

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

Protocol Number: MELO-TFZ-2001

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**MELO-TFZ-2001 CLINICAL STUDY PROTOCOL**

<b>Protocol Title</b>	A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Response Study of Meloxicam in the Treatment of Post-Surgical Dental Pain.
<b>Protocol Number</b>	MELO-TFZ-2001
<b>Product</b>	Meloxicam (MR-107A-02)
<b>Study Type</b>	Phase 2b
<b>Version</b>	Version 1.0, 15 February 2022
<b>Protocol Date</b>	<u>Original Date</u> 15 February 2022
<b>Registry Name</b>	ClinicalTrials.gov
<b>IND Number</b>	██████
<b>Legal/Filing Sponsor</b>	Mylan Specialty LP, a Viatris Company 3711 Collins Ferry Rd. Morgantown, WV 26505 USA

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**DOCUMENT HISTORY**

<b>Document Version, Date</b>	<b>Summary of Changes with Rationale</b>
Version 1.0 15 February 2022	N/A

## PROTOCOL SYNOPSIS

<b>Protocol Title</b>	A Randomized, Double Blind, Placebo-Controlled, Parallel Group, Dose-Response Study of Meloxicam in The Treatment of Post-Surgical Dental Pain.
<b>Protocol Number</b>	MELO-TFZ-2001
<b>Study Sites</b>	The study is planned to be conducted at 1 study site.
<b>Study Period Planned</b>	The study is planned to be conducted over a period of approximately 3 months.
<b>Duration of Individual Treatment</b>	<p>The duration from screening to follow up is expected to be approximately 1.5 months.</p> <p>Subjects will be dosed with study drug twice on Day 1.</p>
<b>End of Study</b>	End of study is defined as last subject, last visit.
<b>Background and Rationale</b>	<p>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.</p> <p>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.</p> <p>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 intravenous (IV) formulation of meloxicam has recently demonstrated efficacy in models of acute pain.</p> <p>This formulation of meloxicam is being developed to provide a rapid absorption of meloxicam from an oral dose.</p> <p>This is the first assessment of efficacy of this formulation of meloxicam in subjects with acute pain; however, it is anticipated to provide analgesia to these subjects due to the rapid absorption demonstrated in Study [REDACTED] and the efficacy observed for a co-crystal of meloxicam (MECC-SA) that demonstrated efficacy in Study MECC-TBZ-2001. The efficacy dose-response profile of meloxicam is currently unknown, and the purpose of this study is to establish an understanding of the dose-response relationship for this formulation.</p> <p>The dental pain model is considered an ideal model of post-surgical acute pain as it has high assay sensitivity and is 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</p>

	demonstrated efficacy for an IV formulation of meloxicam.		
<b>Objectives, Estimands and Endpoints</b>	<b>Objectives</b>	<b>Estimands</b>	<b>Endpoints</b>
	<b>Primary</b>	<b>Primary</b>	<b>Primary</b>
	To evaluate the efficacy of meloxicam in subjects following dental surgery and to establish the dose-response relationship.	The primary estimand will be the summed pain intensity difference (SPID) over 0-24 hours for meloxicam vs. placebo for the modified Intent To Treat (mITT) analysis set under the assumption that rescue medication use is managed by a 6h windowed last observation carried forward (W6LOCF) principle.	Summed pain intensity difference (SPID) over 0-24 hours.
	<b>Secondary</b>	<b>Secondary</b>	<b>Secondary</b>
	To further evaluate the efficacy of meloxicam in subjects following dental surgery and to establish the dose-response relationship using other efficacy measures.	An estimand similar to the one defined for the primary endpoint will be applied.	<p>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.</p> <p>Pain intensity difference (PID) over time.</p> <p>Time to perceptible relief (as measured by double stopwatch technique) after first dose.</p> <p>Time to meaningful pain relief (as measured by double stopwatch technique) after first dose.</p> <p>Proportion of subjects with overall pain reductions from baseline of <math>\geq 30\%</math> and <math>\geq 50\%</math> within 4 hours following the first dose.</p>

			<p>Patient's global assessment (PGA) of pain control from 0-24 hours.</p> <p>Elapsed time from the start of study medication to first rescue medication administration.</p> <p>Proportion of subjects using rescue medication from 0-24 hours.</p> <p>Number of subjects using zero doses of rescue medication from 0-24 hours.</p> <p>Number of times rescue medication used from 0-24 hours.</p>
	To evaluate the safety of meloxicam in subjects following dental surgery.	Descriptive statistics corresponding to each separate safety endpoint and for each treatment group will be presented for all participants randomly assigned to study intervention and who take at least 1 dose of study intervention.	<p>Incidence of adverse events (AEs).</p> <p>Absolute values and changes from baseline in vital signs, laboratory tests (hematology, chemistry and urinalysis [qualitative]), and 12-lead ECG.</p>
	To evaluate the exposure of meloxicam in subjects following dental surgery.	Descriptive statistics corresponding to each separate PK endpoint and for each treatment group will be presented for all participants randomly assigned to study intervention and who take at least 1 dose of study intervention and provide at least one post-dose value for concentration data.	PK parameters for meloxicam ( $C_{max}$ , $T_{max}$ , $AUC_{0-2}$ , $AUC_{0-4}$ , $AUC_{0-8}$ , $AUC_{0-12}$ and $AUC_{0-24}$ ).
<b>Methodology</b>	<p>This will be a randomized, double-blind, placebo-controlled, parallel-group, dose-response study, randomizing and dosing approximately 108 male or female subjects who have had dental surgery (removal of <math>\geq 2</math> third molars) performed. Subjects will receive study drug on Day 1.</p> <p>The study design is consistent with research design recommendations of the IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in</p>		

	<p>Clinical Trials) group for trials involving subjects with short-duration acute pain.</p> <p>Subjects will attend screening at Visit 1, to occur within 30 days prior to the planned dental surgery.</p> <p>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.</p> <p>Pain Intensity (PI) (using a 0-10-point numeric rating scale [NRS] 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 an NRS <math>\geq 5</math> 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 (eligibility assessment). An additional PI assessment will be made immediately prior to dosing which will be used as the baseline value; a subject will be dosed only if the NRS score of the second assessment is <math>\geq 5</math> (baseline assessment). Randomization will take place between eligibility and baseline PI assessment. A diary/source document will be used to record the pain scores.</p> <p>Subjects will be randomized to receive either meloxicam tablets (1.25 mg BID, 5 mg BID, 15 mg BID) or placebo after the assessment of the subject's eligibility pain score at Visit 2. Thus, randomization will take place between eligibility and baseline PI assessment.</p> <p>Dosing of study medication must be within 15 minutes of the eligible PI score assessment (eligibility assessment) and immediately after the pre-dose PI score assessment (baseline assessment).</p> <p>PI scores (NRS) will be measured at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 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.</p> <p>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.</p> <p>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. If a subject takes rescue medication prior to recording perceptible or meaningful pain relief, the stopwatches will be collected, and no further assessments of these endpoints will be collected.</p> <p>Rescue medication of [REDACTED] will be allowed at any time, but subjects will be encouraged to wait until at least [REDACTED] post-dose if possible. A PI score assessment will be made immediately prior to any rescue medication.</p> <p>PK samples will be taken pre-dose and 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4,</p>
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	<p>6, 8, 10, 12, 13, 14, 16, 20, and 24 hours after the first dose at Day 1.</p> <p>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.</p> <p>A final follow-up telephone call will occur approximately 5 days after the last dose of study drug administration.</p> <p>Safety will be assessed via recording of AEs, safety laboratory testing, and pre-and post-dose 12-lead ECGs and vital signs.</p> <p>Adverse events of special interest will include those related to gastrointestinal (GI) AEs, particularly bleeds and those related to serious cardiovascular (CV) events.</p> <p>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.</p>
<b>Study Treatment</b>	<p>Treatments to be received during the study will include one of the following treatment arms:</p> <ol style="list-style-type: none"> <li>1. Meloxicam 1.25 mg BID.</li> <li>2. Meloxicam 5 mg BID.</li> <li>3. Meloxicam 15 mg BID</li> <li>4. Placebo BID.</li> </ol> <p>To maintain the blind due to differences in appearance between the tablets, subjects will receive in a double dummy design, three tablets when dosed (one that is representative of a 1.25 mg tablet, one that is representative of a 5 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. Per the clinic procedures, subjects will also be blindfolded during dosing.</p>
<b>Inclusion/exclusion criteria</b>	<p><b>Inclusion criteria</b></p> <ol style="list-style-type: none"> <li>1. Males and females <math>\geq 18</math> 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.</li> <li>2. Requirement for dental surgery for extraction of <math>\geq 2</math> third molars, at least 1 of which involves partial or complete mandibular bony impaction.</li> <li>3. Pain Intensity (PI) using a Numeric Rating Scale (NRS) <math>\geq 5</math> during the 5 hours following the end of surgery in the eligibility assessment as well as in the baseline assessment immediately pre-dosing.</li> <li>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.</li> </ol>



