AE does not require a separate AE entry
- Events meeting the definition of an AE also include:
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug or drug-food interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. (Please refer to the Section 10.2 for further details)
- A symptom or medical complication related to a protocol-mandated intervention, including screening procedures

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening

NOTE: The term **"life-threatening"** in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- requires inpatient hospitalization or prolongation of existing hospitalization

Note: In patient hospitalization is defined as 24 hours in a hospital or an overnight stay. An elective hospital admission to treat a condition present before exposure to the study drug or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE. Further, an overnight stay in the hospital that is only due to transportation, organization or accommodation problems and without medical background does not need to be considered an SAE.

  - Events NOT to be reported as SAEs are hospitalizations for the following:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen
    - Admission to a hospital or other institution for general care due to social or economic reasons (e.g., no access to local ambulatory medical care)
    - Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission

        - Hospitalization also does not include the following: Rehabilitation facilities, Hospice facilities, Respite care (e.g., caregiver relief), Skilled nursing facilities, Nursing homes

- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event (medically significant)
    - Note: medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject and / or may require intervention to prevent one of the other outcomes listed in the definition above. 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 hospitalization, or development of drug dependency or drug abuse.
    - The seriousness criterion of "medically significant" should **only** be selected when none of the other seriousness criteria apply to the event but the investigator still considers the event as serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Drug Reaction

All noxious and unintended responses to an investigational product related to any dose of the investigational product should be considered adverse drug reactions (ADRs). The phrase "responses to an investigational product" means that a causal relationship between an investigational product and an AE is at least a reasonable possibility. All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to an investigational product will be designated as ADRs.

All AEs, with the causal relationship to the study drug reported as "possible", "probable" or "definite" will be considered ADRs. If the relationship to the study drug is not given, then the AE must be treated as if the relationship were "possible."

Expected/Unexpected Adverse Event

An expected AE is defined as one whose nature, severity or outcome is consistent with the applicable reference safety information described of the study drugs.

An AE is to be considered unexpected if the nature, severity or outcome is not consistent with the applicable product reference safety information.

Preexisting Condition

Any medical condition that is present at the time that the participant is screened will be considered as baseline medical history and not reported as an AE. A baseline or preexisting condition should be recorded as an adverse event only if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

Any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event/Serious Adverse Event

At the last scheduled contact with the subject the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator becomes aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

10.2 Special Situations

The following situations may by associated with a serious outcome and should be evaluated for expedited reporting to the sponsor.

- Any diagnosis of **Cancer** or **Neoplasm** is to be reported as a serious adverse event.
- **Emergency Room Visits:** Events that result in emergency room visits that do not result in admission to the hospital are not routinely considered to be serious events; however, these events should be evaluated for one of the other serious outcomes (e.g., life-threatening, other serious [medically significant] events).
- **Overdose:** Overdose *per se* will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent; this should be reported regardless of sequelae. Signs and symptoms associated with accidental overdose are to be recorded as adverse events or as serious AEs. If adverse events associated with overdose fulfil any of the serious criteria (as defined in section '**Serious Adverse Event**'), a completed SAE report form is required to be submitted.
- Reports of **Drug-drug interaction and Drug Abuse and Medication Errors**: drug interactions or abuse of the study medication must be recorded as AEs. Medication errors will be captured as protocol deviations while any associated signs or symptoms must be recorded as AEs on the CRF. In addition, any serious consequence of drug

interactions, drug abuse, or medication error must be reported immediately if these fulfil any of the SAE criteria.

10.2.1 Adverse Events of Special Interest

Adverse events of special interest given that MECC-SA is an NSAID will include the following:

- Myocardial Infarction/Unstable Angina
- Stroke/transient ischemic attack (TIA)
- Heart Failure
- Cardiac Arrhythmia (Atrial & Ventricular)
- Gastrointestinal haemorrhages NEC
- Gastrointestinal ulceration and perforation

Any AESI should be reported per the SAE reporting process per Section 10.5.

10.3 Collection and Recording of Adverse Events

During the Adverse Event Reporting Period, the PI will record all adverse events. At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and in the appropriate adverse event module of the case report form (CRF). Information to be collected includes AE name or term (in standard medical terminology) and final diagnosis, event description, time and date of onset, clinician's assessment of severity, seriousness, relationship to study product (assessed only by those with the training and authority to make a diagnosis), action taken with the study drug, treatment for the event and time (if available) and date of resolution/stabilization of the event.

Any findings from protocol specified safety assessments that are associated with the indication being studied are not to be reported as AEs or SAEs, unless judged by the investigator to be more severe than expected for the subject's condition.

All clearly related signs, symptoms, and abnormal results of diagnostic procedures should be grouped under one diagnosis on the CRF where possible and appropriate.

The clinical course of each event should be followed until resolution or stabilization. Adverse events that are still ongoing at the end of the study period must be followed up to determine the outcome. Any adverse event that occurs after the study period and is related to the study treatment or study participation should be recorded; and if serious, the investigator should also immediately report it to the Sponsor.

10.4 Classification of an Adverse Event

10.4.1 Severity

The Investigator will assign a severity rating to each AE. For purposes of consistency, the following scale is to be used:

Grade 1 - MILD	Does not interfere with subject's usual function.
Grade 2 - MODERATE	Interferes to some extent with subject's usual function.
Grade 3 - SEVERE	Interferes significantly with subject's usual function.

It is important to distinguish between severe AEs and Serious AEs. Severity is a classification of intensity, whereas an SAE is an AE that meets any of the regulatory specified criteria (see definitions, Serious Adverse Event).

10.4.2 Causality

For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality of each AE.

An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE. The Investigator must make an assessment of the relationship of each AE (serious and non-serious) to the study treatment(s) and record this relationship in the CRF.

Factors that need to be considered when making a causality assessment include: Temporal relationship, Clinical and pathological characteristics of the event(s), Pharmacological plausibility, Exclusion of confounding factors (medical and medication history), Drug interactions, De-challenge/re-challenge, Dose relationship.

