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A randomized, double-blind, placebo-controlled, parallel group, dose-response study of MR-107A-02 in the treatment of post-surgical dental pain

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Subtitle: Efficacy and safety of MR-107A-02 tablets in post-surgical dental pain, a randomized controlled trial

Abstract

Background: **MR-107A-02 is a novel, oral meloxicam formulation designed to enhance dissolution and absorption for rapid analgesia in acute pain. It demonstrates a favorable pharmacokinetic profile, with a higher C_{max} and shorter T_{max} than Mobic® (meloxicam tablets), while maintaining similar overall extent of exposure.**

Methods: **This phase 2b, randomized, double-blind, placebo-controlled, dose-ranging study assessed the efficacy and safety of MR-107A-02 at doses of 1.25, 5, and 15 mg twice daily (BID) following third molar extraction. The primary endpoint was $SPID_{0–24}$, analyzed in the mITT population using W6LOCF to account for rescue medication use. Pain intensity and categorical ratings were evaluated using standardized pain scales. Onset of perceptible and meaningful pain relief were measured using the double-stopwatch technique. Effect sizes and associated standard errors, *p*-values, and 95% CIs were estimated using an E_{max} model.**

Results: **Among 110 participants, MR-107A-02 demonstrated positive dose-dependent analgesia, with mean $SPID_{0-24}$ E_{max} values of 70.7 (1.25 mg), 86.7 (5 mg), and 94.8 (15 mg), versus 52.0 for placebo. Significant improvement in $SPID_{0-24}$ occurred at 5 mg and 15 mg versus placebo ($p < .001$). The 15 mg dose achieved perceptible and meaningful pain relief within 0.6 and 1.5 hours, respectively, and had the lowest rescue medication use (29.6%) compared to 42.9%, 57.1%, and 74.1% in the 1.25 mg, 5 mg, and placebo. No severe TEAEs, SAEs, or discontinuations were reported.**

Conclusions: **MR-107A-02 was generally well tolerated and demonstrated dose-dependent efficacy, with the 15 mg BID dose providing rapid analgesia and a reduction in rescue medication use.**

Clinicaltrial.gov identifier: **NCT05317312 https://clinicaltrials.gov/study/NCT05317312**

Keywords: acute pain; fast-release; meloxicam; rapid analgesia; safety.

Introduction

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) that has shown efficacy in treatment of both acute and chronic pain.[1–3] The apparent primary mechanism of action of meloxicam, and other NSAIDs, involves inhibition of cyclo-oxygenase (COX) enzymes-1 and COX-2 and subsequent reduction of prostaglandin synthesis.[4,5] Meloxicam exhibits preferential binding to COX-2, which is associated with a lower risk of gastrointestinal (GI) adverse effects compared to non-selective NSAIDs.[6–8]

Meloxicam is available in multiple generic formulations including oral tablets, oral suspension, orally disintegrating tablets, and in capsule form, primarily indicated for chronic musculoskeletal disorders such as osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis.[6,9] These products are typically administered once daily in doses ranging from 5 to 15 mg. While they are effectively used for chronic pain, their delayed

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onset (usually 1-2 hours) with peak plasma concentration occurring approximately 5 to 6 hours after administration, restricts their use in acute postoperative pain scenarios.[7,10] Although an intravenous formulation has been approved for moderate-to-severe pain, a therapeutic gap remains for a fast-acting, orally administered alternative.[11]

To address this unmet need for rapid pain relief in acute settings, MR-107A-02 is being developed as a novel, fast-acting formulation of meloxicam. This formulation is designed to achieve rapid absorption and onset of analgesia while maintaining adequate safety and efficacy. In a pharmacokinetic study, MR-107A-02 demonstrated significantly faster absorption than reference meloxicam (Mobic®), with a higher peak plasma concentration (geometric mean C_{max}: 2734.3 vs. 1592.1 ng/mL) and a shorter time to maximum concentration (median T_{max}: 0.75 vs. 4.00 hours).[12] These pharmacokinetic advantages relative to currently available oral meloxicam products support its use in acute pain conditions.

The dental surgical pain model involving molar extraction includes both soft tissue and bony trauma. It is a well-established approach for evaluating analgesic efficacy and conducting dose-ranging studies in acute pain, making it ideal for early-phase trials of novel analgesics such as MR-107A-02.[13]

This phase II study was designed with an objective to evaluate the dose-response relationship, efficacy, and safety of MR-107A-02 in adults experiencing post-surgical dental pain following extraction of two or more third molar teeth.

Participants and methods

The study protocol and consent forms were reviewed and approved by an institutional review board. The study was conducted in accordance with the principles of Good Clinical Practice (as referenced in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use guideline E6), local regulatory requirements, and the principles of the Declaration of Helsinki. All study participants provided written informed consent before study participation.

Study design

This was a single-center, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study conducted in healthy, adult male or female volunteers who were undergoing dental surgery (removal of ≥2 third molars). The study was conducted at JBR Clinical Research (now called CenExel Clinical Research), Salt Lake City, Utah, United States between March and June 2022.

Study population

Inclusion criteria

Males and females aged 18 years and older who required dental surgery for extraction of 2 or more third molars, with at least 1 third molar with partial or complete mandibular bony impaction were considered for the study. Study participants were enrolled in the study if they reported scores of ≥5 on a numeric rating scale and moderate to severe pain on the categorical pain rating scale within 5 hours post- surgery.

Exclusion criteria

Participants were not eligible if they had prior exposure to meloxicam within 7 days; NSAIDs or other analgesics within 72 hours; tranquilizers or muscle relaxants within 60 days; or known hypersensitivity to the study drug or surgical materials. Participants with an active GI bleeding or a history of peptic ulcer disease, stroke, moderate to severe hypertension, inflammatory bowel disease, and bleeding disorders were also not considered. Detailed exclusion criteria are provided in the supplementary appendix.

Study procedure

Study participation involved screening (visit 1), in-patient surgery, randomization and dosing on day 1 (visit 2), and telephone follow-up on days 5 to 7 (visit 3). Study participants underwent screening for their eligibility, 1 to 30 days before surgery. On day 1, the eligible participants were scheduled for molar extraction surgery. The surgery was performed using nitrous oxide sedation and a local injection of lidocaine with epinephrine. Participants received prophylactic antibiotics as part of routine postoperative clinical care.

Following dental surgery, the participants who reported moderate to severe pain within 5 hours were randomized to receive oral doses of MR-107A-02 (1.25 mg, 5 mg, or 15 mg) or matching placebo twice daily. Randomization was conducted in a 1:1:1:1 ratio using an interactive web response system (IWRS) and treatment was administered in a double-blind manner.

Hydrocodone/acetaminophen (5/325 mg) tablets were provided as needed for rescue medication, administered up to one tablet every 2 hours, not exceeding 6 tablets in 24 hours (equivalent to 30 mg hydrocodone and 1950 mg acetaminophen) for breakthrough pain management. Study participants were monitored for 24 hours following study drug administration for safety and efficacy assessments (in-clinic confinement period), followed by a safety follow-up via telephone call 3 to 5 days later.

Dose selection

Based on prior evidence of meloxicam's efficacy in acute and chronic pain, doses of 1.25 mg, 5 mg, and 15 mg were strategically selected to explore the dose-response relationship. This strength range enabled evaluation of efficacy, safety, and tolerability, supporting dose optimization through assessment of minimal effective and maximal tolerable concentrations.[14–16] The 1.25 mg dose was intended to be sub-therapeutic.

Assessments of efficacy and safety

Efficacy

The primary efficacy endpoint was the time weighted summed pain intensity difference (SPID) over 0-24 hours ($SPID_{0–24}$) for MR-107A-02 versus placebo, assessed in modified intent-to-treat (mITT) analysis set. This mITT analysis was conducted under the assumption that the rescue medication use was managed by a 6-hour windowed (W6) last observation carried forward (LOCF)

principle (or W6LOCF) approach to adjust for rescue medication use. Pain intensity was measured on a 0-10-point Numerical Rating Scale (NRS), which ranged from "no pain" at 0 to "worst possible pain" with a score of 10. Pain intensity was assessed at 15.0, 30.0, and 45.0 minutes and 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 14.0, 16.0, 20.0, and 24 hours after the first dose of study drug. Additional assessments were conducted immediately before any rescue medication use and/or at the time of early termination. The pain intensity score immediately before rescue medication was used in place of observed pain intensity scores for 6 hours subsequently (the W6LOCF approach).