	<p>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.</p> <p><b>Exclusion Criteria</b></p> <ol style="list-style-type: none"> <li>1. Previously dosed with this formulation of meloxicam tablets.</li> <li>2. Subject with known hypersensitivity to aspirin, NSAIDs, or other medication used in the study.</li> <li>3. Subjects with known hypersensitivity to items used in surgery.</li> <li>4. Known active GI bleeding or a history of peptic ulcer disease.</li> <li>5. Known active inflammatory bowel disease, e.g., Crohn's Disease or ulcerative colitis.</li> <li>6. A history of bleeding disorders that may affect coagulation.</li> <li>7. Subjects with prior stroke or transient ischemic attack.</li> <li>8. Subjects with moderate or severe hypertension with systolic blood pressure of <math>\geq 160</math> mmHg and / or diastolic blood pressure <math>\geq 100</math> mmHg.</li> <li>9. 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.</li> <li>10. History of Hepatitis B, Hepatitis C, or HIV infection.</li> <li>11. History of alcohol or drug abuse within 5 years prior to consent.</li> <li>12. History of myocardial infarction or coronary artery bypass graft surgery within the 12 months prior to consent.</li> <li>13. 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).</li> <li>14. Current or history of long QT syndrome or screening ECG with QTcF <math>&gt;470</math> milliseconds for female or <math>&gt;450</math> milliseconds for male subjects.</li> <li>15. Current evidence of, or history within the 6 months prior to consent of unstable ischemic heart disease, NYHA Class II-IV right or left ventricular failure.</li> <li>16. History of malignancy of any organ system treated or untreated, within 5 years prior to consent whether or not there is evidence of local</li> </ol>
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	<p>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.</p> <p>17. Use of any investigational drug within 28 days, or 5 half-lives, prior to consent whichever is longer.</p> <p>18. Use of medications with the potential to interact with meloxicam (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:</p> <ul style="list-style-type: none"> <li>• Strong CYP2C9 inhibitors or inducers (orally or parenterally administered) within 28 days or 5 half-lives (whichever is longer) prior to consent.</li> <li>• Strong CYP2C9 inhibitors or inducers (topically or locally administered) within 7 days prior to consent.</li> <li>• Long-term opioid use (&gt;30 consecutive days in the past year) and/or use of extended release opioids within 30 days of the dental extraction.</li> <li>• Antiepileptic drugs within 60 days prior to consent.</li> <li>• Tricyclic anti-depressants, monoamine oxidase inhibitors, or SNRIs within 60 days prior to consent.</li> <li>• Sedative or hypnotic drugs within 60 days prior to consent (other than the nitrous oxide used during the operation).</li> <li>• Use of "medical" or recreational marijuana within 60 days prior to consent.</li> <li>• Warfarin within 28 days prior to consent.</li> <li>• Apixaban within 28 days prior to consent.</li> <li>• Lithium within 28 days prior to consent.</li> <li>• Methotrexate within 28 days prior to consent.</li> <li>• Calcineurin inhibitors (e.g., cyclosporine and tacrolimus) within 28 days prior to consent.</li> <li>• Pemetrexed within 28 days prior to consent.</li> <li>• Combination of diuretic with ACE inhibitor or angiotensin receptor blocker within 28 days prior to consent.</li> <li>• Gabapentin or pregabalin within 60 days prior to consent.</li> </ul>
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	<ul style="list-style-type: none"> <li>• Cholestyramine within 7 days prior to consent.</li> <li>• Meloxicam within 7 days prior to the surgery.</li> <li>• Aspirin within 7 days prior to the surgery.</li> <li>• Analgesics (including opioids, acetaminophen, and NSAIDs) within 72 hours prior to the surgery.</li> </ul> <p>19. Inability to refrain from any of the following medications pre-, intra-, or post-surgery:</p> <ul style="list-style-type: none"> <li>• Systemically administered corticosteroids.</li> <li>• Epidural or spinal anesthetics.</li> <li>• General anesthesia.</li> <li>• Analgesia other than those pre-specified for breakthrough pain relief.</li> </ul> <p>20. BMI &gt;35 kg/m<sup>2</sup>.</p> <p>21. Pregnant or nursing females or females intending to become pregnant during the course of the study.</p> <p>22. Serum creatinine &gt;1.5 x Upper Limit of Normal.</p> <p>23. Serum ALT, AST, or bilirubin &gt;2 x Upper Limit of Normal.</p> <p>24. Hemoglobin &lt;10.5 g/dL.</p> <p>25. Clinically significant abnormal laboratory test(s) at screening deemed exclusionary by the Investigator.</p> <p>26. Signs or symptoms of an infection or a fever that would increase the risk of surgery.</p> <p>27. Chronic pain disorders (e.g., fibromyalgia) that may affect a subject's pain reporting during the study.</p> <p>28. 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.</p>
<b>Planned Number of Subjects</b>	Approximately 108 subjects (N=27/treatment arm) dosed to give approximately 100 evaluable subjects for the primary endpoint (N=25/treatment arm).
<b>Statistical Methods</b>	In order to derive the required sample size for the primary estimand, [REDACTED] for 10 mg BID, 15 mg BID and placebo reported from a previous meloxicam study conducted by the Sponsor (MECC-TBZ-2001 in dental pain). Simulations were

performed [REDACTED]

[REDACTED]. The numerical dose values were [REDACTED] for, 1.25 mg BID, 5 mg BID, 15 mg BID and placebo respectively.

The results of the simulations indicate the following values for power, for 25 subjects per group, assuming a standard deviation (SD) of [REDACTED]:

Dose	Expected Effect Size (versus Placebo)	Power
[REDACTED]		

Note that the expected standardized effect sizes (expected effect size divided by SD) are approximately [REDACTED] (15 mg BID, 5 mg BID and 1.25 mg BID, respectively); therefore, the comparisons 15 mg BID vs. placebo, 5 mg BID vs. placebo and 1.25 mg BID vs. placebo have approximately [REDACTED]%, [REDACTED]% and [REDACTED]% power to declare statistical significance for standardized effect sizes of [REDACTED], respectively.

To analyze W6LOCF SPID 0-24 hours, a 3-parameter  $E_{\max}$  model will be fitted to the observed mean for each dose and placebo. Effect sizes for each dose versus placebo and associated standard errors, p-values and 95% CIs will be calculated. Standardized effect sizes will also be estimated from the  $E_{\max}$  model (effect sizes for each dose versus placebo divided by the pooled SD together with their 95% confidence intervals. Baseline pain intensity score (PI) will be used as a covariate in the  $E_{\max}$  model. Baseline is defined as the pre-dosing PI score. The numerical dose values will be 2.5, 10, 30, and 0 for 1.25 mg BID, 5 mg BID, 15 mg BID, and placebo, respectively.

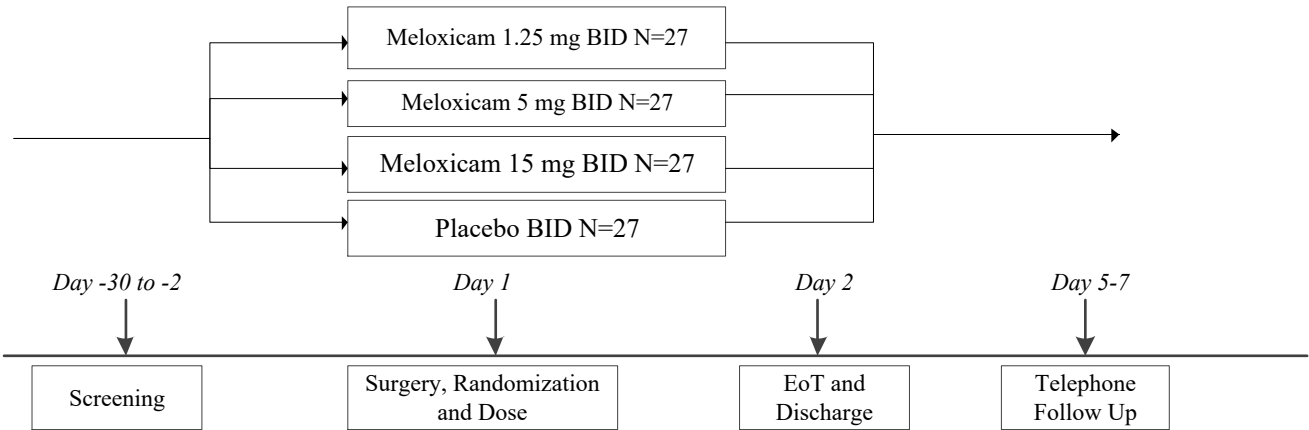
If the  $E_{\max}$  model fails to converge, an analysis of covariance (ANCOVA) will be used to assess the difference between treatment groups. The ANCOVA model will include treatment as fixed effect and baseline PI score as a covariate. The difference between meloxicam and placebo will be estimated from the least squares means (LS means) along with the 95% 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.