A suspected relationship (definite, probable, possible) between the events and the study medication means, in general, that there are facts (evidence) or arguments to suggest a causal relationship. Receipt of additional or clarifying information may warrant reassessment of causality. The Investigator is responsible for assessing relationship of AEs to study treatment in accordance with the following definitions:

Category	Causality	Description
DEFINITE	Causal relationship is certain	For example: the temporal relationship between drug exposure and the adverse event (AE) onset/course is reasonable, there is a clinically compatible response to de-challenge, other causes have been eliminated; the event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.
PROBABLE	High degree of certainty for	For example: the temporal relationship between drug exposure and AE onset/course is reasonable,

Category	Causality	Description
	causal relationship	there is a clinically compatible response to de-challenge (re-challenge is not required), and other causes have been eliminated or are unlikely.
POSSIBLE	Causal relationship is uncertain	For example: the temporal relationship between study treatment exposure and the AE onset/course is reasonable or unknown, de-challenge information is either unknown or equivocal; could also be explained by disease or other drugs.
UNLIKELY	Causal relationship is improbable	Another explanation is more likely such as disease, environment, or other medication. Does not represent a known reaction to study drug.
UNRELATED/NOT RELATED	No possible relationship	The temporal relationship between drug exposure and the AE onset/course is unreasonable or incompatible, or a causal relationship to study drug is impossible

For SAEs, if the relationship to the study treatment(s) is considered to be unlikely or not related, an alternative suspected etiology should be provided when possible (e.g., concomitant medications, intercurrent illness/events, study-related procedure).

10.4.3 Expectedness

The Sponsor or its designated representative will be responsible for determining whether an AE is expected or unexpected based on the reference safety information. The reference safety information mentioned in the IB will be used in this study for the expectedness assessment of SAEs.

10.4.4 Outcome

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Sponsor or its designated representative.

The outcome at the time of last observation will be classified as:

RECOVERED/RESOLVED where the subject recuperated and is free of any pathological conditions resulting from the prior disease or injury.

RECOVERED WITH SEQUELAE where the subject recuperated but retained pathological conditions resulting from the prior disease or injury.

NOT RECOVERED/NOT RESOLVED (i.e. ongoing) where the subject has not recuperated from the condition or injury and the event is still considered ongoing.

RECOVERING where the subject has begun to recuperate from the condition or injury, but the event is considered ongoing at a reduced intensity.

FATAL the condition or injury results in the subject's death. The investigator should identify the principal cause of death and assign Fatal outcome to that event. Other concurrent ongoing AE/SAEs present at the time of death would remain Not recovered/Not resolved.

UNKNOWN can be selected if none of the other situations apply or are known. Follow-up should be conducted to obtain one of the preceding outcomes.

10.4.5 Action Taken With the Study Treatment

Action	Description
Treatment interrupted	The treatment was temporarily discontinued
Treatment withdrawn	The treatment was permanently discontinued
Unknown	Not known, not observed, not recorded, or refused
No action taken	The AE did not result in any modification of dose or frequency of dosing
Not applicable	The AE occurred prior to first dose or following last scheduled dose

10.5 Reporting of Serious Adverse Events and Pregnancy Exposures

Investigators and the Sponsor or its designated representative must conform to the serious adverse event reporting timelines, formats and requirements of the various entities to which they are responsible.

10.5.1 Investigator Reporting: Notifying the Study Sponsor

Immediate notification of SAEs by the investigator to Mylan PSRM is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

Mylan will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Serious adverse events must be reported to the study sponsor within 24 hours of awareness. To report such events, a Serious Adverse Event (SAE) Report form must be completed and signed by the investigator or designee and forwarded to:

[redacted]

If the initial notification using the completed 'SAE report form' is not possible, the notification may be made via email/fax or over telephone with the following minimum necessary information

- Study identifier
- Study Center
- Subject number
- A description of the event
- Current status (outcome of event-if known and whether study medication is continuing)
- The reason why the event is classified as serious
- Investigator assessment of the causality between the event and study treatment

The investigator should provide further information on the as soon as possible, preferably within 48 hours of awareness. This should include a copy of the completed SAE Report form, and any other diagnostic information and medical records that will assist in the understanding of the event.

Subject identifying information must not be visible on SAE forms or any supporting documentation provided by the Investigator. Any information that could be used to identify the subject (e.g., name, address, medical record number) must be de-identified before submission to Mylan or its designee. The subject's study specific ID number should be recorded on every page of documentation forwarded to the sponsor.

The PI should provide the final diagnosis as the SAE term whenever possible in the SAE report form and CRF. The signs and symptoms should be provided in the narrative only, not as SAE terms. The PI should only list all signs and symptoms as SAE terms if no diagnosis is available at the time of report.

10.5.2 Follow-up

New information and any important missing information from prior reports on a serious adverse event must be provided promptly to the study sponsor. In addition, the Investigator may be requested by Mylan/designee to obtain specific additional follow-up information in an expedited fashion. The investigator should respond to targeted follow-up requests as soon as possible and preferably within 48 hours from receipt of the request.

10.5.3 Investigator reporting: Notifying the Ethics Committee

Investigators are responsible for safety reporting to their local Ethics Committee (LEC) and complying with their local EC's reporting requirements. Copies of each report and documentation of LEC notification and receipt will be kept in the investigator's study file.

10.5.4 Investigator Reporting of Pregnancy: Notifying the Study Sponsor

All subjects who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation as

detailed in the inclusion and exclusion criteria. Pregnancy testing will be conducted throughout the study, as detailed in the schedule of assessments.

A subject who is found to be pregnant at the screening visit will be excluded from the study and will be a screening failure.

Subjects who have been enrolled in the study should be instructed to contact the Investigator or study staff immediately if pregnancy occurs or is suspected. Early termination visit assessments are required as soon as possible after learning of the pregnancy. Pregnant females will be discontinued from study treatment by the Investigator. A male that has a partner that becomes pregnant during the study will not be discontinued from study treatment.