Secondary endpoints included measurement of pain intensity score and pain intensity difference (PID) from baseline to each time point described above. Additional SPIDs were assessed at the following intervals: 0–2 hours ($SPID_{0-2}$), 0–4 hours ($SPID_{0-4}$), 0–8 hours ($SPID_{0-8}$), 0–12 hours ($SPID_{0-12}$), and 12–24 hours ($SPID_{12-24}$) after initial dose of the study drug.

The proportion of participants with overall pain reduction from baseline of ≥30% and ≥50% within 4 hours following the first dose were measured. The onset of perceptible and meaningful pain relief following the first dose of study drug was assessed using the double-stopwatch technique. Perceptible pain relief was defined as the post-dose time at which the participant first experienced any noticeable reduction in pain, indicated by stopping the first stopwatch. Meaningful pain relief was defined as the post-dose time at which the participant perceived a clinically significant reduction in pain, based on their own judgment, indicated by stopping the second stopwatch. If rescue medication was taken before either event was recorded, the corresponding stopwatch assessment was censored. The pain control was further evaluated with the patient-reported global assessment (PGA), rated on a 5-point rating scale (poor, fair, good, very good, excellent) from initial dosing up to 24 hours for the study drug. Those participants who rated good, very good or excellent were considered as "responders," while those who rated with poor, fair or had missing values as "non responders." In addition, the proportion of participants who used rescue medication within 0-24 hours, the number of participants requiring no rescue doses, and the total number of rescue medication administrations during this period were recorded.

Safety

Safety assessments during the 24-hour post-dose period included monitoring adverse events (AEs), laboratory investigations, electrocardiograms (ECGs) and vital signs (heart rate, systolic and diastolic blood pressure). A telephone follow-up (days 5–7) was conducted post-discharge to record any ongoing AEs. The AEs were assessed and classified based on their causality, severity, expectedness and outcome. Study participants were also monitored for adverse events of special interest (AESIs) related to meloxicam including myocardial infarction/unstable angina, stroke/transient ischemic attack, heart failure, cardiac arrhythmia (atrial and ventricular), GI hemorrhages (not elsewhere classified) and GI ulceration and perforation.

Pharmacokinetics

Blood samples were collected at pre-dose and post-dose, at following time intervals: 15.0, 30.0, and 45.0 minutes and 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 13.0, 14.0, 16.0, 20.0, and 24 hours after the first dose of study drug. The samples were processed (stored, centrifuged) and analyzed for meloxicam concentrations using validated bioanalytical methods. The pharmacokinetics endpoints included population pharmacokinetic (PK) parameters: Maximum plasma concentration (C_{max}); time to maximum plasma concentration (T_{max}); and the area under the plasma concentration–time curve (AUC) measured over various intervals: 0–2 hours (AUC_{0-2}), 0–4 hours (AUC_{0-4}), 0–8 hours (AUC_{0-8}), 0–12 hours (AUC_{0-12}), and 0–24 hours (AUC_{0-24}) post-dosing.

Statistical analyses

Sample size estimation for the primary endpoint ($SPID_{0-24}$) was based on a prespecified 3-parameter E_{max} model fitted using W6LOCF data from a prior meloxicam dental pain study (MECC-TBZ-2001), with simulations ($n = 1000$) for 1.25 mg BID, 5 mg BID, 15 mg BID, doses versus placebo. Assuming a standard deviation of 39.8 and 25 participants per group, the expected effect sizes and power were 42.7 (91%) for 15 mg, 27.3 (83%) for 5 mg, and 10.4 (69%) for 1.25 mg. Standardized effect sizes were approximately 1.0, 0.7, and 0.3, respectively, yielding ∼90%, ∼80%, and ∼70% power to detect statistically significant differences versus placebo.

To address the potential confounding effects of rescue medication use on post-dose pain assessments, the primary endpoint was analyzed using a windowed last observation carried forward approach. A 6-hour censoring window following rescue medication use was prespecified in the statistical analysis plan, based on the expected duration of action of commonly used rescue analgesics in the dental pain model and established practice in acute pain studies.[14,17]

The dose–response relationship was evaluated using a prespecified three-parameter Emax model, with baseline pain intensity included as a covariate, to characterize the relationship between dose and analgesic effect across treatment groups.

Pain intensity scores over time were analyzed using Mixed Model Repeated Measures (MMRM). Time to event endpoints (meaningful and perceptible pain relief onset, and time to rescue medication) were analyzed using Kaplan–Meier curves with *P* values from Log Rank Tests. Proportions were analyzed using χ^2 tests.

Safety data were summarized by treatment group. AEs were coded using the *Medical Dictionary for Regulatory Activities* (MedDRA; version 25.0).

Statistical analysis was carried out using statistical software, SAS version 9.4. Additional information on statistical analysis is available in the supplementary appendix.

Results

Demographic characteristics

A total of 155 participants were screened, of whom 111 were enrolled and randomized (28 participants each to MR-107A-02 1.25 mg, 5 mg, and 15 mg groups, and 27 participants to placebo). The modified intent-to-treat (mITT) population included all randomized participants who received at least one dose of study drug and provided at least one post-baseline pain

assessment, in accordance with the prespecified analysis plan. Of these 111 randomized participants, one participant, who was randomized to the MR-107A-02 15 mg BID group, discontinued prior to dosing due to baseline pain intensity below the eligibility threshold and was excluded from all the analysis sets (Figure 1). Consequently, 110 participants received study drug and were included in the safety, modified intent-to-treat (mITT), and pharmacokinetic analysis sets. A total of 108 (97.3%) participants completed the study; one participant withdrew consent after treatment, and one participant was lost to follow-up after completion of the in-clinic confinement period. Among the total study participants, 57.3% were male, and the median age was 18.0 years (range 18 to 24 years). Most participants were White (96.4%), were not Hispanic or Latino (89.1%), and had 4 molars extracted (90.9%). The median BMI was 22.7 kg/m^2 (range 16 to 35 kg/m^2), and the median baseline pain intensity was 7.5 (range 5 to 10). The 4 treatment groups were comparable with respect to demographic and baseline characteristics (Table 1).

Efficacy

The primary endpoint analysis demonstrated a dose-response relationship, with mean E_{max} estimates for $SPID_{0\text{-}24}$ increasing with dose: 70.7, 86.7, and 94.8 for MR-107A-02 1.25 mg, 5 mg, and 15 mg, respectively, compared to 52.0 for placebo. Statistically significant improvements in the $SPID_{0\text{-}24}$ post-dose