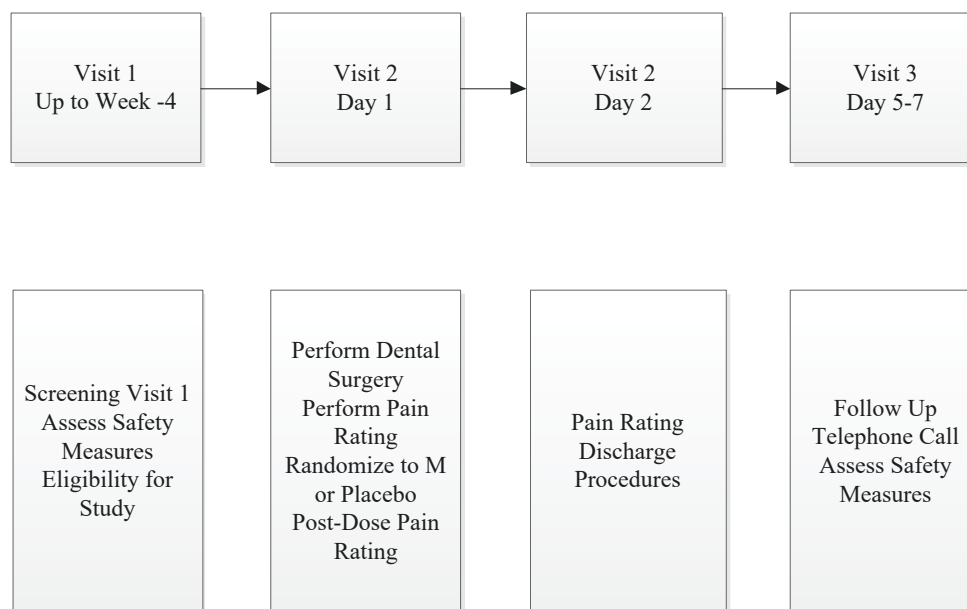
Pharmacokinetic (PK) parameters for meloxicam ( $C_{\max}$ ,  $AUC_{0-2}$ ,  $AUC_{0-4}$ ,  $AUC_{0-8}$ ,  $AUC_{0-12}$  and  $AUC_{0-24}$ ) will also be calculated. The relationship between PK parameters and efficacy will be explored graphically.

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





**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 screening registration	X			
Demography and medical history	X			
Review concomitant medications	X	X	X	X
General physical examination <sup>1</sup>	X		X <sup>16</sup>	
Height	X			
Weight	X			
Temperature		X <sup>2</sup>		
Vital Signs (supine/semi-recumbent blood pressure, pulse rate)	X	X <sup>3</sup>	X <sup>16</sup>	
12-lead ECG (supine/semi-recumbent)	X	X <sup>4</sup>	X <sup>16</sup>	
Serum or urine pregnancy test <sup>5</sup>	X	X <sup>2</sup>	X <sup>16</sup>	
Urinalysis <sup>6</sup>	X		X <sup>16</sup>	
Urine drug screen	X	X <sup>2</sup>		
Blood safety labs (hematology, chemistry) including FSH (V1) <sup>7</sup>	X		X <sup>16</sup>	
PK Sample <sup>8</sup>		X	X	
Diary training		X <sup>2</sup>		
Review AEs <sup>9</sup>	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, eligibility assessment)		X <sup>10</sup>		
Randomize to study via IVRS/IWRS		X		
Pain Assessment (Pain Intensity) (immediately prior to dosing, baseline assessment)		X <sup>11</sup>		
Dispense study drug		X <sup>12</sup>		
Administer study drug (within 15 minutes of eligible pain assessments)		X <sup>13</sup>		
Administer study drug (approximately 12 hours after first dose)		X	X	
Pain Intensity Assessments (post-randomization)		X <sup>14</sup>	X <sup>14</sup>	
Patient Global Assessment of Pain Control			X <sup>15</sup>	

VISIT	1 (Screen)	2 (In-clinic)	2 (In-clinic)	Follow up Telephone Call
DAY	-30 to -2	1	2	5-7
Record Rescue Medication Use		X	X	X

- <sup>1</sup> Including respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurological systems, lymph nodes, skin, extremities, head, ears, eyes, nose, and thyroid gland.
- <sup>2</sup> Prior to surgery.
- <sup>3</sup> 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.
- <sup>4</sup> 12-lead ECG will be performed both pre-dose and 24 hours post-dose as single measures.
- <sup>5</sup> Serum pregnancy test at screening, urine at other visits.
- <sup>6</sup> 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.
- <sup>7</sup> FSH to be measured in females who have been amenorrheic for at least 2 years, to confirm non-childbearing potential.
- <sup>8</sup> PK sample taken pre-dose and 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 13, 14, 16, 20, and 24 hours after the first dose of study medication.
- <sup>9</sup> 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.
- <sup>10</sup> Pain assessments (Pain Intensity and Categorical Pain Rating) performed for up to 5 hours after completion of surgery. Subjects with NRS  $\geq 5$  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 will take place between eligibility and baseline assessment.
- <sup>11</sup> Pain assessment (Pain Intensity) performed immediately pre-dosing. The subject will be dosed only if the pre-dose PI NRS score is  $\geq 5$ . This pre-dose pain assessment serves as the baseline assessment.
- <sup>12</sup> Drug is dispensed at 'time zero' and approximately 12 hours later.
- <sup>13</sup> Dosing of study medication must be within 15 minutes of the eligibility pain assessment and immediately after baseline PI assessment.
- <sup>14</sup> Post-dose pain assessments made at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 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.

- <sup>15</sup> Patient's Global Assessment of Pain Control measured at 24 hours post-dose, or at time of early termination if applicable.
- <sup>16</sup> 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	MI	Missing imputation
ACE	Angiotensin Converting Enzyme	mg	Milligram
ALT	Alanine transaminase	NYHA	New York Heart Association
ANCOVA	Analysis of covariance	INN	International Non-proprietary Name
AST	Aspartate transaminase	ITT	Intent To Treat
AUC	Area Under the Curve	IVRS/IWRS	Interactive Voice Response System/ Interactive Web Response System
BID	Twice Daily	MR-107A-02	Internal Identification Code for Meloxicam
BMI	Body Mass Index	mL	Milliliter
BP	Blood Pressure	mmHg	Millimeter of mercury
bpm	Beats per minute	MMRM	Mixed Model Repeated Measures
cm	Centimeter	MNAR	Missing Not At Random
C <sub>max</sub>	Maximum plasma concentration	ms	Millisecond
CRF	Case Report Form	NSAID	Non-Steroidal Anti-Inflammatory Drug
COX	Cyclooxygenase	NRS	Numeric Rating Scale
CRO	Contract Research Organization	PGA	Patient Global Assessment
CV	Cardiovascular	PI	Pain Intensity
CV	Coefficient of Variation	PK	Pharmacokinetic
ECG	Electrocardiogram	PPAS	Per Protocol Analysis Set
EU	European Union	PR	Pulse Rate
FAS	Full Analysis Set	<i>prn</i>	<i>pro re nata</i>
FDA	Food and Drug Administration	QC	Quality Control
FSH	Follicle stimulating hormone	QD	Once Daily
GCP	Good Clinical Practice	QTc	QT corrected
GI	Gastrointestinal	QTcF	QT corrected (Fredericia's correction)
GM	Geometric Mean	RoW	Rest of World
HIV	Human Immunodeficiency Virus	SAE	Serious Adverse Event
HR	Heart Rate	SAP	Statistical Analysis Plan
ICF	Informed Consent Form	SD	Standard Deviation
ICH	International Conference on Harmonization	SID	Subject Identification
IRB	Institutional Review Board	SOP	Standard Operating Procedure
kg	Kilogram	SPID	Summed Pain Intensity Difference
LOCF	Last Observation Carried Forward	T <sub>½</sub>	Half life
LS mean	Least Squares mean	T <sub>max</sub>	Time of maximum concentration
MAR	Missing At Random	US	United States
mFAS	Modified Full Analysis Set	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 US, 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]. Opioid related deaths have been hugely problematic for several years with an opioid drug overdose rate in 2015 of 10.4 per 100,000 [3], increasing to 14.9 per 100,000 in 2017 [4]. In 2018, there were 67,367 deaths that occurred due to drug overdose with 69.5% involving an opioid [4] and the opioid death rate remained high at 14.6 per 100,000 [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 the US 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  $\geq 60$  kg). An IV formulation of meloxicam is currently approved in the US 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 been approved by the 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  $\geq 7.5$  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]. *Ex 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  $\geq 2\%$  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
<b>No. of Patients</b>	8955	256	169	306
<b>Gastrointestinal</b>	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
<b>Body as a Whole</b>				
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
<b>Central and Peripheral Nervous System</b>				
Dizziness	1.1	1.6	2.4	2.6
Headache	2.4	2.7	3.6	2.6
<b>Hematologic</b>				
Anemia	0.1	0.0	4.1	2.9
<b>Musculoskeletal</b>				
Arthralgia	0.5	0.0	5.3	1.3
Back pain	0.5	0.4	3.0	0.7
<b>Psychiatric</b>				
Insomnia	0.4	0.0	3.6	1.6
<b>Respiratory</b>				
Coughing	0.2	0.8	2.4	1.0
Upper respiratory tract infection	0.2	0.0	8.3	7.5
<b>Skin</b>				
Pruritus	0.4	1.2	2.4	0.0
Rash (b)	0.3	1.2	3.0	1.3
<b>Urinary</b>				
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, however the predicted exposure associated with 22.5 mg MOBIC is greater than that observed with this formulation of meloxicam 15 mg in Study [REDACTED].

Furthermore, a recently completed study in dental extraction (MECC-TBZ-2001, [REDACTED], NCT04571515) of an oral co-crystal formulation of meloxicam: salicylic acid (MECC-SA), studied doses up to 15 mg (meloxicam) BID and was well-tolerated. The most

common adverse events from Study MECC-TBZ-2001 are summarized in [Table 4](#). Additionally, no clinically significant changes in vital signs, ECG parameters, or laboratory safety tests occurred, and no SAEs were reported during the study.