Details of the pregnancy should be recorded on the Pregnancy Report form and reported to [redacted] within 24 hours of awareness by email [redacted] or [redacted] from the time of initial awareness, even if beyond the closure of the clinical database.

The Investigator is also responsible for following the pregnancy every 3 months or until delivery or termination and informing the Sponsor about its outcome. Reports where the embryo or fetus may have been exposed to the study drug(s), should be followed-up in order to collect information on the:

- outcome of the pregnancy,
- outcome for both mother and fetus (malformation/anomalies diagnosed since initial report)
- development of the child after birth (developmental assessment, infant illnesses, hospitalizations, drug therapies, breastfeeding)

Healthy newborns should be followed-up at 1 month after birth to confirm no congenital anomalies were subsequently detected (if possible).

While pregnancy itself is not considered an AE or SAE, any pregnancy complication or termination of a pregnancy for medical reasons will be recorded as an AE or an SAE. A spontaneous abortion is always considered to be a SAE and will be reported to the Sponsor.

Elective termination (i.e., without medical reasons) of an uncomplicated pregnancy is considered an elective procedure and not an AE; nevertheless, Mylan requests the outcome (e.g., elective termination) be reported within 24 hours of awareness and sent as a follow-up on the Delivery and Infant Follow-up Form).

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as at least possibly related to the study treatment, must be promptly reported to Mylan PSRM.

If the study center becomes aware of a pregnancy in a female partner of a male subject, study personnel should contact their clinical research associate to obtain a partner pregnancy ICF.

Consent of the pregnant partner must be obtained before any details of the pregnancy can be shared with Mylan or its designated representative. If the pregnant partner provides consent to have the pregnancy followed, the study center should collect the information specified on the Pregnancy Report form and forward the completed form to Mylan PSRM every 3 months until the pregnancy outcome has been obtained.

11 PROTOCOL AMENDMENT DETAILS

11.1 Global Amendment 1, 11 May 2020

11.1.1 Reason for Amendment

[redacted] exclude subjects <18 years of age was made along with a request to ensure proactive monitoring for GI adverse events.

In addition, clarifications and correction of typographical errors/inconsistencies have been made. The corrections include minor changes to the sample size justification sections to reflect the BID dosing regimens; this does not change the number of subjects required for the study.

11.1.2 Sections Changed

Synopsis – Study Treatment

Changed From

To maintain the blind due to differences in appearance between the tablets, subjects will be blindfolded and receive two tablets when dosed; to maintain the blind between QD and BID arms, subjects assigned to QD arms will receive placebo at the second dose.

Changed To

To maintain the blind due to differences in appearance between the tablets, subjects will receive in a double dummy design, two tablets when dosed (one that is representative of a 10 mg tablet and one that is representative of a 15 mg tablet). Due to the double dummy design, neither the subject, nor the Investigator will know what treatment a subject receives. To maintain the blind between QD and BID arms, subjects assigned to QD arms will receive placebo at the second dose. Per the clinic procedures, subjects will also be blindfolded during dosing.

Synopsis Inclusion Criteria

Changed From

1. Males and females ≥16 years of age. Females may be of either childbearing or non-childbearing potential. All females of childbearing potential must be using an acceptable, highly effective method of contraception and have a negative serum pregnancy test at screening.

Changed To

1. Males and females ≥18 years of age. Females may be of either childbearing or non-childbearing potential. All females of childbearing potential must be using an acceptable, highly effective method of contraception and have a negative serum pregnancy test at screening.

Synopsis – Statistical Methods

Changed From

In order to derive the required sample size for the primary endpoint, a [redacted]

Changed To

In order to derive the required sample size for the primary endpoint, a [redacted]

[redacted]

Table 1: Study Schedule

Changed From

9 All AEs will be recorded from time of consent until the telephone follow up/End of Study (EOS) Visit. The Investigator is also responsible for notifying the sponsor if they become aware of any AE after the study period has ended and it is considered related to the study medication.

Changed To

9 All AEs will be recorded from time of consent until the telephone follow up/End of Study (EOS) Visit. The Investigator is also responsible for notifying the sponsor if they become aware of any AE after the study period has ended and it is considered related to the study medication. When assessing AEs, the subject will be specifically asked regarding the presence of any GI symptoms.

1.2 Background and Rationale

Changed From

Higher doses of MOBIC (22.5 mg and greater) have been associated with an increased risk of serious GI events, [redacted]

Changed To

Higher doses of MOBIC (22.5 mg and greater) have been associated with an increased risk of serious GI events, [redacted]

MECC-SA contains salicylic acid as a co-former, this is at a low dose (up to 11.6 mg for BID dosing of MECC-SA 15 mg) which is anticipated to have negligible physiological effects. However, it is acknowledged that salicylic acid (and acetylsalicylic acid) at higher doses can cause adverse effects, such as local gastrointestinal effects such as ulceration of the GI tract, particularly when administered with other NSAIDs. As the potential for local GI toxicity for salicylic acid is not known all GI symptoms should be assessed and documented.

1.3 Investigational Product

Changed From

Salicylic acid is used as the co-former in the MECC-SA tablets. Considering that meloxicam is a BCS Class II compound, the rate-limiting step for meloxicam absorption is solubility. The intended use of salicylic acid in MECC-SA is to increase the rate of absorption of meloxicam by increasing its solubility and dissolution.

Changed To

Salicylic acid is used as the co-former in the MECC-SA tablets. Considering that meloxicam is a BCS Class II compound, the rate-limiting step for meloxicam absorption is solubility. The intended use of salicylic acid in MECC-SA is to increase the rate of absorption of meloxicam by increasing its solubility and dissolution. The dose of salicylic acid (5.8 mg and 11.6 mg considering QD and BID dosing of MECC-SA 15 mg, respectively) used in MECC-SA formulation is considered as a subtherapeutic dose (approved oral clinical doses of acetylsalicylic acid are in the range of 50- 325 mg/day) with negligible physiological effects. Whilst the side effect profile of acetylsalicylic acid is well known, including local effects on the GI tract, it is acknowledged that the local side effects of its metabolite (via hydrolysis in the GI tract, liver and plasma) salicylic acid when given orally are unknown, although a fraction of acetylsalicylic acid is metabolized to salicylic acid in the GI tract prior to absorption. Considering the low dose of salicylic acid in the formulation, MECC-SA is not considered a new fixed combination drug.