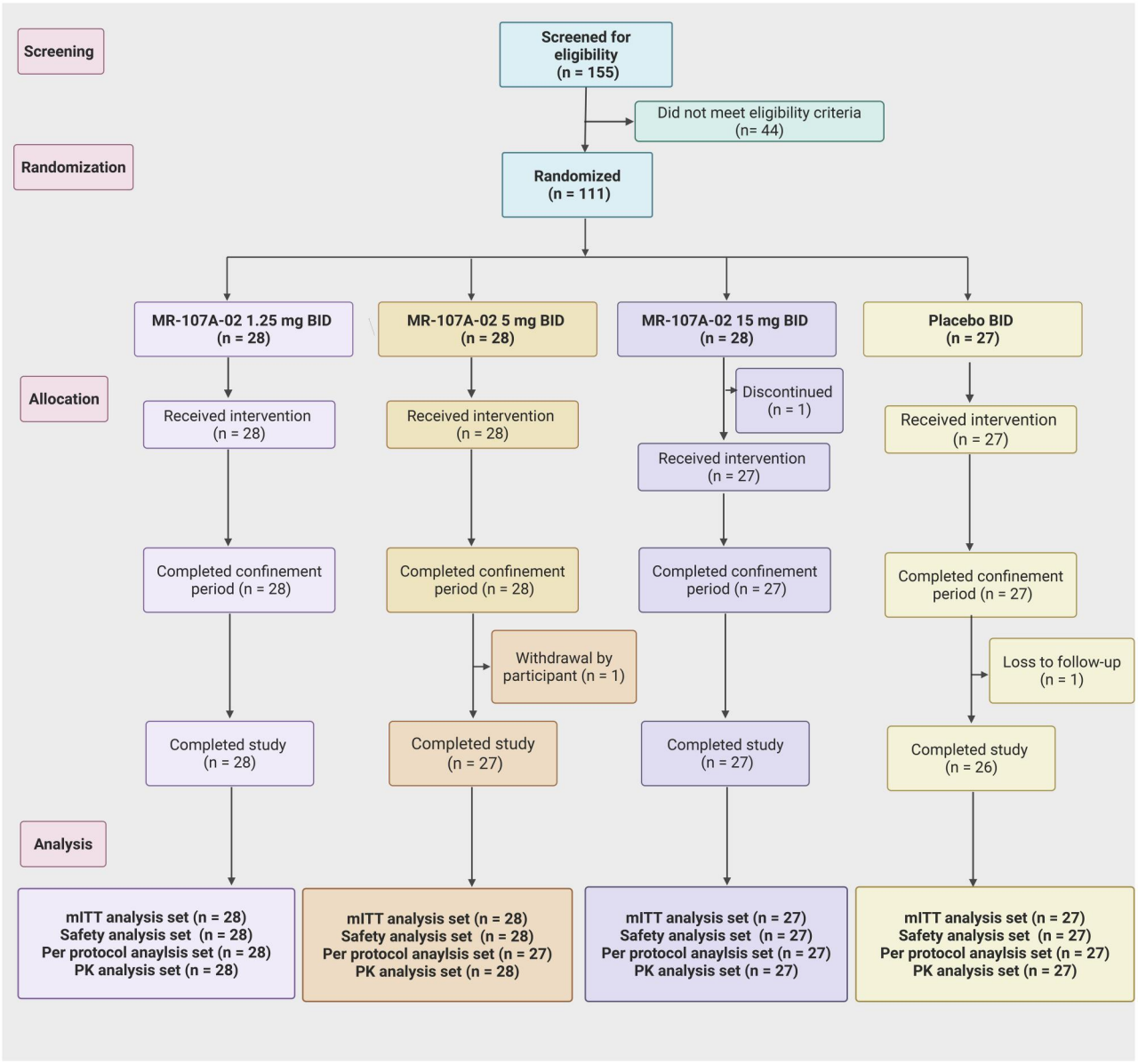


Figure 1 CONSORT flow diagram. Note: One participant randomized to the 15 mg BID group was discontinued prior to dosing due to baseline pain intensity below the eligibility threshold and was excluded from all the analysis sets. Confinement period refers to the approximately 24-hour in-clinic observation phase from dosing on day 1 through discharge on day 2, during which study participants remained under continuous supervision for efficacy, pharmacokinetic, and safety assessments.

Table 1 Summary of demographics.

	MR-107A-02				
Characteristics	**1.25 mg (*N* = 28)**	**5 mg (*N* = 28)**	**15 mg (*N* = 27)**	**Placebo (*N* = 27)**	**Total (*N* = 110)**
Age (years), mean (SD)	18.9 (1.45)	19.0 (1.52)	19.3 (1.94)	18.7 (1.13)	19.0 (1.53)
Range	(18-24)	(18-23)	(18-24)	(18-22)	(18-24)
Sex, n (%)					
Male	17 (60.7)	16 (57.1)	16 (59.3)	14 (51.9)	63 (57.3)
Female	11 (39.3)	12 (42.9)	11 (40.7)	13 (48.1)	47 (42.7)
Ethnicity, n (%)					
Hispanic or Latino	2 (7.1)	4 (14.3)	2 (7.4)	4 (14.8)	12 (10.9)
Not Hispanic or Latino	26 (92.9)	24 (85.7)	25 (92.6)	23 (85.2)	98 (89.1)
Race, n (%)					
Asian	–	–	1 (3.7)	–	1 (0.9)
Black or African American	–	1 (3.6)	1 (3.7)	–	2 (1.8)
White	27 (96.4)	27 (96.4)	25 (92.6)	27 (100.0)	106 (96.4)
Multiple	1 (3.6)	–	–	–	1 (0.9)
Number of third molars extracted, n (%)					
2	1 (3.6)	2 (7.1)	1 (3.7)	–	4 (3.6)
3	2 (7.1)	1 (3.6)	–	3 (11.1)	6 (5.5)
4	25 (89.3)	25 (89.3)	26 (96.3)	24 (88.9)	100 (90.9)
Baseline pain intensity, mean (SD)	7.4 (1.16)	7.9 (1.13)	7.2 (1.21)	7.4 (1.12)	7.5 (1.17)
Range	(5-10)	(6-10)	(5-10)	(5-10)	(5-10)

Note: All 3 doses of MR-107A-02 and placebo were administered twice daily.
No participants identified as American Indian or Alaskan Native or Native Hawaiian or Other Pacific Islander; only categories with enrolled participants are presented.
Abbreviation: SD, standard deviation.

were observed for the MR-107A-02 5 mg and 15 mg doses ($P < .001$) versus placebo. This trend was observed at 0-2 hours ($SPID_{0-2}$), 0-4 hours ($SPID_{0-4}$), 0-8 hours ($SPID_{0-8}$), 0-12 hours ($SPID_{0-12}$), and 12-24 ($SPID_{12-24}$) post-dose. In particular, all MR-107A-02 doses demonstrated statistically significant improvements versus placebo for the early time-interval endpoints $SPID_{0-2}$ and $SPID_{0-4}$, suggesting an early analgesic effect (Table 2).

Analysis of NRS pain scores over time using the W6LOCF method, showed numerically lower least squares (LS) mean scores in all 3 MR-107A-02 dose groups compared to placebo (Table 3 and Figure S1A). This was evident as early as 0.5 hours post-dose that sustained throughout the 24-hour assessment period (Figure S1B).

Sensitivity analyses evaluating alternative approaches for handling rescue medication use showed results consistent with the primary W6LOCF analysis. The overall dose–response pattern was preserved across W4LOCF, W8LOCF, ALLOCF, uncensored, and per-protocol analyses, with statistically significant improvements versus placebo observed for the MR-107A-02 5 mg and 15 mg BID doses, but not for the 1.25 mg BID dose. Exploratory and sensitivity analyses confirming the robustness of the primary findings are presented in the supplementary appendix.

Several secondary endpoints reinforced the findings of the primary efficacy analysis. Perceptible pain relief was reported in MR-107A-02 1.25 mg and 5 mg groups (75.0% of participants in each group) and 15 mg group (96.3%) compared to placebo group (37.0%) (Table S1). The median time to first perceptible pain relief was shortest in the MR-107A-02 15 mg group (median: 0.6 hours), followed by the 5 mg (0.7 hours) and 1.25 mg (0.9 hours) groups, all significantly faster than placebo (NA, as <50% of the participants had the event) ($P < .001$; Figure 2A).

Meaningful pain relief was reported by participants in the MR-107A-02 treatment arms: 50.0% in the 1.25 mg group, 46.4% in the 5 mg group, and 77.8% in the 15 mg group, compared with 22.2% in the placebo group (Table S2). The median time to first meaningful pain relief was significantly shorter in the 15 mg group (median: 1.5 hours; $P < .001$), while the 5 mg (24.2 hours) and 1.25 mg (NA, as <50% of the participants had the event) doses did not demonstrate statistically significant differences compared to placebo (NA) (Figure 2B).

The proportion of PGA responders was higher in all MR-107A-02 treatment groups, with the 15 mg group showing the greatest response at 85.2% compared to 33.3% in the placebo group, a statistically significant difference ($P < .001$; Table S3). The MR-107A-02 15 mg group had the lowest mean number of rescue medication uses, at 0.3, followed by the 5 mg and 1.25 mg groups with 1.0 use each, compared to 1.9 uses in the placebo group. All 3 MR-107A-02 dose groups showed statistically significant reductions in the mean rescue medication use versus placebo, with P values of 0.031, 0.044, and < 0.001 for the 1.25 mg, 5 mg, and 15 mg groups, respectively (Table S4). When assessed as the proportion of participants requiring rescue medication, the MR-107A-02 15 mg group had the lowest proportion of participants requiring rescue medication at 29.6%, followed by 42.9% for 1.25 mg and 57.1% for 5 mg, compared to 74.1% with placebo (Table S4). The time to rescue use is depicted in Figures 3 and 4.

Table 2 Summed pain intensity difference ($SPID_{0-24}$) by treatment group using W6LOCF (mITT analysis set).