**Table 4: Adverse Events Reported in  $\geq 5\%$  of Subjects in Study MECC-TBZ-2001**

System Organ Class Preferred Term	MECC-SA 10 mg QD N = 21 n (%)	MECC-SA 15 mg QD N = 24 n (%)	MECC-SA 10 mg BID N = 23 n (%)	MECC-SA 15 mg BID N = 23 n (%)	Placebo N = 21 n (%)	Total N = 112 n (%)
Subjects with any event	7 (33.3)	7 (29.2)	5 (21.7)	5 (21.7)	4 (19.0)	28 (25.0)
<b>Gastrointestinal disorders</b>	3 (14.3)	4 (16.7)	3 (13.0)	1 (4.3)	2 (9.5)	13 (11.6)
Nausea	0 (0.0)	3 (12.5)	3 (13.0)	0 (0.0)	1 (4.8)	7 (6.3)
<b>Nervous system disorders</b>	4 (19.0)	3 (12.5)	3 (13.0)	0 (0.0)	1 (4.8)	11 (9.8)
Headache	3 (14.3)	3 (12.5)	1 (4.3)	0 (0.0)	1 (4.8)	8 (7.1)
Dizziness	1 (4.8)	0 (0.0)	2 (8.7)	0 (0.0)	0 (0.0)	3 (2.7)

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]. Some data are suggestive that IM meloxicam has a more rapid onset than oral meloxicam in rheumatoid arthritis pain [21] and sciatica [22]. Furthermore, a recently completed study (MECC-TBZ-2001, IND [REDACTED], NCT04571515) demonstrated efficacy in a study in dental extraction for an oral co-crystal formulation of meloxicam: salicylic acid (MECC-SA). This study demonstrated that MECC-SA, at both doses (10 and 15 mg) and regimens (QD and BID) tested, was more effective than placebo at reducing subjects' post-surgical dental pain ([Table 5](#)).

**Table 5: MECC-TBZ-2001 Primary Efficacy Analysis: Summary of SPID<sub>0-24</sub> E<sub>max</sub> Model ( )**

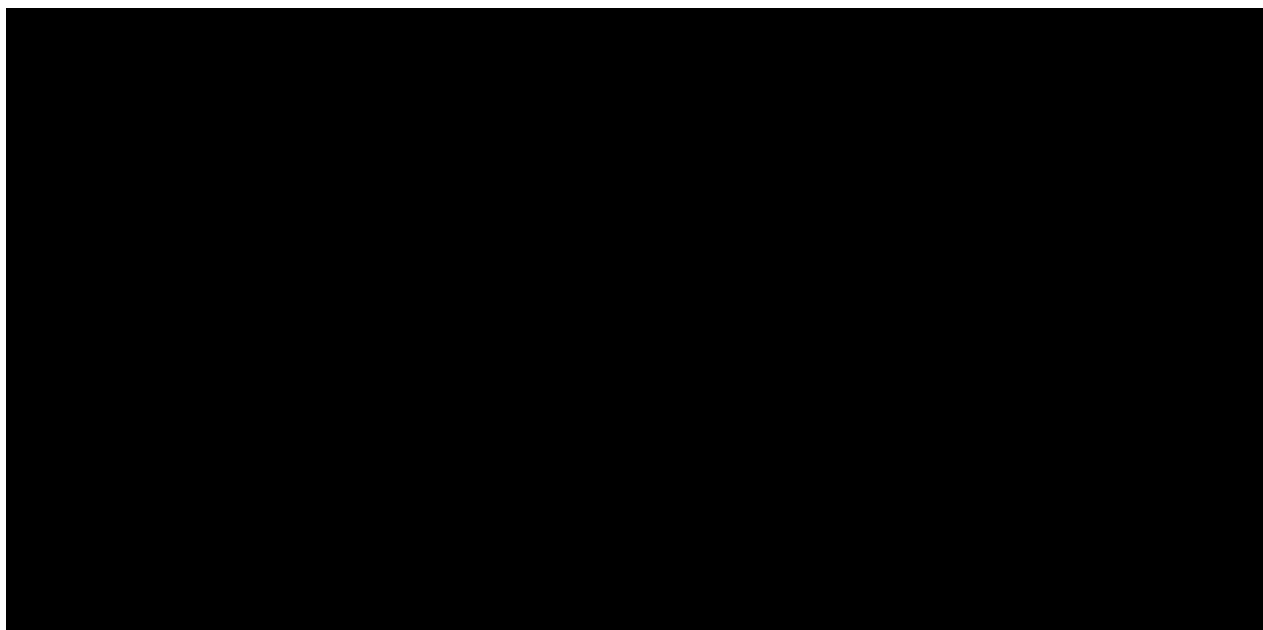
Interval Statistic	MECC-SA 10 mg QD N = 21	MECC-SA 15 mg QD N = 24	MECC-SA 10 mg BID N = 23	MECC-SA 15 mg BID N = 23	Placebo N = 21
SPID <sub>0-24</sub> , n	21	24	23	23	21
Mean (SD)	109.5 (32.82)	111.8 (40.37)	108.8 (33.85)	108.6 (40.20)	80.0 (39.78)
Median	107.6	103.5	102.3	120.4	78.5
Min, Max	(59, 182)	(36, 187)	(50, 173)	(20, 172)	(-21, 148)
<b>E<sub>max</sub> estimates</b>					
Mean (SE)	108.1 (5.97)	109.5 (3.53)	110.2 (3.71)	110.9 (5.26)	79.9 (7.12)
95% CI	(96.3, 120.0)	(102.5, 116.5)	(102.8, 117.5)	(100.5, 121.4)	(65.8, 94.0)
<b>E<sub>max</sub> estimated difference vs Placebo</b>					
Mean (SE)	28.3 (9.25)	29.6 (7.94)	30.3 (8.04)	31.1 (8.87)	-
95% CI	(9.9, 46.6)	(13.8, 45.3)	(14.4, 46.2)	(13.5, 48.6)	-
p-value	0.003	<0.001	<0.001	<0.001	-

It is important to note that for these data using the W2LOCF approach, the rescue medication that subjects received ( ), with a recommended dosage of every 4-6 hours) was likely to still be exerting analgesic effects at the end of the 2-hour censoring period. In addition, the majority of subjects in each dose group received rescue medication within 2 hours after surgery, indicating a longer censoring period may be useful to interpret the data considering the likely impact of rescue medication use on a large number of subjects. While a clear dose-response relationship was not established for any individual endpoint, the overall results (including secondary endpoints such as time to perceptible pain relief and rescue medication use) indicated that 15 mg may be more effective than 10 mg, and that BID regimens may be more effective than QD regimens.

This formulation of meloxicam is being developed to provide a rapid absorption of meloxicam from an oral dose and has been studied in two Phase 1 studies ( ) and ( ) in healthy subjects. The product demonstrated . The absorption of meloxicam was , MECC-SA also demonstrated . A comparison

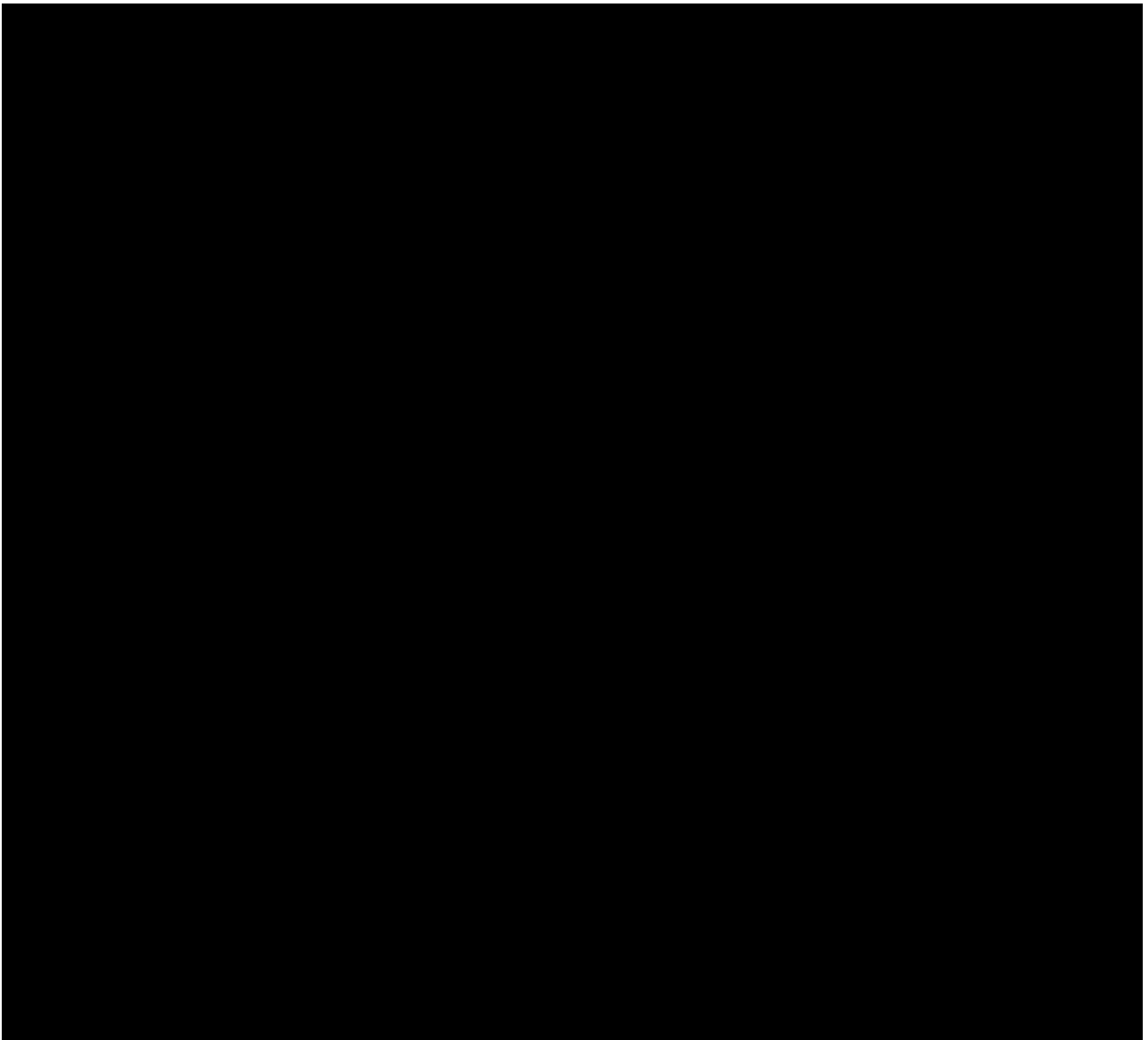
of the two formulations of meloxicam demonstrated a [REDACTED]  
[REDACTED] Meloxicam was well-tolerated in both studies.