1.4 Ethics and Benefit-Risk Considerations

Changed From

The age of subjects (including those aged 16-18 years) is reflective of the population of subjects needing the removal of third molars. The use of NSAIDs in adolescent subjects is common, with side effects similar to those of adult subjects [28]; [29]. Further, the systemic exposure of meloxicam in adolescent subjects is similar to that of adult subjects [30].

Changed To

~~The age of subjects (including those aged 16-18 years) is reflective of the population of subjects needing the removal of third molars. The use of NSAIDs in adolescent subjects is common, with side effects similar to those of adult subjects [28]; [29]. Further, the systemic exposure of meloxicam in adolescent subjects is similar to that of adult subjects [30].~~

4.2.1 Inclusion Criteria

Changed From

1. Males and females ≥16 years of age. Females may be of either childbearing or non-childbearing potential. All females of childbearing potential must be using an acceptable,

highly effective method of contraception and have a negative serum pregnancy test at screening.

Changed To

1. Males and females ≥18 years of age. Females may be of either childbearing or non-childbearing potential. All females of childbearing potential must be using an acceptable, highly effective method of contraception and have a negative serum pregnancy test at screening.

5.1 Investigational Drug

Changed From

MECC-SA will be provided as 10 and 15 mg tablets.

- 15 mg tablets (and matching placebo) [redacted]
- 10 mg tablets (and matching placebo) [redacted]

Placebo is a tablet identical to the corresponding dose of active study drug.

To maintain the blind, subjects will be blindfolded and take two tablets of study drug or placebo will be administered on one day, Visit 2 (Day 1). To maintain the blind, regarding QD and BID dosing, subjects assigned to QD treatment arms will receive placebo at the second dose.

Study drugs will be administered following randomization and approximately 12 hours following the first dose.

Changed To

MECC-SA will be provided as 10 and 15 mg tablets.

- 15 mg tablets (and matching placebo) [redacted]
- 10 mg tablets (and matching placebo) [redacted]

Placebo is a tablet identical to the corresponding dose of active study drug.

To maintain the blind, subjects will take in a double dummy design, two tablets (one that is representative of a 10 mg tablet and one that is representative of a 15 mg tablet) of study drug or placebo will be administered on one day, Visit 2 (Day 1). Due to the double dummy design, neither the subject, nor the Investigator will know what treatment a subject receives. To maintain the blind, regarding QD and BID dosing, subjects assigned to QD treatment arms

will receive placebo at the second dose. Additionally, per the clinic procedures, subjects will be blindfolded during dosing.

Study drugs will be administered following randomization and approximately 12 hours following the first dose.

5.1.1 Administration of Study Drugs

Changed From

Study drug (two tablets containing MECC-SA or matching placebo) will be administered in the clinic at each dosing time.

Changed To

Study drug (two tablets containing MECC-SA or matching placebo) will be administered in a double dummy design at the clinic at each dosing time.

6.2.1.2 Dosing and Post Dose Procedures

Changed From

- Adverse events should be assessed throughout the day.

Changed To

- Adverse events should be assessed throughout the day.
    - When assessing AEs, the subject will be specifically asked regarding the presence of any GI symptoms.

6.2.2 Visit 2 (Day 2)

Changed From

- Adverse events should be assessed throughout the day.

Changed To

- Adverse events should be assessed throughout the day.
    - When assessing AEs, the subject will be specifically asked regarding the presence of any GI symptoms.

6.2.2.1 Discharge Procedures

Changed From

- Adverse events should be assessed throughout the day.

Changed To

- Adverse events should be assessed throughout the day.

- When assessing AEs, the subject will be specifically asked regarding the presence of any GI symptoms.

6.2.3 Early Termination (ET) visit

Changed From

- Adverse Event assessment.

Changed To

- Adverse Event assessment.
  - When assessing AEs, the subject will be specifically asked regarding the presence of any GI symptoms.

6.3 End of Study (EOS) Visit

Changed From

- Adverse Event assessment.

Changed To

- Adverse Event assessment.
  - When assessing AEs, the subject will be specifically asked regarding the presence of any GI symptoms.

7.3.1 Adverse Event Assessment

Changed From

Subjects will be routinely queried in regard to the presence or absence of AEs using open ended questions.

Changed To

Subjects will be routinely queried in regard to the presence or absence of AEs using open ended questions. When assessing AEs, the subject will be specifically asked regarding the presence of any GI symptoms.

7.3.6 Blood Volume

Changed From

Total blood sampling volume for an individual subject is approximately 201.5 mL. Additional blood samples may be taken for safety assessments, provided the total volume taken during the study does not exceed 500 mL during any period of 30 consecutive days, and the ethics committee/IRB is notified of the blood collection.

Sample Type	Sample Volume (mL)	Number of Sampling Times		Total Volume (mL)
		Screening	Study Period	
Safety Labs	21 (Screen) 10.5 (Discharge)	1	1	21.5
PK	10	0	18	180
TOTAL				**201.5**

Changed To

Total blood sampling volume for an individual subject is approximately 103.5 mL. Additional blood samples may be taken for safety assessments, provided the total volume taken during the study does not exceed 500 mL during any period of 30 consecutive days, and the ethics committee/IRB is notified of the blood collection.