	MR-107A-02			
Interval statistic	**1.25 mg (*N* = 28)**	**5 mg (*N* = 28)**	**15 mg (*N* = 27)**	**Placebo (*N* = 27)**
SPID $_{0-24}$				
Mean (SD)	74.5 (46.49)	82.4 (37.78)	96.8 (35.31)	50.5 (37.26)
E_{max} estimates[a]				
Mean (SE)	70.7 (7.86)	86.7 (4.88)	94.8 (7.47)	52.0 (7.85)
95% CI	(55.1, 86.3)	(77.0, 96.4)	(80.0, 109.6)	(36.4, 67.5)
E_{max} estimated difference vs PBO[a]				
Mean (SE)	18.7 (12.08)	34.7 (10.25)	42.8 (9.53)	–
95% CI	(−5.2, 42.7)	(14.4, 55.0)	(23.9, 61.7)	–
***P*-value**	0.123	<0.001	<0.001	–
SPID $_{0-2}$				
Mean (SD)	1.5 (3.13)	2.9 (2.53)	3.5 (2.51)	0.3 (2.45)
E_{max} estimates[a]				
Mean (SE)	1.6 (0.41)	2.8 (0.33)	3.5 (0.46)	0.3 (0.50)
95% CI	(0.8, 2.4)	(2.2, 3.5)	(2.6, 4.5)	(−0.7, 1.2)
E_{max} estimated difference vs PBO[a]				
Mean (SE)	1.3 (0.61)	2.6 (0.64)	3.3 (0.66)	–
95% CI	(0.1, 2.5)	(1.3, 3.9)	(2.0, 4.6)	–
***P*-value**	0.031	<0.001	<0.001	–
SPID $_{0-4}$				
Mean (SD)	5.1 (7.53)	7.9 (6.13)	10.9 (6.45)	0.8 (5.92)
E_{max} estimates[a]				
Mean (SE)	4.7 (1.09)	8.4 (0.85)	10.6 (1.19)	0.9 (1.25)
95% CI	(2.5, 6.8)	(6.7, 10.1)	(8.2, 13.0)	(−1.5, 3.4)
E_{max} estimated difference vs PBO[a]				
Mean (SE)	3.7 (1.64)	7.5 (1.67)	9.6 (1.62)	–
95% CI	(0.5, 7.0)	(4.2, 10.8)	(6.4, 12.9)	–
***P*-value**	0.026	<0.001	<0.001	–
SPID $_{0-8}$				
Mean (SD)	15.2 (17.17)	19.5 (14.19)	27.3 (14.45)	5.5 (14.15)
E_{max} estimates[a]				
Mean (SE)	13.4 (2.68)	21.4 (2.15)	26.4 (2.94)	6.2 (3.02)
95% CI	(8.1, 18.7)	(17.2, 25.7)	(20.6, 32.2)	(0.2, 12.2)
E_{max} estimated difference vs PBO[a]				
Mean (SE)	7.2 (4.21)	15.2 (4.25)	20.2 (3.73)	–
95% CI	(−1.1, 15.6)	(6.8, 23.6)	(12.8, 27.6)	–
***P*-value**	0.090	<0.001	<0.001	–
SPID $_{0-12}$				
Mean (SD)	26.2 (24.26)	32.6 (18.04)	42.4 (18.56)	14.4 (18.85)
E_{max} estimates[a]				
Mean (SE)	23.8 (3.31)	34.4 (3.13)	42.0 (3.98)	15.5 (4.00)
95% CI	(17.2, 30.4)	(28.2, 40.6)	(34.1, 49.8)	(7.6, 23.5)
E_{max} estimated differencevs PBO[a]				
Mean (SE)	8.2 (5.30)	18.9 (5.95)	26.4 (4.93)	–
95% CI	(−2.2, 18.7)	(7.1, 30.7)	(16.6, 36.2)	–
***P*-value**	0.122	0.002	<0.001	–
SPID $_{12-24}$				
Mean (SD)	48.3 (25.07)	49.7 (22.76)	54.4 (19.96)	36.1 (22.13)
E_{max} estimates[a]				
Mean (SE)	47.5 (4.43)	51.6 (2.50)	52.9 (3.68)	36.4 (4.19)
95% CI	(38.7, 56.3)	(46.6, 56.5)	(45.7, 60.2)	(28.1, 44.7)
E_{max} estimated difference vs PBO[a]				
Mean (SE)	11.1 (6.32)	15.2 (4.92)	16.5 (5.36)	–
95% CI	(−1.4, 23.6)	(5.4, 24.9)	(5.9, 27.2)	–
***P*-value**	0.082	0.003	0.003	–

Note: All 3 doses of MR-107A-02 and placebo were administered twice daily.

SPID was calculated using the trapezoidal rule and available NRS pain scores at actual times. W6LOCF utilized "pain right now" just prior to rescue medication use and censored subsequent pain intensity values for 6 hours when calculating SPIDs.

[a] Model estimates, CIs, and *P* values were based on a 3-parameter E_{max} model with covariate for baseline NRS score.

Abbreviations: CI, confidence interval; E_{max}, term referring to the asymptotic maximum dose effect (model); max, maximum; min, minimum; mITT, modified intent-to-treat; NRS, numeric rating scale; PBO, placebo; SD, standard deviation; SE, standard error; SPID, summed pain intensity difference; W6LOCF, 6-hour windowed last observation carried forward.

Table 3 Least square means of NRS pain scores at each nominal time point (W6LOCF, mITT set).

	MR-107A-02			
Interval Statistic	**1.25 mg (*N* = 28)**	**5 mg (*N* = 28)**	**15 mg (*N* = 27)**	**Placebo (*N* = 27)**
15 min				
Mean (SD)	7.0 (1.62)	7.7 (1.44)	7.2 (1.42)	7.2 (1.49)
MMRM estimates[a]				
LS mean (SE)	7.1 (0.18)	7.3 (0.18)	7.4 (0.18)	7.2 (0.18)
95% CI	(6.8, 7.5)	(6.9, 7.7)	(7.1, 7.8)	(6.8, 7.6)
MMRM difference vs PBO[a]				
LS mean (SE)	−0.1 (0.25)	0.1 (0.25)	0.2 (0.26)	–
95% CI	(−0.6, 0.4)	(−0.4, 0.6)	(−0.3, 0.8)	–
30 min				
Mean (SD)	6.9 (1.97)	7.1 (1.62)	6.7 (1.80)	7.2 (1.53)
MMRM estimates[a]				
LS mean (SE)	7.0 (0.24)	6.7 (0.24)	6.9 (0.24)	7.2 (0.24)
95% CI	(6.5, 7.5)	(6.2, 7.2)	(6.5, 7.4)	(6.8, 7.7)
MMRM difference vs PBO[a]				
LS mean (SE)	−0.2 (0.34)	−0.5 (0.34)	−0.3 (0.34)	–
95% CI	(−0.9, 0.4)	(−1.2, 0.1)	(−1.0, 0.4)	–
45 min				
Mean (SD)	6.6 (2.04)	6.5 (1.99)	5.9 (2.17)	7.1 (1.55)
MMRM estimates[a]				
LS mean (SE)	6.7 (0.29)	6.1 (0.29)	6.2 (0.30)	7.1 (0.30)
95% CI	(6.1, 7.2)	(5.5, 6.7)	(5.6, 6.7)	(6.5, 7.7)
MMRM difference vs PBO[a]				
LS mean (SE)	−0.5 (0.41)	−1.0 (0.42)	−1.0 (0.42)	–
95% CI	(−1.3, 0.4)	(−1.8, −0.2)	(−1.8, −0.1)	–
1 hour				
Mean (SD)	6.5 (2.24)	6.3 (2.08)	5.1 (2.36)	7.3 (1.82)
MMRM estimates[a]				
LS mean (SE)	6.6 (0.34)	5.8 (0.34)	5.4 (0.34)	7.4 (0.34)
95% CI	(6.0, 7.3)	(5.2, 6.5)	(4.7, 6.1)	(6.7, 8.0)
MMRM difference vs PBO[a]				
LS mean (SE)	−0.7 (0.48)	−1.5 (0.48)	−1.9 (0.48)	–
95% CI	(−1.7, 0.2)	(−2.5, −0.6)	(−2.9, −1.0)	–
1.5 hours				
Mean (SD)	6.4 (2.12)	5.8 (2.32)	4.4 (2.29)	7.4 (1.84)
MMRM estimates[a]				
LS mean (SE)	6.5 (0.34)	5.4 (0.34)	4.7 (0.35)	7.4 (0.35)
95% CI	(5.9, 7.2)	(4.7, 6.1)	(4.0, 5.4)	(6.7, 8.1)
MMRM difference vs PBO[a]				
LS mean (SE)	−0.9 (0.49)	−2.0 (0.49)	−2.7 (0.49)	–
95% CI	(−1.8, 0.1)	(−3.0, −1.0)	(−3.7, −1.7)	–
2 hours				
Mean (SD)	6.2 (2.18)	5.7 (2.47)	4.1 (2.23)	7.6 (1.69)
MMRM estimates[a]				
LS mean (SE)	6.3 (0.35)	5.3 (0.35)	4.4 (0.36)	7.6 (0.36)
95% CI	(5.6, 7.0)	(4.6, 6.0)	(3.7, 5.1)	(6.9, 8.3)
MMRM difference vs PBO[a]				
LS mean (SE)	−1.3 (0.50)	−2.3 (0.50)	−3.2 (0.51)	–
95% CI	(−2.3, −0.3)	(−3.3, −1.3)	(−4.2, −2.2)	–
3 hours				
Mean (SD)	5.6 (2.54)	5.6 (2.52)	3.5 (2.61)	7.2 (2.17)
MMRM estimates[a]				
LS mean (SE)	5.7 (0.41)	5.2 (0.42)	3.7 (0.42)	7.2 (0.42)
95% CI	(4.9, 6.5)	(4.3, 6.0)	(2.9, 4.6)	(6.4, 8.0)