**Table 6: MELO-TFZ-1001 Pharmacokinetic Summary, Fasting Conditions**



Comparing the data from Study [REDACTED] to previous studies of MECC-SA and the direct comparison between the formulations in [REDACTED], it is estimated that a 15 mg dose of meloxicam may have more rapid absorption than MECC-SA but with similar overall exposure and therefore acute analgesia could be anticipated to be similar or better than that observed for MECC-SA in Study MECC-TBZ-2001.

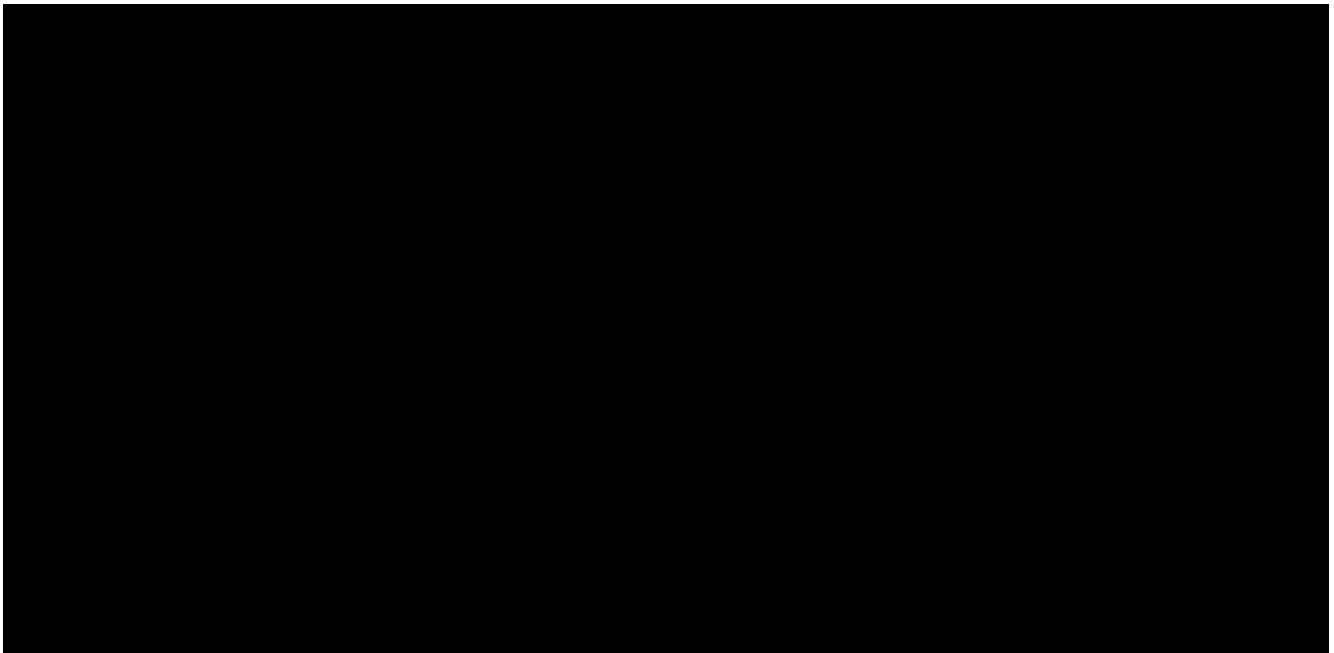
It should be noted that while the  $C_{\max}$  of meloxicam following dosing with 15 mg meloxicam was approximately [REDACTED] than that of 15 mg MOBIC, the overall exposure (AUC) was [REDACTED]. The combination of similar overall exposure with the anticipated acute use of this formulation of meloxicam means that use of 15 mg meloxicam is considered safe, especially as ANJESO (IV meloxicam) 30 mg has a reported  $C_{\max}$  of 7972.5 ng/mL and an  $AUC_{\text{inf}}$  of 121437.6 ng.hr/mL.

**Table 7: MR-107A-02-TFZ-1001 Pharmacokinetic Summary**

Acknowledging that a BID dosing regimen is planned in this study, and based on the [REDACTED] data from Study [REDACTED], predicted exposure for BID dosing of meloxicam are summarized in [Table 8](#).



**Table 8: Meloxicam Predicted Exposure After Single Doses, and Twice Daily Dosing vs. MECC-SA BID, MOBIC, and ANJESO**



The predicted (using data from Study [REDACTED]) exposure for 15 mg BID (i.e., two doses over 24 hours) meloxicam will [REDACTED], however, the overall exposure and  $C_{\max}$  (after the second dose) would be [REDACTED] and therefore for use in the treatment of acute pain it can be anticipated that meloxicam will be well-tolerated. Furthermore, the meloxicam exposure of 15 mg BID meloxicam is anticipated to be similar to that of [REDACTED] in a study of dental extraction (Study MECC-TBZ-2001); as MECC-SA was well-tolerated in that study it can be anticipated that meloxicam will also be well-tolerated.

Meloxicam was well tolerated in Studies [REDACTED] and [REDACTED]. No adverse events were reported during [REDACTED] and only a small number of mild adverse events were reported during [REDACTED].

No clinically significant changes in vital signs, ECG parameters, or laboratory safety tests (other than mentioned above) occurred, and no SAEs occurred during the studies.

### 1.3 Investigational Product

This formulation of meloxicam is being developed to provide a rapid absorption of meloxicam from an oral dose.

Considering that meloxicam is a BCS Class II compound, the rate-limiting step for meloxicam absorption is solubility. This formulation of meloxicam includes within the formulation [REDACTED] for the 15 mg strength, [REDACTED] for the 5 mg strength and [REDACTED] for the 1.25 mg strength to increase the rate of absorption of meloxicam by increasing its solubility and dissolution. The efficacy

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

#### 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 this formulation of meloxicam in subjects with acute pain, however it is anticipated to provide analgesia to these subjects due to [REDACTED] demonstrated in [REDACTED]. It is estimated that a 15 mg dose of meloxicam would exceed [REDACTED] within approximately [REDACTED] of dosing, therefore acute analgesia could be anticipated at or around this time. Lower doses of meloxicam may not exceed [REDACTED] and may not provide adequate analgesia; however, they are needed in this study to fully understand the dose-response profile of meloxicam.

As the meloxicam exposure data for this formulation of meloxicam is similar to MECC-SA it is appropriate to use the data from MECC-TBZ-2001 to dose-select for the study of meloxicam. Using the data from MECC-TBZ-2001 and an  $E_{\max}$  model to identify the ideal dosing regimen for meloxicam the doses of 1.25 mg BID, 5 mg BID and 15 mg BID have been selected. This is on the basis that 1.25 mg BID can be anticipated to be [REDACTED], 5 mg BID would likely be [REDACTED] and 15 mg BID would be approximately [REDACTED]. The selection of these doses should enable an exploration of the dose-response curve for meloxicam.

Some studies of ANJESO [19]; [20] might indicate loss of efficacy prior to 24 hours whereby the confidence intervals for the IV meloxicam and placebo overlap at later timepoints. Data from MECC-TBZ-2001 indicates that BID regimes of MECC-SA were more effective than QD regimens MELO-TFZ-2001 will study BID doses of meloxicam. The predicted (using data from Study [REDACTED]) exposure of 15 mg BID meloxicam is anticipated to [REDACTED]. However, it is expected that [REDACTED] [REDACTED] [REDACTED] (Table 8).

The administration of meloxicam 15 mg BID should therefore be well tolerated.

As meloxicam 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 and low doses of meloxicam 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 and for an exploration of the dose-response of meloxicam. 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 meloxicam may be found in the Single Reference Safety Document, which for this study is the meloxicam Investigator’s Brochure.

## **2 OBJECTIVES, ESTIMANDS AND ENDPOINTS**

### **2.1 Objectives**

#### **2.1.1 Primary Objectives**

To evaluate the efficacy of meloxicam in subjects following dental surgery and to establish the dose response relationship.