Sample Type	Sample Volume (mL)	Number of Sampling Times		Total Volume (mL)
		Screening	Study Period	
Safety Labs	21 (Screen) 10.5 (Discharge)	1	1	31.5
PK	4	0	18	72
TOTAL				**103.5**

8.1 Sample Size Determination

Changed From

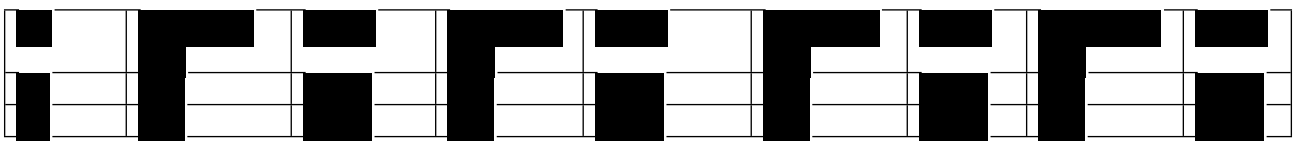
[redacted]

[redacted]

[redacted]

Changed To

[redacted]



[redacted]

The same power calculation method was applied to the secondary endpoints SPID 0-8 and TOTPAR24. [redacted]

9.8 Informed Consent

Changed From

A properly executed, written informed consent in compliance with current GCP guidelines and ICH guidelines shall be obtained from each volunteer prior to entering the study. For subjects <18 years of age, where necessary, according to local regulations, parental consent and subject assent will be obtained.

Changed To

A properly executed, written informed consent in compliance with current GCP guidelines and ICH guidelines shall be obtained from each volunteer prior to entering the study.

11.2 Global Amendment 2, 25 June 2020

11.2.1 Reason for Amendment

[redacted] the role of CYP2C9 in the metabolism of meloxicam, Mylan has amended the Protocol to exclude subjects taking strong inhibitors and inducers of CYP2C9.

11.2.2 Sections Changed

Synopsis – Exclusion Criteria

Changed From

16. Use of medications with the potential to interact with MECC-SA (as indicated in the current Investigator's Brochure), or medications required during the study such as local anesthesia or sedatives, or medications with the potential to affect or confound pain status during the study. This includes (but not limited to) use of any of the following medications:

- Long term opioid use (>30 consecutive days in the past year) and/or use of extended release opioids within 30 days of the dental extraction.
- Antiepileptic drugs within 28 days prior to the study.
- Tricyclic anti-depressants, monoamine oxidase inhibitors, or SNRIs within 28 days prior to the study.
- Sedative or hypnotic drugs within 28 days prior to the study (other than the nitrous oxide used during the operation).
- Use of "medical" or recreational marijuana within 28 days prior to the study.
- Warfarin within 28 days prior to the study.
- Apixaban within 28 days prior to the study.
- Lithium within 28 days prior to the study.
- Methotrexate within 28 days prior to the study.
- Calcineurin inhibitors (e.g., cyclosporine and tacrolimus) within 28 days prior to the study.
- Pemetrexed within 28 days prior to the study.
- Combination of diuretic with ACE inhibitor or angiotensin receptor blocker within 28 days prior to the study.
- Gabapentin or pregabalin within 28 days prior to the study.
- Cholestyramine within 7 days prior to the study.
- Meloxicam within 7 days prior to the surgery.

- Aspirin within 7 days prior to the surgery.
- Analgesics (including opioids, acetaminophen and NSAIDs) within 24 hours prior to the surgery.

Changed To

16. Use of medications with the potential to interact with MECC-SA (as indicated in the current Investigator's Brochure), or medications required during the study such as local anesthesia or sedatives, or medications with the potential to affect or confound pain status during the study. This includes (but not limited to) use of any of the following medications:

- Strong CYP2C9 inhibitors or inducers within 28 days or 5 half-lives (whichever is longer) prior to the study.
- Long term opioid use (>30 consecutive days in the past year) and/or use of extended release opioids within 30 days of the dental extraction.
- Antiepileptic drugs within 28 days prior to the study.
- Tricyclic anti-depressants, monoamine oxidase inhibitors, or SNRIs within 28 days prior to the study.
- Sedative or hypnotic drugs within 28 days prior to the study (other than the nitrous oxide used during the operation).
- Use of "medical" or recreational marijuana within 28 days prior to the study.
- Warfarin within 28 days prior to the study.
- Apixaban within 28 days prior to the study.
- Lithium within 28 days prior to the study.
- Methotrexate within 28 days prior to the study.
- Calcineurin inhibitors (e.g., cyclosporine and tacrolimus) within 28 days prior to the study.
- Pemetrexed within 28 days prior to the study.
- Combination of diuretic with ACE inhibitor or angiotensin receptor blocker within 28 days prior to the study.
- Gabapentin or pregabalin within 28 days prior to the study.
- Cholestyramine within 7 days prior to the study.
- Meloxicam within 7 days prior to the surgery.
- Aspirin within 7 days prior to the surgery.

- Analgesics (including opioids, acetaminophen and NSAIDs) within 24 hours prior to the surgery.

3.1 Overall Design

Changed From

This will be a randomized, double-blind, placebo-controlled, parallel group, dose-ranging study, randomizing approximately 110 male or female subjects that have had third molar dental surgery. Subjects will receive a single dose of study drug on Day 1.

Changed To

This will be a randomized, double-blind, placebo-controlled, parallel group, dose-ranging study, randomizing approximately 110 male or female subjects that have had third molar dental surgery. Subjects will receive a dose of study drug on Day 1 after surgery and a further dose approximately 12 hours later.

4.2.2 Exclusion Criteria

Changed From

16. Use of medications with the potential to interact with MECC-SA (as indicated in the current Investigator's Brochure), or medications required during the study such as local anesthesia or sedatives, or medications with the potential to affect or confound pain status during the study. This includes (but not limited to) use of any of the following medications:

- Long term opioid use (>30 consecutive days in the past year) and/or use of extended release opioids within 30 days of the dental extraction.
- Antiepileptic drugs within 28 days prior to the study.
- Tricyclic anti-depressants, monoamine oxidase inhibitors, or SNRIs within 28 days prior to the study.
- Sedative or hypnotic drugs within 28 days prior to the study (other than the nitrous oxide used during the operation).
- Use of "medical" or recreational marijuana within 28 days prior to the study.
- Warfarin within 28 days prior to the study.
- Apixaban within 28 days prior to the study.
- Lithium within 28 days prior to the study.
- Methotrexate within 28 days prior to the study.
- Calcineurin inhibitors (e.g., cyclosporine and tacrolimus) within 28 days prior to the study.
- Pemetrexed within 28 days prior to the study.