(continued)

Table 3 (continued)

	MR-107A-02			
Interval Statistic	**1.25 mg (*N* = 28)**	**5 mg (*N* = 28)**	**15 mg (*N* = 27)**	**Placebo (*N* = 27)**
MMRM difference vs PBO[a]				
LS mean (SE)	−1.5 (0.59)	−2.0 (0.59)	−3.5 (0.60)	–
95% CI	(−2.7, −0.4)	(−3.2, −0.9)	(−4.6, −2.3)	–
4 hours				
Mean (SD)	5.3 (2.69)	5.0 (2.79)	3.2 (2.65)	6.9 (2.56)
MMRM estimates[a]				
LS mean (SE)	5.4 (0.47)	4.6 (0.47)	3.4 (0.48)	6.9 (0.47)
95% CI	(4.4, 6.3)	(3.7, 5.5)	(2.5, 4.4)	(6.0, 7.8)
MMRM difference vs PBO[a]				
LS mean (SE)	−1.6 (0.67)	−2.3 (0.67)	−3.5 (0.67)	–
95% CI	(−2.9, −0.2)	(−3.6, −1.0)	(−4.8, −2.1)	–
5 hours				
Mean (SD)	4.9 (2.57)	5.0 (2.74)	2.9 (2.60)	6.7 (2.51)
MMRM estimates[a]				
LS mean (SE)	5.0 (0.46)	4.6 (0.46)	3.2 (0.47)	6.7 (0.47)
95% CI	(4.1, 5.9)	(3.7, 5.5)	(2.3, 4.1)	(5.8, 7.6)
MMRM difference vs PBO[a]				
LS mean (SE)	−1.7 (0.66)	−2.1 (0.66)	−3.5 (0.67)	–
95% CI	(−3.0, −0.3)	(−3.4, −0.8)	(−4.8, −2.2)	–
6 hours				
Mean (SD)	4.9 (2.62)	5.0 (2.70)	3.1 (2.47)	6.2 (2.47)
MMRM estimates[a]				
LS mean (SE)	5.0 (0.47)	4.6 (0.47)	3.4 (0.47)	6.2 (0.47)
95% CI	(4.0, 5.9)	(3.6, 5.5)	(2.4, 4.3)	(5.3, 7.2)
MMRM difference vs PBO[a]				
LS mean (SE)	−1.3 (0.66)	−1.7 (0.67)	−2.9 (0.67)	–
95% CI	(−2.6, 0.0)	(−3.0, −0.4)	(−4.2, −1.5)	–
7 hours				
Mean (SD)	4.6 (2.41)	5.1 (2.84)	3.3 (2.57)	6.1 (2.42)
MMRM estimates[a]				
LS mean (SE)	4.7 (0.48)	4.7 (0.48)	3.6 (0.48)	6.1 (0.48)
95% CI	(3.7, 5.6)	(3.8, 5.7)	(2.6, 4.6)	(5.1, 7.1)
MMRM difference vs PBO[a]				
LS mean (SE)	−1.4 (0.68)	−1.4 (0.68)	−2.5 (0.69)	–
95% CI	(−2.8, −0.1)	(−2.7, −0.0)	(−3.9, −1.1)	–
8 hours				
Mean (SD)	4.8 (2.16)	4.7 (2.26)	2.9 (1.81)	5.9 (2.20)
MMRM estimates[a]				
LS mean (SE)	4.9 (0.38)	4.4 (0.39)	3.1 (0.39)	5.9 (0.39)
95% CI	(4.2, 5.7)	(3.6, 5.2)	(2.3, 3.9)	(5.2, 6.7)
MMRM difference vs PBO[a]				
LS mean (SE)	−1.0 (0.54)	−1.5 (0.55)	−2.8 (0.55)	–
95% CI	(−2.1, 0.1)	(−2.6, −0.5)	(−3.9, −1.7)	–
10 hours				
Mean (SD)	4.5 (2.24)	4.3 (2.28)	3.4 (1.72)	5.1 (2.07)
MMRM estimates[a]				
LS mean (SE)	4.6 (0.39)	4.0 (0.40)	3.7 (0.40)	5.1 (0.40)
95% CI	(3.8, 5.4)	(3.2, 4.8)	(2.9, 4.5)	(4.3, 5.9)
MMRM difference vs PBO[a]				
LS mean (SE)	−0.5 (0.56)	−1.1 (0.57)	−1.4 (0.57)	–
95% CI	(−1.6, 0.6)	(−2.2, 0.0)	(−2.5, −0.3)	–

(continued)

Table 3 (continued)

	MR-107A-02			
Interval Statistic	**1.25 mg (*N* = 28)**	**5 mg (*N* = 28)**	**15 mg (*N* = 27)**	**Placebo (*N* = 27)**
12 hours				
Mean (SD)	4.6 (2.06)	4.4 (2.50)	3.7 (1.73)	4.9 (2.11)
MMRM estimates[a]				
LS mean (SE)	4.7 (0.40)	4.1 (0.40)	3.9 (0.40)	4.9 (0.40)
95% CI	(4.0, 5.5)	(3.3, 4.9)	(3.1, 4.7)	(4.1, 5.7)
MMRM difference vs PBO[a]				
LS mean (SE)	−0.1 (0.56)	−0.8 (0.57)	−0.9 (0.57)	–
95% CI	(−1.2, 1.0)	(−1.9, 0.4)	(−2.1, 0.2)	–
14 hours				
Mean (SD)	3.6 (2.38)	3.9 (2.07)	3.0 (1.81)	4.9 (2.16)
MMRM estimates[a]				
LS mean (SE)	3.7 (0.40)	3.6 (0.41)	3.2 (0.41)	4.9 (0.41)
95% CI	(2.9, 4.5)	(2.8, 4.4)	(2.4, 4.0)	(4.1, 5.7)
MMRM difference vs PBO[a]				
LS mean (SE)	−1.2 (0.57)	−1.3 (0.58)	−1.6 (0.58)	–
95% CI	(−2.3, −0.1)	(−2.4, −0.1)	(−2.8, −0.5)	–
16 hours				
Mean (SD)	3.4 (2.15)	3.4 (1.84)	2.4 (1.55)	4.7 (2.19)
MMRM estimates[a]				
LS mean (SE)	3.5 (0.38)	3.0 (0.39)	2.7 (0.39)	4.8 (0.39)
95% CI	(2.7, 4.2)	(2.3, 3.8)	(1.9, 3.5)	(4.0, 5.5)
MMRM difference vs PBO[a]				
LS mean (SE)	−1.3 (0.54)	−1.7 (0.55)	−2.0 (0.55)	–
95% CI	(−2.3, −0.2)	(−2.8, −0.6)	(−3.1, −1.0)	–
20 hours				
Mean (SD)	3.3 (2.21)	3.6 (2.49)	2.5 (1.40)	4.4 (2.44)
MMRM estimates[a]				
LS mean (SE)	3.4 (0.40)	3.2 (0.40)	2.8 (0.40)	4.4 (0.40)
95% CI	(2.6, 4.2)	(2.4, 4.0)	(2.0, 3.6)	(3.6, 5.2)
MMRM difference vs PBO[a]				
LS mean (SE)	−1.0 (0.57)	−1.2 (0.57)	−1.6 (0.57)	–
95% CI	(−2.1, 0.1)	(−2.3, −0.0)	(−2.7, −0.5)	–
24 hours				
Mean (SD)	2.5 (1.88)	3.1 (2.32)	2.4 (1.72)	3.5 (2.29)
MMRM estimates[a]				
LS mean (SE)	2.6 (0.39)	2.8 (0.40)	2.7 (0.40)	3.5 (0.40)
95% CI	(1.8, 3.4)	(2.0, 3.6)	(1.9, 3.5)	(2.7, 4.3)
MMRM difference vs PBO[a]				
LS mean (SE)	−0.9 (0.56)	−0.7 (0.56)	−0.8 (0.56)	–
95% CI	(−2.0, 0.2)	(−1.8, 0.4)	(−1.9, 0.3)	–

[a] Least square means estimates, confidence intervals and *P* values are based on a mixed model repeated measures that includes main effects for the treatment group, time point, treatment by time point interaction, and a covariate for baseline pain intensity.
Abbreviations: CI, confidence interval; LS, least square; mITT, modified intent-to-treat; MMRM, mixed model repeated measures; PBO, placebo; SE, standard error; SPID, summed pain intensity difference; W6LOCF, 6-hour windowed last observation carried forward.