### **2.2 Estimands**

#### **2.2.1 Primary Estimand**

The summed pain intensity difference (SPID) over 0-24 hours for meloxicam vs. placebo for the modified Intent To Treat (mITT) analysis set under the assumption that rescue medication use is managed by a 6h windowed last observation carried forward (W6LOCF) principle. Sensitivity and supplementary analyses will also be performed (see Sections 8.4.3 and 8.4.4 for details).

#### **2.2.2 Secondary Efficacy Estimands**

- 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 using the mITT analysis set.
- PI score and Pain intensity difference (PID) from baseline over time using the mITT analysis set
- Time to perceptible relief (as measured by double-stopwatch technique) after first dose using the mITT analysis set.
- Time to meaningful pain relief (as measured by double-stopwatch technique) after first dose using the mITT analysis set.
- Proportion of subjects with overall pain reductions from baseline of  $\geq 30\%$  and  $\geq 50\%$  within 4 hours following the first dose using the mITT analysis set.

- Patient's global assessment (PGA) of pain control from 0-24 hours using the mITT analysis set.
- Elapsed time from the start of study medication to first rescue medication administration using the mITT analysis set.
- Proportion of subjects using rescue medication from 0-24 hours using the mITT analysis set.
- Number of subjects using zero doses of rescue medication from 0-24 hours using the mITT analysis set.
- Number of times rescue medication used from 0-24 hours using the mITT analysis set.

### 2.2.3 Safety Endpoints

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

### 2.2.4 Pharmacokinetic Endpoints

- PK parameters for meloxicam ( $C_{\max}$ ,  $T_{\max}$ ,  $AUC_{0-2}$ ,  $AUC_{0-4}$ ,  $AUC_{0-8}$ ,  $AUC_{0-12}$ , and  $AUC_{0-24}$ ).

## 3 STUDY DESIGN

### 3.1 Overall Design

This will be a randomized, double-blind, placebo-controlled, parallel group, dose-ranging study, randomizing and dosing approximately 108 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 and an oral co-crystal formulation of meloxicam: salicylic acid (MECC-SA) – Study MECC-TBZ-2001, IND [REDACTED]

Study MECC-TBZ-2001 indicated that a BID regimen was potentially advantageous over a QD regime for meloxicam with a similar exposure profile as that for this formulation of meloxicam, hence a BID regimen will be explored in this study.

Based on the data from MECC-TBZ-2001, an appropriate censoring period to account for the use of rescue medication in the study is needed. Study MECC-TBZ-2001 explored the effect of the censoring period on the data and indicated that 2 hours (i.e., a W2LOCF approach) would not be sufficient and that a 4-6 hour window would be a better balance of a). accounting for the analgesic effect of the rescue medication and b). not censoring a large amount of data in placebo or low doses of study medication. For this reason, a W6LOCF approach will be adopted for the primary analysis, with pre-specified sensitivity analyses of W4LOCF and W8LOCF also explored.

This study will specifically identify if meloxicam has efficacy in a model of acute post-operative pain and will enable the identification of the most appropriate dose of meloxicam 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 108 subjects will be randomized and dosed to give approximately 100 evaluable subjects for the primary endpoint (N=25/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  $\geq 18$  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  $\geq 2$  third molars, at least 1 of which involves partial or complete mandibular bony impaction.
3. Pain Intensity (PI) using a Numeric Rating Scale (NRS)  $\geq 5$  during the 5 hours following the end of surgery in the eligibility assessment as well as in the baseline assessment immediately pre-dosing.
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 this formulation of meloxicam.
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. Subjects with prior stroke or transient ischemic attack.
6. Subjects with moderate or severe hypertension with systolic blood pressure  $\geq 160$  mmHg and / or diastolic blood pressure  $\geq 100$  mmHg.
7. Active inflammatory bowel disease, e.g., Crohn's Disease or ulcerative colitis.
8. A history of bleeding disorders that may affect coagulation.
9. 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.
10. History of Hepatitis B or C or HIV infection.
11. History of alcohol or drug abuse within the last 5 years prior to consent.
12. History of myocardial infarction or coronary artery bypass graft surgery within the 12 months prior to consent.
13. 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).

14. Current or history of long QT syndrome or screening ECG with QTcF >470 milliseconds for female or >450 milliseconds for male subjects.
15. 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.
16. 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.
17. Use of any investigational drug within 28 days, or 5 half-lives, prior to consent whichever is longer.
18. Use of medications with the potential to interact with meloxicam (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 (orally or parenterally administered) within 28 days or 5 half-lives (whichever is longer) prior to consent.
  - Strong CYP2C9 inhibitors or inducers (topically or locally administered) within 7 days prior to consent.
  - 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 60 days prior to consent.
  - Tricyclic anti-depressants, monoamine oxidase inhibitors, or SNRIs within 60 days prior to consent.
  - Sedative or hypnotic drugs within 60 days prior to consent (other than the nitrous oxide used during the operation).
  - Use of "medical" or recreational marijuana within 60 days prior to consent.
  - Warfarin within 28 days prior to consent.
  - Apixaban within 28 days prior to consent.
  - Lithium within 28 days prior to consent.
  - Methotrexate within 28 days prior to consent.

- Calcineurin inhibitors (e.g., cyclosporine and tacrolimus) within 28 days prior to consent.
  - Pemetrexed within 28 days prior to consent.
  - Combination of diuretic with ACE inhibitor or angiotensin receptor blocker within 28 days prior to consent.
  - Gabapentin or pregabalin within 60 days prior to consent.
  - Cholestyramine within 7 days prior to consent.
  - Meloxicam within 7 days prior to the surgery.
  - Aspirin within 7 days prior to the surgery.
  - Analgesics (including opioids, acetaminophen, and NSAIDs) within 72 hours prior to the surgery.
19. 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.
20. BMI >35 kg/m<sup>2</sup>.
21. Pregnant or nursing females or females intending to become pregnant during the course of the study.
22. Serum creatinine >1.5 x Upper Limit of Normal.
23. Serum ALT, AST, or bilirubin >2 x Upper Limit of Normal.
24. Hemoglobin <10.5 g/dL.
25. Clinically significant abnormal laboratory test(s) at screening deemed exclusionary by the Investigator.
26. Signs or symptoms of an infection or a fever that would increase the risk of surgery.
27. Chronic pain disorders (e.g., fibromyalgia) that may affect a subject's pain reporting during the study.
28. 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 subject's 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 will be withdrawn prior to dosing if:

The pre-dose PI values is <5. This pre-dose PI value will be used as the baseline measure; a subject will only be dosed if this value is ≥5.

Note: If a subject has a baseline score of <5 but is dosed in error, the subject should not be discontinued from the study for this reason.

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 [REDACTED]) 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 for safety purposes 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. Meals in the clinic should be low-fat in composition.

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 follicle stimulating hormone (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 from heterosexual vaginal intercourse (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

Meloxicam will be provided as 1.25, 5 and 15 mg tablets.

- Meloxicam tablets (and corresponding placebo), 1.25 mg is available as [REDACTED]  
[REDACTED]  
[REDACTED].
- Meloxicam tablets (and corresponding placebo), 5 mg is available as [REDACTED]  
[REDACTED]  
[REDACTED].
- Meloxicam tablets (and corresponding placebo), 15 mg is available as [REDACTED]  
[REDACTED]  
[REDACTED].

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

To maintain the blind, subjects will take in a double-dummy design, three tablets (one that is representative of a 1.25 mg tablet, one that is representative of a 5 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. 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 (three tablets containing meloxicam or corresponding placebo) will be administered in a double-dummy design at the clinic at each dosing time.

Subjects should take the study drugs with approximately 240 mL of water at ambient temperature 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:

- Meloxicam and corresponding placebo.

The Investigator site will supply:

- Medication required for sedation and anesthesia during the surgery.
- Rescue medication for pain relief following randomization,  
[REDACTED]
- 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 (where applicable) 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 meloxicam (1.25 mg BID, 5 mg BID, or 15 mg BID) or placebo in a 1:1:1:1 ratio through the IVRS/IWRS after the assessment of the subject’s eligible pain score at Visit 2. Thus randomization will take place between eligibility and baseline assessment.

## **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.

The study may be unblinded prior to completion of all pharmacokinetic bioassays.

## **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 [REDACTED] will be allowed to treat breakthrough pain. Subjects will be encouraged to refrain from rescue medication until [REDACTED] post-dose. A dose of rescue medication will be allowed as needed up to once every 2 hours. A maximum of [REDACTED] [REDACTED] 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).

In addition to specifically named medications in Section 4.2.2 the Clinical Protocol (Exclusion Criteria 18) excludes subjects taking Strong CYP2C9 inhibitors or inducers within 28 days or 5 half-lives (whichever is longer) prior to the study. To facilitate the identification of these drugs a non-exhaustive list is provided in Table 9.