- Combination of diuretic with ACE inhibitor or angiotensin receptor blocker within 28 days prior to the study.
- Gabapentin or pregabalin within 28 days prior to the study.
- Cholestyramine within 7 days prior to the study.
- Meloxicam within 7 days prior to the surgery.
- Aspirin within 7 days prior to the surgery.
- Analgesics (including opioids, acetaminophen and NSAIDs) within 24 hours prior to the surgery.

Changed To

16. Use of medications with the potential to interact with MECC-SA (as indicated in the current Investigator's Brochure), or medications required during the study such as local anesthesia or sedatives, or medications with the potential to affect or confound pain status during the study. This includes (but not limited to) use of any of the following medications:

- Strong CYP2C9 inhibitors or inducers within 28 days or 5 half-lives (whichever is longer) prior to the study.
- Long term opioid use (>30 consecutive days in the past year) and/or use of extended release opioids within 30 days of the dental extraction.
- Antiepileptic drugs within 28 days prior to the study.
- Tricyclic anti-depressants, monoamine oxidase inhibitors, or SNRIs within 28 days prior to the study.
- Sedative or hypnotic drugs within 28 days prior to the study (other than the nitrous oxide used during the operation).
- Use of "medical" or recreational marijuana within 28 days prior to the study.
- Warfarin within 28 days prior to the study.
- Apixaban within 28 days prior to the study.
- Lithium within 28 days prior to the study.
- Methotrexate within 28 days prior to the study.
- Calcineurin inhibitors (e.g., cyclosporine and tacrolimus) within 28 days prior to the study.
- Pemetrexed within 28 days prior to the study.
- Combination of diuretic with ACE inhibitor or angiotensin receptor blocker within 28 days prior to the study.

- Gabapentin or pregabalin within 28 days prior to the study.
- Cholestyramine within 7 days prior to the study.
- Meloxicam within 7 days prior to the surgery.
- Aspirin within 7 days prior to the surgery.
- Analgesics (including opioids, acetaminophen and NSAIDs) within 24 hours prior to the surgery.

8.1 Sample Size Determination

Changed From

Table 9: Power Calculations For The Primary Endpoint

[redacted]

Changed To

Table 9: Power Calculations For The Primary Endpoint

[redacted]

11.3 Global Amendment 3, 10 September 2020

11.3.1 Reason for Amendment

[redacted], the protocol has been amended to include a statement that dental surgery and related anesthesia, sedation, and prophylactic antibiotics are not investigational and will occur regardless of research.

In addition, [redacted] a vital signs assessment has been added prior to surgery and the order of some procedures has been amended to better fit with clinic preferred processes.

Measuring salicylic acid concentrations have also been added to the PK samples.

11.3.2 Sections Changed

Synopsis

Changed From

PK parameters for meloxicam (C_{max}, $pAUC_{0-4}$, $pAUC_{0-24}$) will also be calculated.

Changed To

PK parameters for meloxicam and salicylic acid (C_{max}, $pAUC_{0-4}$, $pAUC_{0-24}$) will also be calculated.

Table 1: Study Schedule

Changed From

3 Vital signs (blood pressure and pulse rate) are taken pre-dose and 24 hours post dose performed after ECG measurements taken at the same nominal time.

Changed To

3 Vital signs (blood pressure and pulse rate) are taken prior to surgery, pre-dose and 24 hours post dose performed after ECG measurements taken at the same nominal time.

Section 2.2.2

Changed From

PK

- Population PK parameters for meloxicam (C_{max}, $pAUC_{0-4}$ and $pAUC_{0-24}$).

Changed To

PK

Population PK parameters for meloxicam and salicylic acid (C_{max}, $pAUC_{0-4}$ and $pAUC_{0-24}$).

Section 6.1.1 Screening (Visit 1)

Changed From

At Screening (Visit 1), the following will be completed in the specified order:

- Written informed consent.
- IVRS/IWRS registration.
- Complete medical history, demographics.
- Complete history of all prescription or non-prescription drugs, dietary supplements taken within 28 days prior to consent. History of alcohol or illicit drug use.

- General physical examination, including respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurological systems, lymph nodes, skin, extremities, head, ears, eyes, nose, and thyroid gland.
- Measure height and weight.
- Record 12-lead ECG – supine or semi-recumbent.
- Record vital signs – supine or semi-recumbent blood pressure (BP) and pulse rate (PR).
- Serum pregnancy test for all female subjects.
- Urinalysis (for blood, protein etc.). Sample to be tested for microscopy/culture if positive for blood, protein, nitrites or leukocyte esterase.
- Urine drug screen.
- Blood will be collected for safety laboratory tests. Laboratory tests at screening include confirmation of non-childbearing potential in any female who has been amenorrheic for at least 2 years, via serum FSH.
- Review AEs (AEs are to be recorded starting from signature of consent).
- Check study inclusion/exclusion criteria.
- Schedule Visit 2 (Day 1) and remind the subject of lifestyle and study drug and concomitant medication requirements for visits.

Changed To

At Screening (Visit 1), the following will be completed; procedures can be performed in a different order, but informed consent must be obtained prior to any procedures and the 12-lead ECG must be performed prior to vital signs or obtaining blood samples.

- Written informed consent.
- IVRS/IWRS registration.
- Complete medical history, demographics.
- Complete history of all prescription or non-prescription drugs, dietary supplements taken within 28 days prior to consent. History of alcohol or illicit drug use.
- Record 12-lead ECG – supine or semi-recumbent.
- Record vital signs – supine or semi-recumbent blood pressure (BP) and pulse rate (PR).
- Measure height and weight.
- Serum pregnancy test for all female subjects.

