Meloxicam (MR-107A-02) Exposure–Response of Pain Relief in Post-Surgery Patients

Saugandhika Sarma Minnikanti[1], Vijay Ivaturi[1], Harissh Chandrasekaran[1], Amit Roy[1], Andrew Shaw[2], Matthew A. Hummel[2]

[1] Pumas-AI Inc., Dover, DE, USA; [2] Mylan Pharmaceuticals Inc., a Viatris Company, Morgantown, WV, USA

BACKGROUND

MR-107A-02 is an oral formulation of meloxicam, a non-steroidal anti-inflammatory drug that inhibits cyclooxygenase-1 and cyclooxygenase-2 and thereby reduces prostaglandin production. Meloxicam is approved in the US for osteoarthritis and rheumatoid arthritis at 7.5 to 15 mg once daily and is being developed as an analgesic for acute post-surgical pain [1,2].

Meloxicam is a biopharmaceutics classification system (BCS) Class II compound, and so the absorption of the initially approved formulation was solubility limited and too slow for acute pain [3]. MR-107A-02 has been formulated to increase solubility and dissolution, and hence the rate of absorption.

A longitudinal exposure–response (E-R) model characterizes the onset, magnitude and duration of relief, and allows the effect of food on absorption to be evaluated against analgesia rather than against pharmacokinetics alone.

OBJECTIVES

- Characterize the E-R relationship between meloxicam concentrations and pain relief in patients receiving MR-107A-02 15 mg BID after bunionectomy or herniorrhaphy.
- Evaluate whether food-related differences in MR-107A-02 pharmacokinetics affect pain relief.

METHODS

Separate exposure–response (E–R) analyses were conducted for the two Phase 3 studies: MR-107A-02-TFZ-3001 (bunionectomy) and MR-107A-02-TFZ-3002 (herniorrhaphy).

Each analysis included participants who received MR-107A-02 15 mg BID or placebo on Day 1 and for whom MR-107A-02 concentrations could be predicted using the population PK model. The analysis populations comprised 128 participants in the bunionectomy study (placebo, n=64; MR-107A-02, n=64) and 226 participants in the herniorrhaphy study (placebo, n=105; MR-107A-02, n=121).

Pain intensity was assessed using an 11-point Numeric Rating Scale (NRS; 0 = no pain, 10 = worst pain imaginable) over 0–48 hours. Rescue medication was permitted at any time. NRS observations after the first rescue medication were censored without imputation. A time-to-event model for time to first rescue medication was developed and used to account for censoring in the simulations.

Individual time-varying MR-107A-02 concentrations were predicted from the population PK model using each participant's actual dosing history and individual empirical Bayes estimates; concentrations were set to zero for placebo-treated participants.

The placebo/time-course model was developed using placebo-arm data and subsequently fixed. Drug-effect models (linear and Emax, with and without an effect compartment) were then evaluated and compared using the Bayesian Information Criterion (BIC) and visual predictive checks (VPCs).

Parameter uncertainty was assessed using a nonparametric bootstrap (200 replicates). Exposure–response profiles were simulated for 1,000 participants across 200 replicates at 0.5-hour intervals through 48 hours. All exploratory data analysis and modelling were performed using Julia (v1.11.5) and Pumas (v2.7.0).

Model equations

Longitudinal ordinal logistic regression model, where Pr is the probability that subject *i* will have a NRS score ≥ *k* at time *j*.

$$\text{logit}[\Pr(Y_{ij} \geq k)] = (\text{tv}\beta_k \cdot \text{BLCov}_\beta) + f_{\text{placebo}}(t_j) + f_{\text{drug}}(C_{ij}) + \eta_i$$

- β_k : Coefficients representing the typical values of log odds of a NRS score at t = 0
- $\eta_i \sim N(0, \omega_\beta^2)$: Normally distributed random variable of log odds of a subject relative to a typical subject
- $f_{\text{placebo}}(t) = d\beta_{\text{time}} \cdot t^{\,d\beta\text{shape}}$: Placebo/ time effect(both studies, power model)
- Bunionectomy drug effect (linear, effect compartment , where Cp and Ce are plasma and effect compartment concentrations
  $f_{\text{drug}}(C) = \text{melxSlope} \cdot C_e$; $dC_e/dt = k_{e0}(C_p - C_e)$
- Herniorrhaphy drug effect (Emax, plasma compartment)
  $f_{\text{drug}}(C) = E_{\max} C_p / (EC_{50} + C_p)$