**Table 9: Excluded CYP2C9 Inhibitors and Inducers**

Excluded Drug	CYP2C9 Inhibitor (Strong)	CYP2C9 Inducer
Capecitabine	X	
Voriconazole	X	
Regorafenib	X	
Sonidegib	X	
Ceritinib	X	
Nilotinib	X	
Gemfibrozil	X	
Amiodarone	X	
Fluconazole	X	
Sulfaphenazole	X	
Efavirenz	X	
Fluvoxamine	X	
Zafirlukast	X	
Ketoconazole	X	
Miconazole	X	
Brexanolone	X	
Nicardipine	X	
Triclabendazole	X	
Carbamazepine		X
Enzalutamide		X
Nevirapine		X
Phenobarbital		X
Rifampin		X
Secobarbital		X
St John's Wort		X
Rifapentine		X
Aminoglutethimide		X
Bosentan		X
Griseofulvin		X



Excluded Drug	CYP2C9 Inhibitor (Strong)	CYP2C9 Inducer
Primidone		X
Rifabutin		X
<p>A Strong inhibitor is one that causes a &gt;5-fold increase in the plasma AUC values or more than 80% decrease in clearance or in absence of <i>in vivo</i> data has reported Ki value &lt;10 µM when tested against a CYP2C9 marker substrate <i>in vitro</i>.</p> <p><u>Sources:</u>  Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). "<a href="https://drug-interactions.medicine.iu.edu">https://drug-interactions.medicine.iu.edu</a>" Accessed 20 September 2021.</p> <p>University of Minnesota:  <a href="https://www.d.umn.edu/~jfitzake/Lectures/DMED/TAA/Q_A/CYP450InteractionTable.htm">https://www.d.umn.edu/~jfitzake/Lectures/DMED/TAA/Q_A/CYP450InteractionTable.htm</a>  Accessed 20 September 2021.</p> <p>Pharmacy Times:  <a href="https://www.pharmacytimes.com/publications/issue/2008/2008-03/2008-03-8462">https://www.pharmacytimes.com/publications/issue/2008/2008-03/2008-03-8462</a>  Accessed 20 September 2021.</p> <p>PharmaPendium FDA Summary Basis of Approval Database Search.  <a href="https://www.pharmapendium.com/home">https://www.pharmapendium.com/home</a>  Accessed 20 September 2021.</p>		

### 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 who 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 screening registration.
- Complete medical history, demographics.
- Complete history of all prescription or non-prescription drugs and 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 rating scale – NRS) and Categorical Pain Rating (4-point scale – none, mild, moderate, severe)) will be made during the 5 hours post-surgery until an eligibility pain assessment is achieved.
  - Subjects with NRS  $\geq 5$  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 (eligibility assessment).
- 12-lead ECG – supine or semi-recumbent taken following surgery and prior to dosing.

- Vital signs (BP and PR) – supine or semi-recumbent taken following surgery and prior to dosing.
- Blood for a PK sample taken following surgery and prior to dosing.
- Randomization using IVRS/IWRS.
  - To occur such that dosing occurs within 15 minutes of the eligibility assessment.

#### 6.2.1.2 Dosing and Post-Dose Procedures

- A further PI assessment will be made immediately prior to dosing (baseline assessment). The pre-dose PI values will be used as the baseline measure; a subject will only be dosed if this pre-dose PI value is  $\geq 5$ .
- Administer first dose of study drug (three tablets to maintain the blind).
  - Within 15 minutes of the eligibility pain scores.
- Administer second dose of study drug (three tablets to maintain the blind).
  - Approximately 12 hours after the first dose.
- Pain Intensity (0-10-point NRS) measured at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 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 within the permitted time window as outlined below 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.
  - If rescue medication is required prior to perceptible relief the stopwatch will be removed and the data censored.
- 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.
  - If rescue medication is required prior to perceptible relief the stopwatch will be removed and the data censored.

- PK sample taken at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 13, 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 (Diarrhea, indigestion, heartburn, nausea, gas, stomach pain and vomiting).
- 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 [REDACTED] post-dose if possible.
- For the pain scores and the pain samples taken the permitted window is:
  - +/- 3 minutes for all time points within the first hour
  - +/- 5 minutes for all time points > 1 hour and ≤ 8 hours
  - +/- 10 minutes for all time points > 8 hours

#### 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 NRS) 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 within the permitted time window as outlined below in the event of more than one procedure taking place at the same nominal time.
- 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.
- For the pain scores, PGA and PK sample taken the permitted window is + / - 10 minutes of the nominal time.

### 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 (Diarrhea, indigestion, heartburn, nausea, gas, stomach pain and vomiting).
- 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  $\geq 2$  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 after surgery.

### 7.2 Efficacy Assessment

#### 7.2.1 Pain Intensity (NRS)

Pain Intensity (PI) (using a 0-10 point numeric rating scale (NRS) 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 NRS  $\geq 5$  (and moderate or severe pain on the categorical scale) within 5 hours following surgery, they will be eligible for randomization (eligibility assessment).

A further PI assessment will be made immediately prior to dosing. The pre-dose PI value will be used as the baseline measure; a subject will only be dosed if both the pre-randomization/eligibility PI and the pre-dose PI is  $\geq 5$ . Randomization will take place between eligibility and baseline assessment.

Assessments will be made at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 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.

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

If the subject records moderate or severe (and a NRS pre-randomization and pre-dose  $\geq 5$ ) within 5 hours following surgery, they will be eligible for randomization.

The categorical pain rating will be recorded in a diary.

### **7.2.3 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.

### **7.2.4 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.

If a subject takes rescue medication prior to recording perceptible pain relief, the stopwatches will be collected, and no further assessment of perceptible pain relief will be collected.

### **7.2.5 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.

If a subject takes rescue medication prior to recording meaningful pain relief, the stopwatches will be collected, and no further assessment of meaningful pain relief will be collected.

### **7.2.6 Rescue Medication Use**

Rescue medication of [REDACTED] will be allowed at any time, but subjects will be encouraged to wait until at least [REDACTED] 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 has 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 10](#)) will be performed at [Screening \(Visit 1\)](#) and [Visit 2 \(Day 2\)](#).

**Table 10: 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 <sub>2</sub> (Bicarbonate) AST, ALT Total Bilirubin Direct/Indirect bilirubin Alkaline phosphatase Uric acid Albumin Total protein CRP	pH Glucose (qual) Protein (qual) Blood (qual) Ketones (qual) Nitrites (qual) Leukocyte esterase (qual) Microscopy/culture <sup>a</sup>	Serum FSH <sup>b</sup> Serum/urine hCG <sup>c</sup> Breath/blood alcohol test <sup>d</sup> Urine drug screen <sup>e</sup>
<p>a. Only if urinalysis is positive for blood, protein, nitrites or leukocyte esterase.</p> <p>b. Females who are amenorrheic for at least 2 years at Screening.</p> <p>c. Serum hCG for all female subjects at Screening and urine hCG for females of childbearing potential at other visits.</p> <p>d. At the Investigator's discretion an alcohol test may be performed. Where necessary blood or breath alcohol tests can be performed.</p> <p>e. Urine drug screen to include the following as a minimum cocaine, cannabinoids, opiates, buprenorphine, benzodiazepines and amphetamines.</p>			

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  $\leq 470$  msec for female or  $\leq 450$  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 11: 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
<b>TOTAL</b>				<b>103.5</b>

## 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, 6, 8, 10, 12, 13, 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  $\leq 8$  hours from dosing and  $\pm 1$  hour for samples  $\geq 12$  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/Viatris 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.

The study may be unblinded prior to completion of all pharmacokinetic bioassays.

### 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

In order to derive the required sample size for the primary estimand, [REDACTED] for 10 mg BID, 15 mg BID, and placebo reported from a previous meloxicam study conducted by the Sponsor ([REDACTED] in dental pain). Simulations were performed [REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]. The numerical dose values were 2.5, 10, 30, and 0 for 1.25 mg BID, 5 mg BID, 15 mg BID, and placebo, respectively.

The results of the simulations indicate the following values for power, for 25 subjects per group, assuming a standard deviation (SD) of [REDACTED]:

**Table 12: Power Calculations for The Primary Estimand**

Dose	Expected Effect Size (versus Placebo)	Power
[REDACTED]		
[REDACTED]		
[REDACTED]		

Note that the expected standardized effect sizes (expected effect size divided by SD) are approximately [REDACTED] (15 mg BID, 5 mg BID and 1.25 mg BID, respectively) therefore the comparisons 15 mg BID vs. placebo, 5 mg BID vs. placebo and 1.25 mg BID vs. placebo have approximately [REDACTED] power to declare statistical significance for standardized effect sizes of [REDACTED] respectively.

## 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.

Subjects who were dosed in error but had a baseline PI score  $<5$  will be included in this analysis set. Data will be summarized and analyzed according to the treatment a subject was randomized to receive.

### **8.2.3 Modified Intent To Treat Analysis Set**

The mITT analysis set includes all subjects in the ITT analysis set who, additionally, have provided at least one post-baseline pain intensity (PI) score. Subjects who were dosed in error but had a baseline PI score  $<5$  will be included in this analysis set. Data will be summarized and analyzed according to the treatment a subject was randomized to receive.

### **8.2.4 Per Protocol Analysis Set**

The per protocol (PP) analysis set will include all subjects in the mITT 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. In particular, subjects who were dosed but had a baseline PI score of  $<5$  will be excluded from this analysis set. 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.

### **8.2.5 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 Intercurrent Events**

### **8.3.1 Impact of Protocol Allowed Rescue Medication Use**

For the primary analysis of the primary estimand a 6-hour windowed last observation carried forward (W6LOCF) 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 6 hours following the rescue dose.

### **8.3.2 Impact of Discontinuation**

Refer to Section 8.4.5.