- Blood will be collected for safety laboratory tests. Laboratory tests at screening include confirmation of non-childbearing potential in any female who has been amenorrheic for at least 2 years, via serum FSH.
- Urinalysis (for blood, protein etc.). Sample to be tested for microscopy/culture if positive for blood, protein, nitrites or leukocyte esterase.
- Urine drug screen.
- General physical examination, including respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurological systems, lymph nodes, skin, extremities, head, ears, eyes, nose, and thyroid gland.
- Check study inclusion/exclusion criteria.
- Review AEs (AEs are to be recorded starting from signature of consent).
- Schedule Visit 2 (Day 1) and remind the subject of lifestyle and study drug and concomitant medication requirements for visits.

Section 6.2.1 Visit 2 (Day 1)

Changed From

6.2.1 Visit 2 (Day 1)

Procedures will be completed in the following order:

6.2.1.1 Pre-Dose Procedures

- Review AEs.
- Check the subject has fasted from midnight.
- Review concomitant medications.
- Perform urine drug screen.
- Urine pregnancy test (if female of childbearing potential).
- Check study inclusion/exclusion criteria.
- Record body temperature.
- Diary training.
- Perform dental surgery, using appropriate local anesthesia and sedation (performed using nitrous oxide and a local injection of lidocaine with epinephrine). Subjects will also receive prophylactic antibiotics post-surgery.
- Pain assessments (Pain Intensity (0-10-point numeric pain rating scale – NPRS) and Categorical Pain Rating (4-point scale – none, mild, moderate, severe)) will be made during the 5 hours post-surgery until a baseline pain assessment is achieved.

- Subjects with NPRS ≥5 and a rating of moderate or severe pain on a 4-point categorical pain rating scale (i.e., none, mild, moderate, severe) during this time they will be eligible for randomization.

- Randomization using IVRS/IWRS.
  - To occur such that dosing occurs within 15 minutes of the eligible pain scores.
- 12-lead ECG – supine or semi-recumbent taken prior to dosing.
- Vital signs (BP and PR) – supine or semi-recumbent taken prior to dosing.
- Blood for a PK sample taken prior to dosing.

Changed To

6.2.1 Visit 2 (Day 1)

The following procedures will be completed; procedures can be performed in a different order as long as they are performed at the correct nominal time and would not impact on other tests, e.g., 12-lead ECGs that are taken at the same nominal time as vital signs or blood samples are taken prior to those other procedures:

6.2.1.1 Pre-Dose Procedures

- Check the subject has fasted from midnight.
- Review AEs.
- Review concomitant medications.
- Record vital signs – supine or semi-recumbent blood pressure (BP) and pulse rate (PR).
- Perform urine drug screen.
- Urine pregnancy test (if female of childbearing potential).
- Check study inclusion/exclusion criteria.
- Record body temperature.
- Diary training.
- Perform dental surgery, using appropriate local anesthesia and sedation (performed using nitrous oxide and a local injection of lidocaine with epinephrine). Subjects will also receive prophylactic antibiotics post-surgery.
- Pain assessments (Pain Intensity (0-10-point numeric pain rating scale – NPRS) and Categorical Pain Rating (4-point scale – none, mild, moderate, severe)) will be made during the 5 hours post-surgery until a baseline pain assessment is achieved.

  - Subjects with NPRS ≥5 and a rating of moderate or severe pain on a 4-point categorical pain rating scale (i.e., none, mild, moderate, severe) during this time they will be eligible for randomization.

- Randomization using IVRS/IWRS.
  - To occur such that dosing occurs within 15 minutes of the eligible pain scores.
- 12-lead ECG – supine or semi-recumbent taken prior to dosing.
- Vital signs (BP and PR) – supine or semi-recumbent taken prior to dosing.
- Blood for a PK sample taken prior to dosing.

Section 6.2.2.1 Discharge Procedures

Changed From

- General physical examination, including respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurological systems, lymph nodes, skin, extremities, head, ears, eyes, nose, and thyroid gland.
- Record 12-lead ECG – supine or semi-recumbent.
- Record vital signs – supine or semi-recumbent BP and PR.
- Urine pregnancy test (if female of childbearing potential).
- Urinalysis (dipstick for blood, protein etc.). Sample to be sent for microscopy/culture if positive for blood, protein, nitrites or leukocyte esterase.
- Blood will be collected for safety laboratory tests.
- Review concomitant medications.
- Adverse Event assessment.
  - When assessing AEs, the subject will be specifically asked regarding the presence of any GI symptoms.
- Discharge subject from the clinic.
  - Provide appropriate post-discharge pain medications, per standard of care.
  - If a subject requires a longer duration of in-patient assessment due to reasons associated with the operation this is acceptable.

Changed To

- Record 12-lead ECG – supine or semi-recumbent.
- Record vital signs – supine or semi-recumbent BP and PR.
- Urine pregnancy test (if female of childbearing potential).

- Urinalysis (dipstick for blood, protein etc.). Sample to be sent for microscopy/culture if positive for blood, protein, nitrites or leukocyte esterase.
- Blood will be collected for safety laboratory tests.
- General physical examination, including respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurological systems, lymph nodes, skin, extremities, head, ears, eyes, nose, and thyroid gland.
- Review concomitant medications.
- Adverse Event assessment.
    - When assessing AEs, the subject will be specifically asked regarding the presence of any GI symptoms.
- Discharge subject from the clinic.
    - Provide appropriate post-discharge pain medications, per standard of care.
    - If a subject requires a longer duration of in-patient assessment due to reasons associated with the operation this is acceptable.

Section 7.1 Dental Surgery

Changed From

The dental surgery (extraction of ≥2 x third molars, at least 1 of which involves partial or complete mandibular bony impaction) will be performed on Visit 2 (Day 1).