Table 1. Baseline characteristics of the E-R analysis populations

Characteristic	Bunionectomy		Herniorrhaphy	
	Meloxicam 15 mg BID (n=64)	Placebo (n=64)	Meloxicam 15 mg BID (n=121)	Placebo (n=105)
Baseline NRS, mean (SD)	7.14 (1.63)	7.56 (1.61)	7.61 (1.61)	7.58 (1.74)
AGE [yrs], mean (SD)	48.2 (12.2)	49.1 (13.7)	47.7 (12.6)	49.6 (11.4)
SEX, female, n (%)	59 (92.2)	52 (81.2)	3 (2.5)	7 (6.7)
SEX, male, n (%)	5 (7.8)	12 (18.8)	118 (97.5)	98 (93.3)
eGFR [mL/min/1.73 m²], mean (SD)	96.6 (17.2)	95.9 (18.3)	96.3 (15.7)	93.9 (14.4)

Table 2. Component role in the model

Component	What it represents
Longitudinal ordered categorical (proportional-odds) logistic regression	Models the probability of reporting an NRS score at or above each level of the 11-point scale.
Placebo / time function: power model	Describes the time-dependent decline in pain intensity in the absence of active treatment; estimated from placebo-arm data and subsequently fixed.
Drug effect, bunionectomy: Linear effect-compartment concentration	Describes a concentration-dependent reduction in the log-odds of reporting a higher NRS score based on effect-site concentration.
Drug effect, herniorrhaphy: Emax model based on plasma concentration	Describes a saturable concentration–response relationship; EC50 represents the concentration associated with 50% of the maximum drug effect.
Effect compartment (ke0)	Characterizes the temporal delay between plasma concentration and the observed pain response.
Baseline NRS effect on the intercept	Accounts for differences in baseline pain intensity.
Subject-level random effect on the intercept	Participant-level random effect on the intercept. Accounts for between-participant variability in reported pain intensity not explained by the model.
Weibull time-to-event model for time to first rescue medication	Accounts for informative censoring associated with rescue medication use and was simulated jointly with the E–R model to censor post-rescue simulated NRS observations.

Table 3. Final E-R model parameter estimates

Parameter	Bunionectomy estimate (RSE %)	Herniorrhaphy estimate (RSE %)	Interpretation
tvβ, logit-Pr(NRS ≥ 10)	−4.14 (8.5)	−4.34 (6.6)	Reference intercept
β6, baseline NRS ≤6	0.27 (37.0)	0.45 (21.7)	Higher log-odds of higher scores than baseline 7–8
β8, baseline NRS >8	−0.70 (9.3)	−0.73 (7.2)	Lower log-odds; larger reduction from a higher starting score
dβtime	−0.835 (fixed)	−0.424 (fixed)	Pain intensity declines with time
dβshape	0.379 (fixed)	0.589 (fixed)	<1: decline is fastest at the start of treatment
melxSlope (per ng/mL)	−0.0011 (26.7)	—	Log-odds of a higher score fall linearly with effect-site concentration
ke0 (h^{-1})	0.620 (55.3)	—	1/ke0 = 1.6 h delay between plasma and response
Emax (logit)	—	−2.73 (25.3)	Maximum reduction in log-odds of a higher score
EC50 (ng/mL)	—	895 (57.4)	Plasma concentration producing half the maximum effect
ωβ	1.94 (7.1)	2.46 (5.3)	Between-subject standard deviation on the intercept

CONTACT

www.pumas.ai/resources

saugandhika@pumas.ai

RESULTS

Figure 1. Observed NRS score distribution and loss of observations to rescue medication

Number and proportion of participants at each NRS score over 48 h, by study and treatment arm. Bar height gives the proportion at each score and the falling totals show observations censored at first rescue medication. In both studies, observations in the placebo arm were censored earlier and at a higher rate than in the MR-107A-02 arm, reflecting greater use of rescue medication.