## **8.4 Statistical Analyses**

### **8.4.1 Definition of the Primary Efficacy Estimand**

The summed pain intensity difference (SPID) over 0-24 hours for meloxicam vs. placebo for the modified Intent To Treat (mITT) analysis set under the assumption that rescue medication use is managed by a 6h windowed last observation carried forward (W6LOCF) principle.



### 8.4.2 Primary Analysis of Primary Estimand

To analyze W6LOCF SPID 0-24 hours, a 3-parameter  $E_{\max}$  model will be fitted to the observed mean for each dose and placebo. Effect sizes for each dose versus placebo and associated standard errors, p-values and 95% confidence intervals (CIs) will be calculated. Standardized effect sizes will also be estimated from the  $E_{\max}$  model (effect sizes for each dose versus placebo divided by the pooled SD together with their 95% confidence intervals. Baseline pain intensity score (PI) will be used as a covariate in the  $E_{\max}$  model. Baseline is defined as the mean of the pre-randomization and pre-dosing PI scores. The numerical dose values will be 2.5, 10, 30, and 0 for 1.25 mg BID, 5 mg BID, 15 mg BID, and placebo respectively.

If the  $E_{\max}$  model fails to converge, an analysis of covariance (ANCOVA) will be used to assess the difference between treatment groups. The ANCOVA model will include treatment as fixed effect and baseline PI score as a covariate. The difference between meloxicam 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.

### 8.4.3 Sensitivity Analyses of Primary Estimand

As a sensitivity analysis of the W6LOCF approach used in the primary analysis of the primary estimand, a W4LOCF and W8LOCF 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 and 8 hours following the rescue dose.

### 8.4.4 Supplementary Analyses of the Primary Estimand

As a supplementary analysis of the primary estimand, which is based on the mITT analysis set, the primary analysis will be repeated using the PP analysis set. In addition, the sensitivity analyses described above will also be repeated in the PP analysis set. If a sufficient number of subjects are excluded from the mITT analysis set due to having no post-treatment PI score, then these analyses will also be repeated using the ITT analysis set. The decision whether or not to conduct the analyses in the ITT analysis set will be made during blinded review of the data from the study.

### 8.4.5 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.
- Subjects with no post-baseline PI score will be included in the ITT analysis set and, if this analysis is conducted, a BOCF approach will be used.
- Intermittent missing pain assessments between two non-missing scores will be imputed using linear interpolation.

The impact on the primary estimand 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.

#### **8.4.6 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.

#### **8.4.7 Definition and Analysis of the Secondary Estimands**

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). All analyses will be based on the mITT analysis set.

##### **8.4.7.1 Secondary SPID Endpoints**

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.

##### **8.4.7.2 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, 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 meloxicam and placebo over 24 hours.

##### **8.4.7.3 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 meloxicam and placebo evaluated using the log-rank test. The median time to event will be calculated and presented.

#### **8.4.7.4 Responder Endpoints**

The following analysis methods apply to the responder endpoints listed:

- Proportion of subjects with overall pain reductions from baseline of  $\geq 30\%$  and  $\geq 50\%$  within 4 hours following the first dose based on the PI scores. Both these analyses will be presented for all methods of handling rescue medication use (W6LOCF and W4LOCF and W8LOCF 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 meloxicam 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.

#### **8.4.7.5 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.

### **8.4.8 Pharmacokinetics**

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 may 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 PK analysis in this study.

The study may be unblinded prior to completion of all pharmacokinetic bioassays.

#### **8.4.9 Safety Analyses**

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

##### **8.4.9.1 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.

##### **8.4.9.2 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.

##### **8.4.9.3 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.

##### **8.4.9.4 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.

#### **8.4.10 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 3<sup>rd</sup> 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.

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  $\pm 10\%$  of the nominal timepoint for assessments  $\leq 8$  hours from dosing and  $\pm 1$  hour for assessments  $\geq 12$  hours from dosing 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 10.5.1. 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 be 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 meloxicam is an NSAID will include the following:

- Myocardial Infarction/Unstable Angina
- Stroke/transient ischemic attack (TIA)
- Heart Failure
- Cardiac Arrhythmia (Atrial & Ventricular)
- Gastrointestinal hemorrhages 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 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 assess 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
<b>DEFINITE</b>	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.
<b>PROBABLE</b>	High degree of certainty for causal relationship	For example: the temporal relationship between drug exposure and AE onset/course is reasonable, there is a clinically compatible response to de-challenge (re-challenge is not required), and other causes have been eliminated or are unlikely.
<b>POSSIBLE</b>	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.
<b>UNLIKELY</b>	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.
<b>UNRELATED/NOT RELATED</b>	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
<b>Treatment interrupted</b>	The treatment was temporarily discontinued
<b>Treatment withdrawn</b>	The treatment was permanently discontinued
<b>Unknown</b>	Not known, not observed, not recorded, or refused
<b>No action taken</b>	The AE did not result in any modification of dose or frequency of dosing
<b>Not applicable</b>	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:



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 event 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 Mylan PSRM within 24 hours of awareness by email [REDACTED] (primary) or facsimile [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.

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**Document Name : Protocol - MELO-TFZ-2001 - [REDACTED]**

**Title : MELO-TFZ-2001 Protocol Version 1.0**

**Status : Approved**

## **Electronic Signatures**

<b>User</b>	<b>Date (EST)</b>	<b>Justification</b>
[REDACTED]	[REDACTED]	Approver
[REDACTED]	[REDACTED]	Approver

**MELO-TFZ-2001 CLARIFICATION MEMORANDUM #1**  
**OF THE CLINICAL STUDY PROTOCOL**

<b>Protocol Title</b>	A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Response Study of Meloxicam in the Treatment of Post-Surgical Dental Pain.
<b>Protocol Number</b>	MELO-TFZ-2001
<b>Product</b>	Meloxicam (MR-107A-02)
<b>Study Type</b>	Phase 2b
<b>Version</b>	Version 1.0, 15 February 2022
<b>Protocol Date</b>	<u>Original Date</u> 15 February 2022
<b>Registry Name</b>	ClinicalTrials.gov
<b>IND Number</b>	██████
<b>Legal/Filing Sponsor</b>	Mylan Specialty LP, a Viatris Company 3711 Collins Ferry Rd. Morgantown, WV 26505 USA
<b>Date of the Clarification Memorandum #1</b>	14 March 2022

### Summary and Rational

During the study set-up 2 typos in **Section 6.2.1.2 Dosing and Post Dose Procedures** (page 53) were identified. It is clarified, that **pain samples** should read as **PK samples** and **+/- 5 minutes** should read as **+/- 5 minutes**. Taking this into account, the text should read as indicated in the below Table:

- For the pain scores and the ~~pain~~ **PK samples** taken the permitted window is:
  - +/- 3 minutes for all time points within the first hour
  - +/-5 minutes for all time points > 1 hour and ≤ 8 hours
  - +/- 10 minutes for all time points > 8 hours

**Document Name : Protocol Amendment - MELO-TFZ-2001 - [REDACTED]**

**Title : Protocol clarification memorandum #1 MELO-TFZ-2001**

**Status : Approved**

## **Electronic Signatures**

<b>User</b>	<b>Date (EST)</b>	<b>Justification</b>
[REDACTED]	[REDACTED]	Approver



**MELO-TFZ-2001 CLARIFICATION MEMORANDUM #2**  
**OF THE CLINICAL STUDY PROTOCOL**

<b>Protocol Title</b>	A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Response Study of Meloxicam in the Treatment of Post-Surgical Dental Pain.
<b>Protocol Number</b>	MELO-TFZ-2001
<b>Product</b>	Meloxicam (MR-107A-02)
<b>Study Type</b>	Phase 2b
<b>Version</b>	Version 1.0, 15 February 2022
<b>Protocol Date</b>	Original Date 15 February 2022
<b>Registry Name</b>	ClinicalTrials.gov
<b>IND Number</b>	██████
<b>Legal/Filing Sponsor</b>	Mylan Specialty LP, a Viatris Company 3711 Collins Ferry Rd. Morgantown, WV 26505 USA
<b>Date of the Clarification Memorandum</b>	Clarification Memorandum #1: 11 March 2022 Clarification Memorandum #2: 12 April 2022

### Summary and Rational

During the study set-up numbering differences between main body of the study protocol and synopsis as well as slight wording differences were identified. This clarification memorandum # 2 is intended to clarify that the correct wording and numbering of the exclusion criteria is this presented in the main body of the protocol. This means that the exact wording and numbering of the exclusion criteria of the synopsis should read as follows:

1. Previously dosed with this formulation of meloxicam ~~tablets~~.
4. ~~Known a~~Active GI bleeding or a history of peptic ulcer disease.
- ~~7~~5. Subjects with prior stroke or transient ischemic attack.
- ~~8~~6. Subjects with moderate or severe hypertension with systolic blood pressure  $\geq 160$  mmHg and / or diastolic blood pressure  $\geq 100$  mmHg.
- ~~5~~ 7. ~~Known a~~Active inflammatory bowel disease, e.g., Crohn's Disease or ulcerative colitis.
- ~~6~~ 8. A history of bleeding disorders that may affect coagulation.
9. ~~A clinically s~~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.

**Document Name : Protocol Amendment - MELO-TFZ-2001 - [REDACTED]**

**Title : Protocol clarification memorandum #2**

**Status : Approved**

## **Electronic Signatures**

<b>User</b>	<b>Date (EST)</b>	<b>Justification</b>
[REDACTED]	[REDACTED]	Manager Approval