The procedure will be performed using appropriate local anesthesia and sedation (performed using nitrous oxide and a local injection of lidocaine with epinephrine). Subjects will also receive prophylactic antibiotics post surgically.

Changed To

The dental surgery and related anesthesia, sedation, and prophylactic antibiotics are not investigational and will occur regardless of research.

The dental surgery (extraction of ≥2 x third molars, at least 1 of which involves partial or complete mandibular bony impaction) will be performed on Visit 2 (Day 1).

The procedure will be performed using appropriate local anesthesia and sedation (performed using nitrous oxide and a local injection of lidocaine with epinephrine). Subjects will also receive prophylactic antibiotics post surgically.

Section 7.4

Changed From

7.4 Pharmacokinetics

7.4.1 Plasma for Analysis of Meloxicam

Changed To

7.4 Pharmacokinetics

7.4.1 Plasma for Analysis of Meloxicam and Salicylic Acid

Section 8.3.7 Pharmacokinetics

Changed From

For all pharmacokinetic data analyses, the PK population will be used.

Samples for PK determination of drug concentrations of meloxicam, in plasma will be determined by a bioanalytical laboratory using validated bioanalytical methods. Details of the validated bioanalytical method used will be provided in a separate bioanalytical report.

The plasma concentration data for meloxicam will be listed, summarized on the basis of time intervals, and plotted using a scatter plot with time relative to the preceding meloxicam dosing time. Summary statistics (mean, standard deviation, minimum, maximum, number of subjects, and coefficient of variation) will be calculated for plasma concentrations for each time interval and by treatment group.

Population PK (PPK) analysis of meloxicam concentrations will be performed using modeling. The PPK analysis will be conducted and reported separately. Details of the PPK model building will be described in a separate PPK analysis plan.

If the dose-response relationship cannot be established in this study (for example, no doses are effective, or all doses are equally effective) then exploratory exposure-response analysis may be conducted using individual predictions of exposure from the PPK analysis in this study. Outcomes from this analysis will be reported separately, if conducted.

Changed To

For all pharmacokinetic data analyses, the PK population will be used.

Samples for PK determination of drug concentrations of meloxicam and salicylic acid, in plasma will be determined by a bioanalytical laboratory using validated bioanalytical methods. Details of the validated bioanalytical method used will be provided in a separate bioanalytical report.

The plasma concentration data for meloxicam and salicylic acid will be listed, summarized on the basis of time intervals, and plotted using a scatter plot with time relative to the preceding meloxicam dosing time. Summary statistics (mean, standard deviation, minimum, maximum, number of subjects, and coefficient of variation) will be calculated for plasma concentrations for each time interval and by treatment group.

Population PK (PPK) analysis of meloxicam and salicylic acid concentrations will be performed using modeling. The PPK analysis will be conducted and reported separately. Details of the PPK model building will be described in a separate PPK analysis plan.

If the dose-response relationship cannot be established in this study (for example, no doses are effective, or all doses are equally effective) then exploratory exposure-response analysis may be conducted using individual predictions of exposure from the PPK analysis in this study. Outcomes from this analysis will be reported separately, if conducted.

Section 10.1 Definitions

Changed From

Events NOT to be reported as SAEs are hospitalizations for the following:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen
- Admission to a hospital or other institution for general care due to social or economic reasons (e.g., no access to local ambulatory medical care)
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission
- Hospitalization also does not include the following: Rehabilitation facilities, Hospice facilities, Respite care (e.g., caregiver relief), Skilled nursing facilities, Nursing homes

Changed To

- Events NOT to be reported as SAEs are hospitalizations for the following:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen
  - Admission to a hospital or other institution for general care due to social or economic reasons (e.g., no access to local ambulatory medical care)
  - Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission
  - Hospitalization also does not include the following: Rehabilitation facilities, Hospice facilities, Respite care (e.g., caregiver relief), Skilled nursing facilities, Nursing homes

11.4 Global Amendment 4, 15 September 2020

11.4.1 Reason for Amendment

Due to the discontinuation of hydrocodone/acetaminophen 5/500 mg tablets, the rescue medication for the study has been changed to 5/325 mg tablets.

11.4.2 Sections Changed

4.2.3 Criteria for Study Drug Termination, Withdrawal From the Study and Study Termination

Changed From

- The subject requires more than 6 tablets/day (equivalent to 3000 mg acetaminophen) rescue medication.

Changed To

- The subject requires more than 6 tablets/day (equivalent to 30 mg hydrocodone and 1950 mg acetaminophen) rescue medication.

5.2 Drug Inventory

Changed From

The Investigator site will supply:

- Medication required for sedation and anesthesia during the surgery.
- Rescue medication for pain relief following randomization, hydrocodone/acetaminophen (5/500 mg).
- All materials associated with the surgical procedure.

Changed To

The Investigator site will supply:

- Medication required for sedation and anesthesia during the surgery.
- Rescue medication for pain relief following randomization, hydrocodone/acetaminophen (5/325 mg).
- All materials associated with the surgical procedure.

5.7.2 Post-Dose

Changed From

Rescue medication of immediate release hydrocodone/acetaminophen (5/500 mg) will be allowed to treat breakthrough pain, subjects will be encouraged to refrain from rescue medication until at least 1-hour post-dose. A dose of rescue medication will be allowed as needed up to once every two hours. A maximum of 6 tablets (equivalent to 3000 mg

acetaminophen) will be allowed; if a subject requires greater than this the subject should be withdrawn from the study.

Pain Intensity will be measured immediately before any rescue medication is administered.

Changed To

Rescue medication of immediate release hydrocodone/acetaminophen (5/325 mg) will be allowed to treat breakthrough pain, subjects will be encouraged to refrain from rescue medication until at least 1-hour post-dose. A dose of rescue medication will be allowed as needed up to once every two hours. A maximum of 6 tablets (equivalent to 30 mg hydrocodone and 1950 mg acetaminophen) will be allowed; if a subject requires greater than this the subject should be withdrawn from the study.

Pain Intensity will be measured immediately before any rescue medication is administered.

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