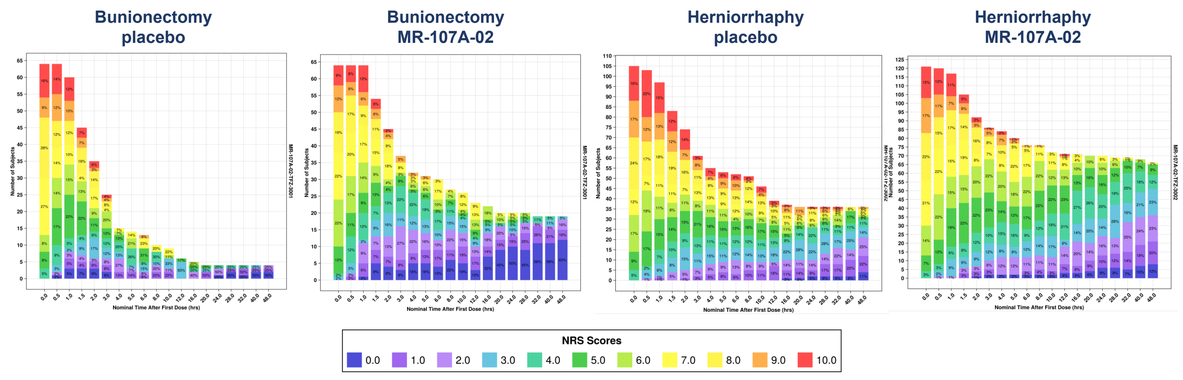


Figure 2. Visual predictive checks for both arms for bunionectomy and herniorrhaphy

Inverse cumulative proportion at each NRS score. Solid lines are observed; dashed lines and shaded areas are the median and 95% interval of simulated proportions, with simulated observations censored using the time-to-event rescue-medication model. The intervals encompass the observations in both arms of both studies.

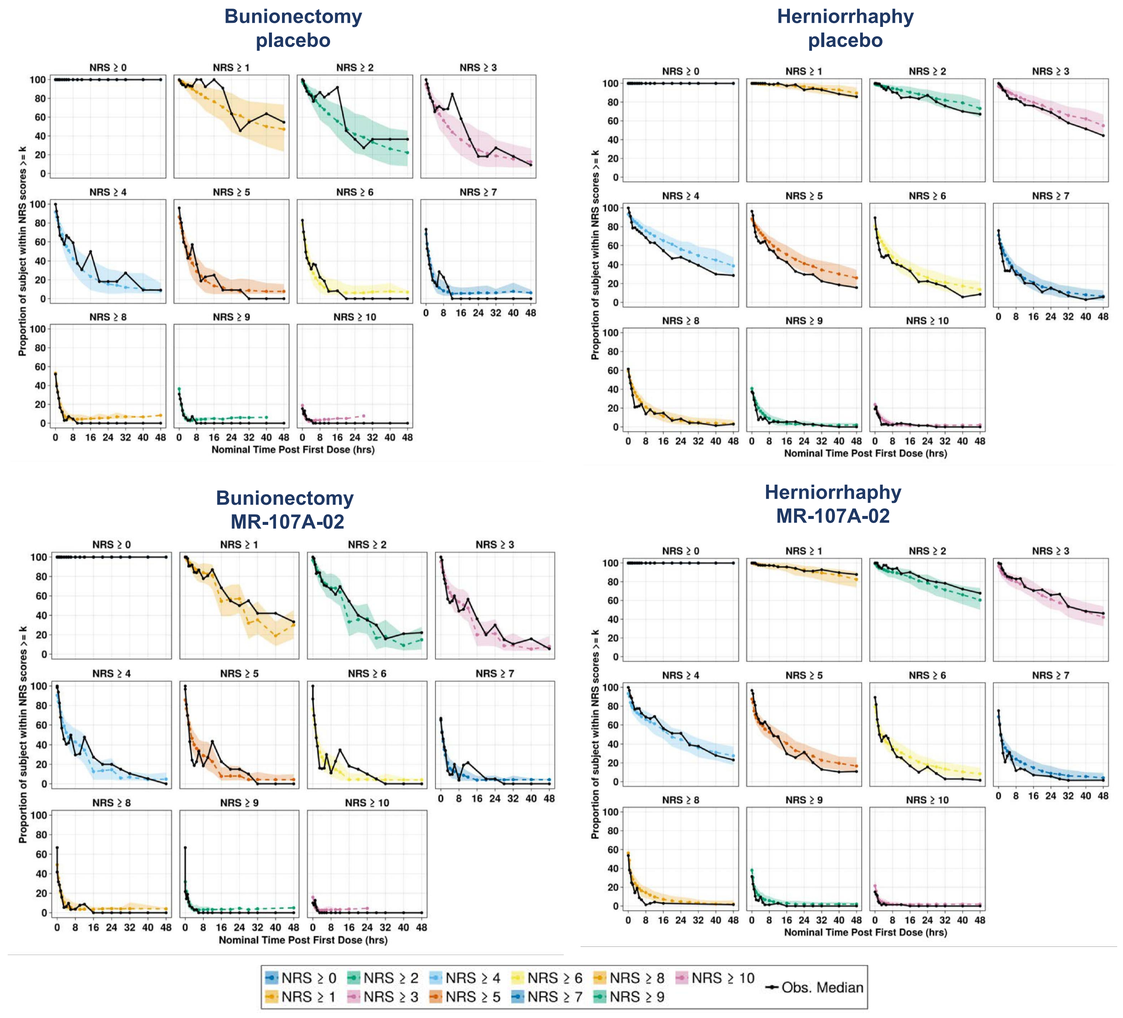
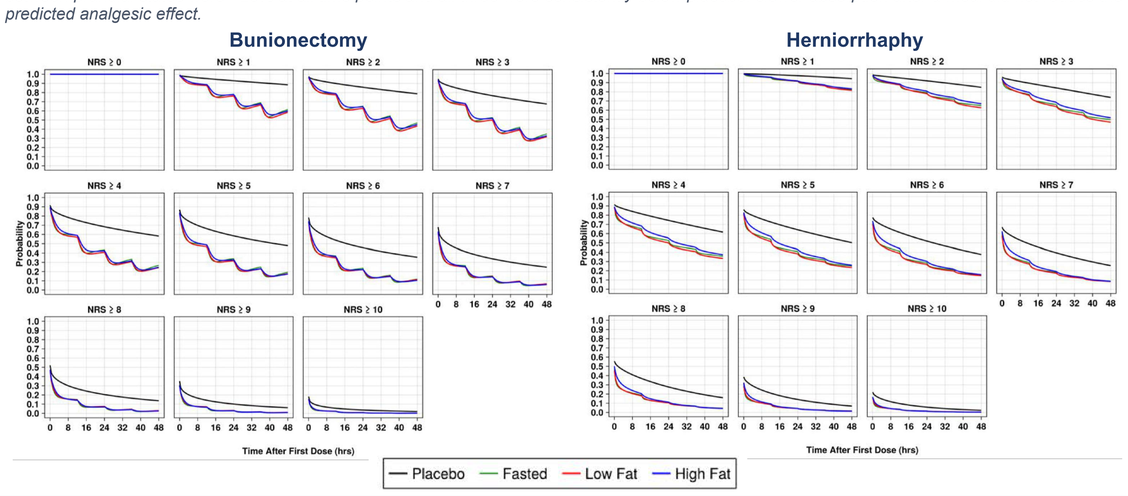