Pharmacokinetics

Pharmacokinetic analyses demonstrated a dose-proportional increase in plasma MR-107A-02 concentrations. Following the first dose, C_{max} values were 196.6 ng/mL, 858.8 ng/mL, and 2517.9 ng/mL for the 1.25 mg, 5 mg, and 15 mg doses, respectively. The median T_{max} were 1.2 hours, 1.0 hour, and 0.9 hour respectively. Corresponding $AUC_{0\text{-}24}$ values were 3418.3 ng·hr/mL (1.25 mg), 13 298.1 ng·hr/mL (5 mg), and 41 741.9 ng·hr/mL (15 mg) (Figure 5 and Table S5).

Safety

Safety evaluations demonstrated that MR-107A-02 was generally well tolerated across all dose groups. All TEAEs were mild or

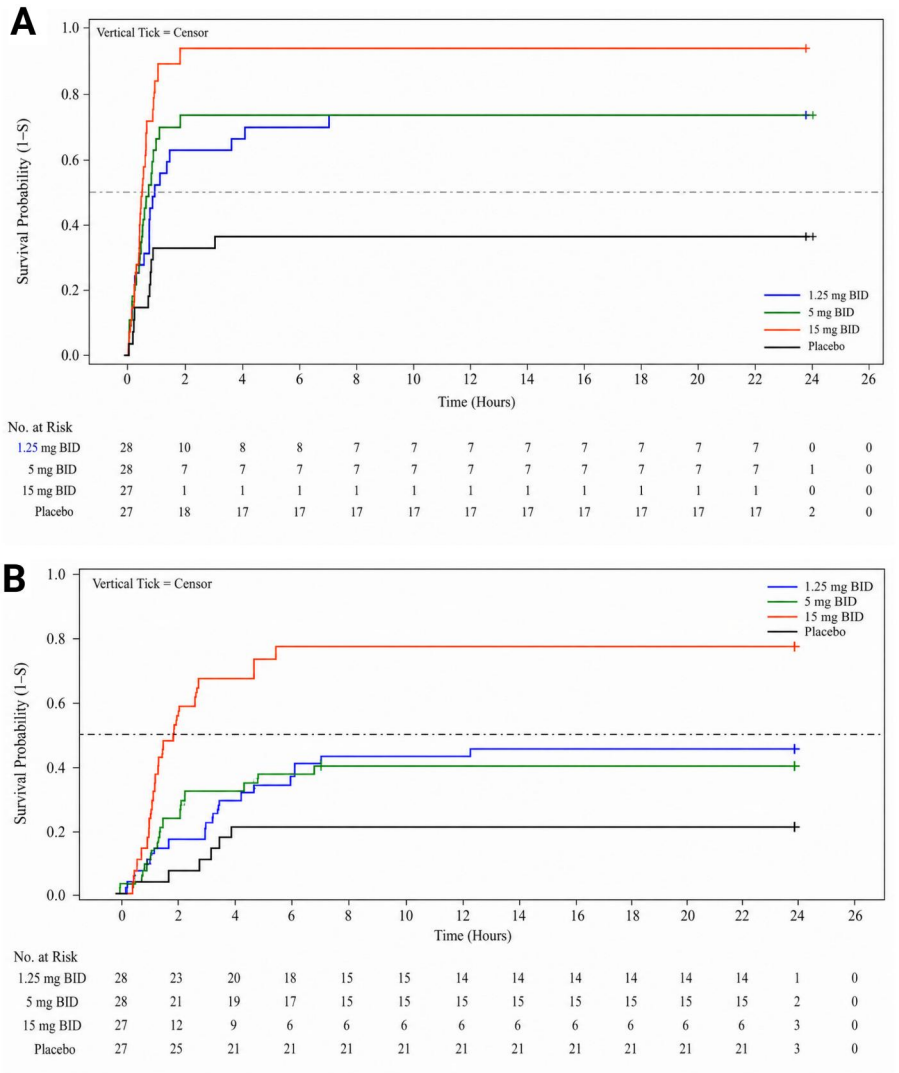


Figure 2 Time to first perceptible and meaningful pain relief across treatment groups (mITT analysis set). Note: Survival analysis of (A) time to perceptible and (B) time to meaningful pain relief. Abbreviations: BID, twice daily; mITT, modified intent-to-treat.

moderate in severity; no severe TEAEs, serious adverse events (SAEs), or study discontinuations due to TEAEs were reported. A total of 33 participants (30.0%) reported 45 treatment-emergent adverse events (TEAEs) in the safety analysis set. The incidence of TEAEs was 14.3% in the MR-107A-02 1.25 mg, 39.3% in the 5 mg, 37.0% in the 15 mg, and 29.6% in the placebo group. Sixteen participants (14.5%) reported at least 1 TEAE considered related to treatment, with the proportion being greater in the 5 mg, 15 mg, and placebo groups (17.9%, 14.8%, and 18.5%, respectively) than in the MR-107A-02 1.25 mg group (7.1%). Nausea was the most common TEAE, occurring more frequently in 17.9% of MR-107A-02 5 mg group compared to 3.6%, 7.4%, and 7.4%, in 1.25 mg, 15 mg, and placebo groups respectively (Table 4).

Overall, no dose-effect pattern was observed with respect to the incidence of common TEAEs. Laboratory evaluations, vital signs, ECGs, and physical examinations revealed no clinically significant abnormalities. Notably, no meaningful changes were observed in liver enzymes, renal, or cardiac parameters across treatment groups.

Discussion

This phase 2 b exploratory, randomized, double-blind, placebo-controlled study evaluated the efficacy and dose-response relationship of three different doses of MR-107A-02 administered twice daily in participants following dental surgery.[9,13,14]

The study design was consistent with research design recommendations of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group for trials involving participants with short-duration acute pain.[18] It was specifically designed to evaluate the efficacy of MR-107A-02 in an acute postoperative pain model and identify the most appropriate dose for further development.

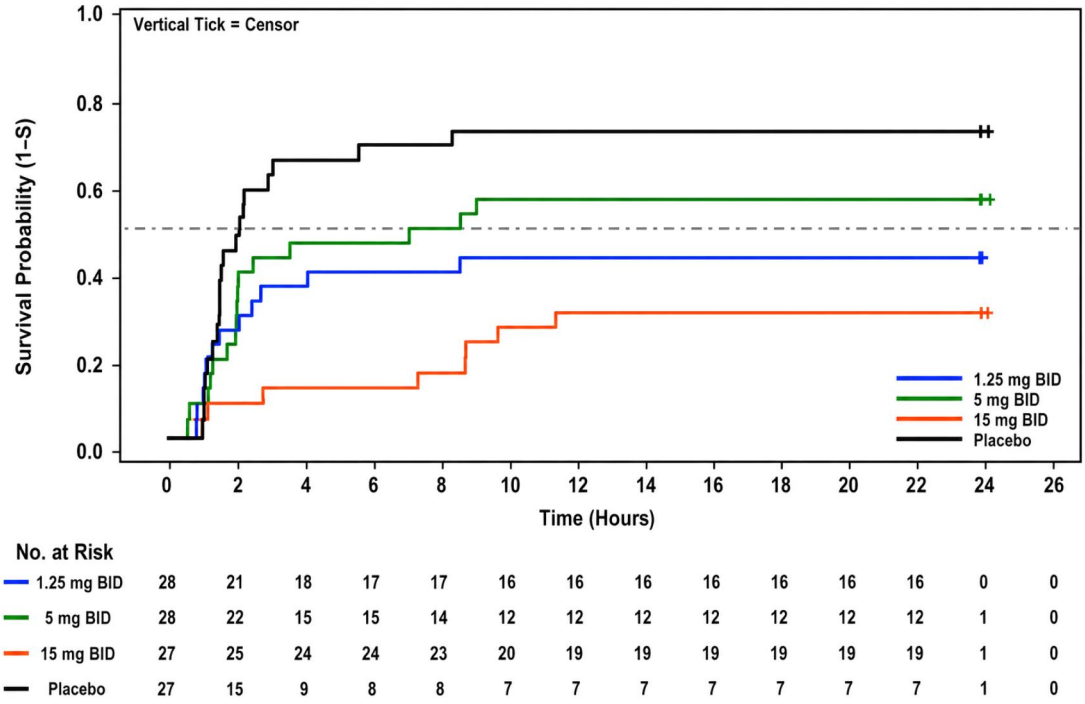


Figure 3 Time to first rescue medication use across treatment arms (mITT analysis set). Note: This analysis includes only rescue medications given in clinic during the confinement (days 1 and 2) period. Abbreviations: BID, twice daily; mITT, modified intent-to-treat.