Figure 3. Effect of meal type on simulated pain relief

Mean cumulative probability of an NRS score above each threshold under fasting, low-fat and high-fat conditions, with placebo for reference. Differences between prandial states were <20% at all time points and all three were consistently below placebo: slower absorption after a meal did not reduce the predicted analgesic effect.



CONCLUSIONS

- Longitudinal ordered categorical models adequately characterized the exposure–response relationship between meloxicam concentrations and NRS pain scores following both bunionectomy and herniorrhaphy.
- Higher MR-107A-02 concentrations were associated with a lower probability of reporting higher NRS pain scores in both surgical models.
- The functional form of the exposure–response relationship differed between surgical models: a linear relationship with effect-site concentration following bunionectomy and an Emax relationship with plasma concentration following herniorrhaphy. Despite these differences, the direction of the treatment effect was consistent across both models.
- Model-predicted NRS profiles over 48 hours were comparable across fasting, low-fat, and high-fat conditions, suggesting that food-related differences in MR-107A-02 absorption did not meaningfully alter the predicted pain-response profile at 15 mg BID.

REFERENCES

1. Gates BJ, et al. Meloxicam: a reappraisal of pharmacokinetics, efficacy and safety. Expert Opin Pharmacother 2005;6:2117–40.
2. Mobic (meloxicam) US Prescribing Information, 2021.
3. Moore RA, et al. Single dose oral meloxicam for acute postoperative pain in adults. Cochrane Database Syst Rev 2009.

Companion poster: Population Pharmacokinetic Analysis of an Oral Meloxicam Formulation (MR-107A-02) in Healthy Volunteers and Surgical Patients — Submission ID 2405397.

During the preparation of this work the authors used Claude (Anthropic) to assist with drafting and organizing poster text and layout, which has been reviewed and approved by the authors.