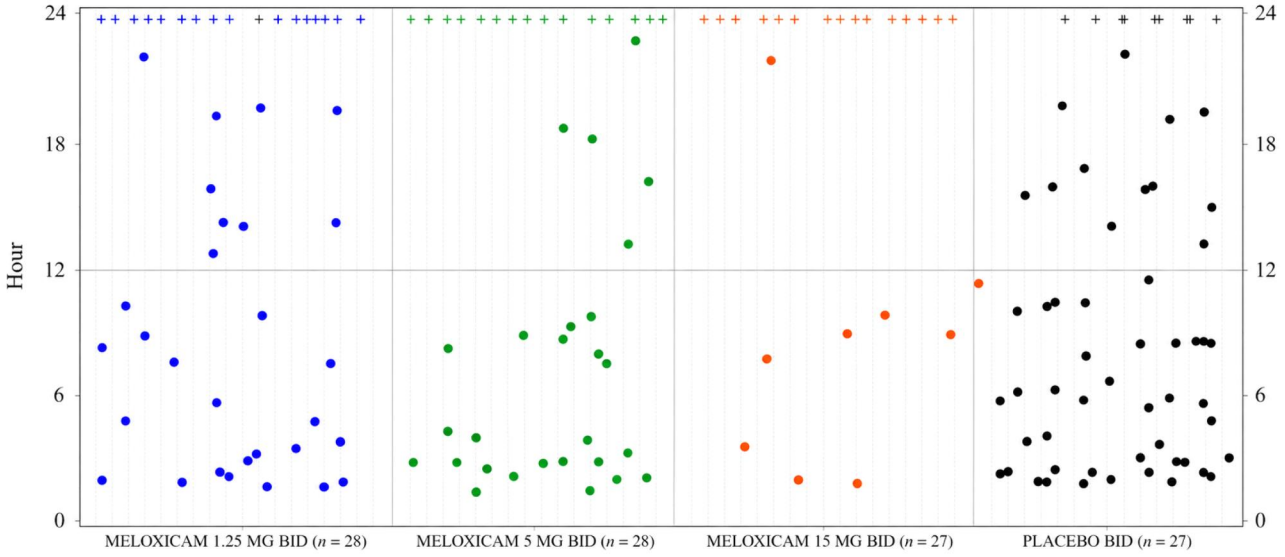


Figure 4 Rescue medication usage by treatment group (mITT analysis set). Note: In this figure, each vertical line represents a study participant; dots show the time of rescue medication use; participants who did not use rescue medications are represented with "+" at 24 hours. Abbreviations: BID, twice daily; mITT, modified intent-to-treat.

The primary efficacy endpoint was met, with 5 mg and 15 mg BID doses of MR-107A-02 showing the greatest reduction in acute postoperative dental pain ($P < .001$ versus placebo). Secondary efficacy endpoints reinforced the primary findings. Time-to-event analyses showed that study participants receiving MR-107A-02 15 mg experienced perceptible pain relief with a median of 0.6 hours and meaningful pain relief within 1.5 hours, both significantly faster than placebo. The proportion of participants achieving ≥30% and ≥50% pain reduction within 4 hours was highest in the 15 mg group, with 92.6% and 74.1%

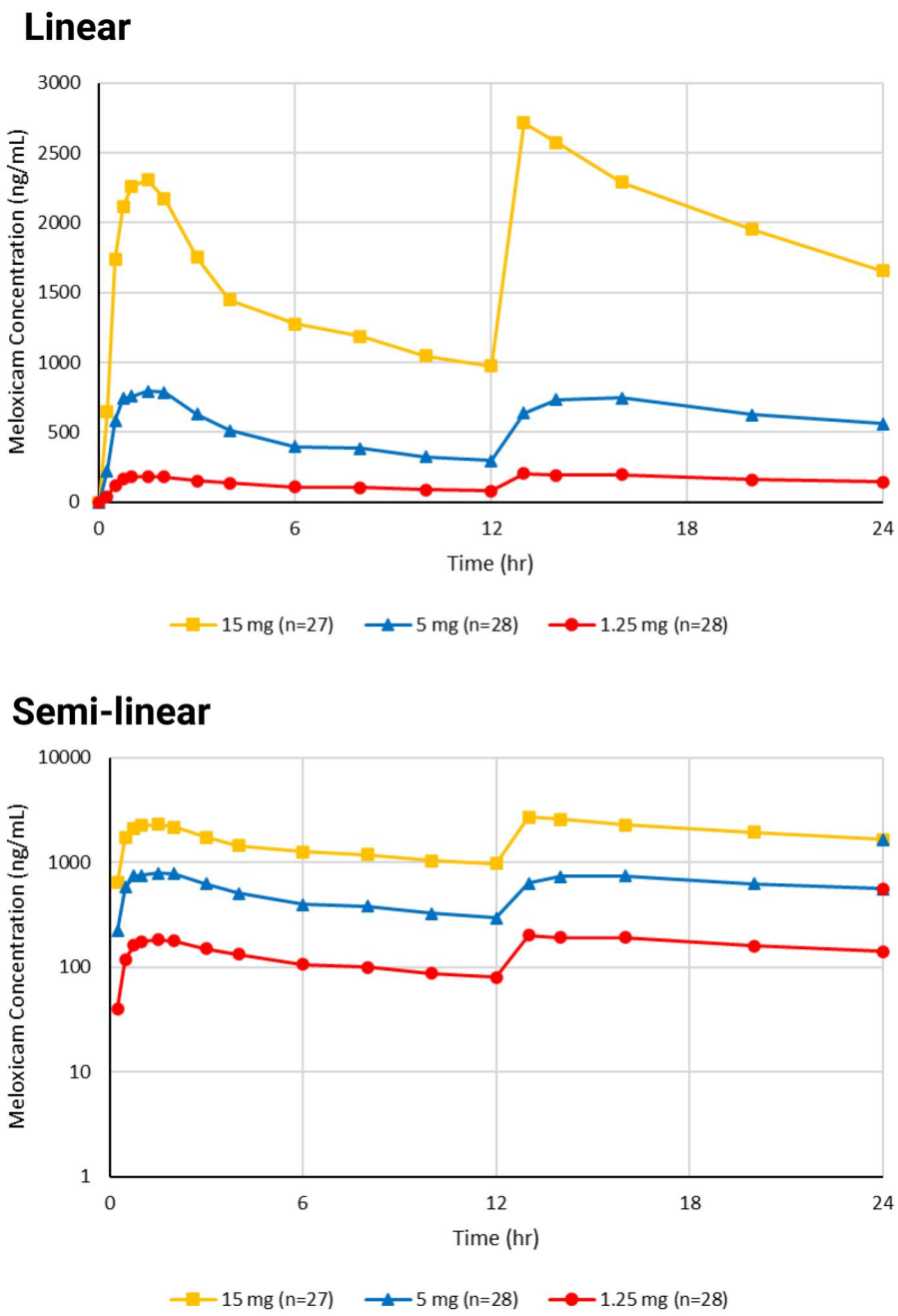


Figure 5 Plasma concentration versus time curve of MR-107A-02 (linear and semi-log) (pharmacokinetic analysis set).

responders, respectively. These clinical outcomes align with pharmacokinetic data, which demonstrated that all participants in the 15 mg group reached meloxicam plasma concentrations previously associated with effective analgesia within 1-hour post-dose.[16]

Importantly, the primary efficacy findings were robust across multiple analytical approaches used to address rescue medication use. Consistent dose–response patterns were observed across shorter and longer censoring windows, complete censoring following rescue medication, uncensored analyses, and per-protocol analyses, with statistically significant analgesic effects preserved for the 5 mg and 15 mg BID doses. These findings indicate that the observed treatment effects were not driven by analytical assumptions related to rescue medication handling and support the suitability of the prespecified primary analysis approach. In addition, protocol deviations related to baseline pain intensity were minimal; one participant was randomized but not dosed due to failure to meet the baseline pain criterion.

While the 1.25 mg dose showed early analgesic effects ($SPID_{0-2}$ and $SPID_{0-4}$), its overall efficacy was not statistically significant, indicating that higher doses are necessary to achieve clinically meaningful pain relief. Specifically, the rapid onset of analgesia observed with the 15 mg dose of MR-107A-02 not only translated into superior pain relief but also contributed to a meaningful reduction in opioid rescue medication use. This reduced rescue opioid use is particularly relevant in the context of postoperative pain management, where minimizing opioid exposure is a key

Table 4 Treatment-emergent adverse events by system organ class and preferred term (safety analysis set).

	MR-107A-02				
System organ class preferred term	1.25 mg (*N* = 28) n (%)	5 mg (*N* = 28) n (%)	15 mg (*N* = 27) n (%)	Placebo (*N* = 27) n (%)	Total (*N* = 110) n (%)
Participants with any event	4 (14.3)	11 (39.3)	10 (37.0)	8 (29.6)	33 (30.0)
Gastrointestinal disorders	1 (3.6)	6 (21.4)	4 (14.8)	5 (18.5)	16 (14.5)
Nausea	1 (3.6)	5 (17.9)	2 (7.4)	2 (7.4)	10 (9.1)
Vomiting	0 (0)	0 (0)	2 (7.4)	1 (3.7)	3 (2.7)
Diarrhea	0 (0)	0 (0)	0 (0)	2 (7.4)	2 (1.8)
Abdominal pain	0 (0)	1 (3.6)	0 (0)	0 (0)	1 (0.9)
Abdominal pain upper	0 (0)	0 (0)	1 (3.7)	0 (0)	1 (0.9)
Aphthous ulcer	0 (0)	0 (0)	0 (0)	1 (3.7)	1 (0.9)
Injury, poisoning and procedural complications	0 (0)	0 (0)	1 (3.7)	0 (0)	1 (0.9)
Incision site discharge	0 (0)	0 (0)	1 (3.7)	0 (0)	1 (0.9)
Investigations	2 (7.1)	0 (0)	1 (3.7)	0 (0)	3 (2.7)
Blood bilirubin increased	2 (7.1)	0 (0)	0 (0)	0 (0)	2 (1.8)
WBC count increased	0 (0)	0 (0)	1 (3.7)	0 (0)	1 (0.9)
Metabolism and nutrition disorders	0 (0)	1 (3.6)	1 (3.7)	0 (0)	2 (1.8)
Dehydration	0 (0)	1 (3.6)	0 (0)	0 (0)	1 (0.9)
Hyperglycaemia	0 (0)	0 (0)	1 (3.7)	0 (0)	1 (0.9)
Nervous system disorders	1 (3.6)	5 (17.9)	3 (11.1)	4 (14.8)	13 (11.8)
Headache	0 (0)	1 (3.6)	2 (7.4)	3 (11.1)	6 (5.5)
Dizziness	0 (0)	1 (3.6)	2 (7.4)	1 (3.7)	4 (3.6)
Syncope	1 (3.6)	1 (3.6)	0 (0)	1 (3.7)	3 (2.7)
Hypoaesthesia	0 (0)	1 (3.6)	0 (0)	0 (0)	1 (0.9)
Migraine	0 (0)	1 (3.6)	0 (0)	0 (0)	1 (0.9)
Respiratory, thoracic and mediastinal disorders	0 (0)	1 (3.6)	1 (3.7)	0 (0)	2 (1.8)
Cough	0 (0)	1 (3.6)	0 (0)	0 (0)	1 (0.9)
Epistaxis	0 (0)	0 (0)	1 (3.7)	0 (0)	1 (0.9)

Note: *N* is the number of unique participants with at least 1 occurrence of the event. A participant reporting more than 1 adverse event for a system organ class and preferred term was counted only once for that system organ class and preferred term combination. Adverse events are sorted alphabetically by system organ class and then by descending order of frequency for the total participant column within each system organ class. Treatment-emergent adverse events included all events starting after the administration of study drug. Adverse events were coded using MedDRA Version 25.0.
Abbreviations: BID, twice daily; MedDRA, medical dictionary for regulatory activities; WBC, white blood cell.

clinical objective. The alignment between clinical efficacy and pharmacokinetic data further supports the therapeutic potential of MR-107A-02 as a fast-acting, non-opioid analgesic option.

The 15 mg group was associated with the lowest rescue-medication utilization across endpoints, including both the proportion of participants requiring rescue medication and the mean number of rescue-medication uses. These findings support the clinical relevance of the observed analgesic effect and suggest a reduced need for supplemental opioid rescue medication, particularly with the 15 mg BID regimen in this controlled postoperative pain model. The results should be interpreted in the context of evolving acute dental pain evidence and guidance that favor nonopioid regimens (NSAIDs alone or with acetaminophen) as first-line therapy, with opioids reserved for limited indications.[19] In addition, evidence syntheses in third-molar extraction trials consistently show that NSAIDs perform strongly versus placebo across oral analgesics, and overall rankings frequently favor NSAID-containing strategies, supporting continued evaluation of NSAID formulations that may optimize onset while considering expected class risks.[20,21]

The pharmacokinetic profile of MR-107A-02 was dose-proportional, with rapid absorption and consistent T_{max} values across doses (median, approximately 0.9–1.2 hours). The observed C_{max} and AUC values support the rapid onset and sustained analgesic effect of the formulation. The rapid onset observed for MR-107A-02, particularly at 15 mg BID, is consistent with its fast-absorbing design and the substantially shorter T_{max} demonstrated versus reference oral meloxicam in a phase I PK comparison.[12]

Although a direct comparison was not conducted, the 15 mg BID regimen of MR-107A-02 achieved lower plasma exposures compared to published data for a single 30 mg intravenous dose of meloxicam (Anjeso®), while showing a favorable safety profile.[11] These findings suggest potential advantages in exposure and tolerability, supporting further evaluation of MR-107A-02 as a non-opioid analgesic option.

The 3 MR-107A-02 dose regimens were generally well tolerated in this small, short-term phase 2 study. No dose effect pattern was observed with respect to TEAEs, vital signs, or ECG findings.

Study limitations

This study has a few limitations that warrant consideration. First, the single-center design and predominantly young and

healthy study population may restrict the generalizability of the findings to older patients and broader postoperative pain settings. Second, the short follow-up duration (limited to 24 h post-dose) precluded the evaluation of longer-term analgesic efficacy, safety, and functional recovery. Third, the absence of an active comparator limits the ability to contextualize the observed analgesic effects of meloxicam relative to standard of care treatments. However, it is not unusual for phase 2 studies to lack active comparators. The absence of an active comparator limits contextualization vs recommended first-line nonopioid strategies (eg, NSAIDs ± acetaminophen) commonly used for acute dental pain management.[22,23]

Additionally, while imputation methods such as W6LOCF were employed to manage the influence of rescue medication use, such approaches may introduce bias and affect the robustness of pain intensity assessment. The exclusion of individuals with significant comorbidities and the limited ethnic diversity of the study population further constrain the external validity of the results. Future studies should consider multicenter trials, broader patient populations, longer follow-up, and active comparators to enhance generalizability and clinical relevance.

Conclusions

These study findings suggest that the 5 mg and 15 mg doses of MR-107A-02 demonstrated significantly greater analgesic efficacy compared to placebo, with marked reduction in acute postoperative pain. Notably, the 15 mg BID regimen was associated with the lowest use of rescue medication. Based on these findings, the 15 mg BID dose has been advanced to Phase III clinical program.

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Author contributions

Conceptualization: S.V. and J.S.; Methodology: T.B., S.V., S.H., K.O. and J.S.; Supervision and project administration: T.B., S.V., K.O. and S.H.; Validation: S.V., and S.H.; Writing–review & editing: T.B., S.G., S.V., S.H., K.O., and J.S.

Supplementary material

Supplementary material is available at *Pain Medicine* online.

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Conflicts of interest

S.V., S.H., K.O., and J.P.S. are employees of Viatris; Few of these authors held Viatris stocks during the conduct of the program. T.B., S.G. are employed at CenExel JBR.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Ethics approval and consent to participate

This study received approval from the Advara- Institutional Review Board (IRB), and written informed consent was obtained from all clinical study participants.

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