# #40

# Phase 1 Trial Results for NTM-001 (Novel Alcohol-free Formulation for Continuous 24h IV Infusion of Ketorolac from a Pre-Mixed Bag) Meet Targets of Model-Informed Development: *Preliminary Results for Healthy Young Volunteers of a Randomized, Controlled Pharmacokinetic Study of NTM-001 Compared with a Standard Bolus Regimen of IV Ketorolac*


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Neumentum™ A Better Way In Pain Management

## PURPOSE

The opioid crisis in the United States demands effective and safe alternatives to opioids.

### NTM-001

- NTM-001 is a novel, alcohol-free formulation of the well-established potent NSAID analgesic ketorolac tromethamine administered by continuous intravenous infusion for 24 hours from a pre-mixed bag.

### NTM-001 Target Indication

- NTM-001 is in development for the short-term management of moderately severe acute pain that requires analgesia at the opioid level, usually in a postoperative setting, for up to 24 hours.

### NTM-001 Dosing Regimen

The regimen in adult patients < 65 years of age without hepatic/renal impairment comprises

- 12.5 mg **loading dose**
- Immediately followed by a **continuous infusion** of 3.5 mg/h

administered by pre-programmed infusion pumps in standard hospital use for 24 hours.

### Product and Dosing Rational

- The approved IV ketorolac bolus regimen (30 mg q6h) yields high peak exposure (Cmax), with safety-related risks, no evidence of increased analgesic efficacy, while troughs (Cmin) between repeat IV doses may provide insufficient analgesia.
- NTM-001 mitigates those drawbacks by providing a constant exposure to effective dose levels during 24 hr following surgery with a lower total daily dose (96.5 mg) compared to a generic ketorolac injection regimen (120 mg applied as 30 mg boli q6h).
- The current target dosing regimen of NTM-001 was selected – supported by PK/PD modeling- to achieve the following outcomes compared to the standard 30 mg q6h bolus regimen:

***Efficacy***

- At least comparable overall, stable analgesia over 24 h
- Avoiding ineffective trough exposures
- A fast onset of meaningful analgesia
- Without unnecessary overexposure

***Safety***

- Targeting an improved safety profile
- reducing peak exposure as with the bolus regimen
  - ❑ not adding to more analgesia
  - ❑ increasing safety risk
- reducing overall 24-hour ketorolac exposure and dose - addressing dose-dependency of side effects
- Reducing the treatment time to 24 h (vs. up to 5 days with generic ketorolac bolus regimen) – addressing increased side effects with prolonged treatment times

**(For more background reference is made to posters 41/42, PAINWeek 2019)**

### Modeling and Simulation

- Based on a population PK/PD model describing analgesia after ketorolac injection (Mandema et al. 1996), exposure-response modeling and simulation were used to predict the time courses of drug exposure and analgesic effect for a series of candidate IV loading dose/24-hour constant-rate (LD/CR) infusion regimens, comparing to a reference regimen of 30 mg bolus IV ketorolac q6h for 24 hours.

### FIRST-IN-MAN STUDY NTM-001-HP001

This first-in-man study aimed to explore a data-informed, model-based candidate dosage regimen and safety of NTM-001, according to the targeted product profile, assessing suitability for use in further clinical development and practice.

### STUDY OBJECTIVES

***Primary:***

- To evaluate the pharmacokinetics (PKs), bioavailability, and exposure of NTM-001 compared with an intravenous (IV) bolus regimen of ketorolac tromethamine (KETO-BOLUS) in healthy young and elderly subjects with normal renal function, and in elderly subjects with mildly or moderately impaired renal function.

***Exploratory:***

- To explore and identify a data-informed, model-based candidate dosage regimen of NTM-001 that is predicted to safely achieve post-operative analgesia similar to the FDA approved KETO-BOLUS regimen.
- To assess and update the PK/PD model parameters, including addition of PK covariates informed by the new PK data observed in this trial.

***Safety:***

- To assess the safety and tolerability of NTM-001 compared to IV ketorolac (KETO-BOLUS) in healthy young and elderly subjects with normal renal function, and in elderly subjects with mildly or moderately impaired renal function.

### FIGURE 1. LINKING EXPLORATORY TO CLINICAL OBJECTIVES OF TRIAL NTM-001-HP001

**Pharmacometric objectives**

- To compare plasma ketorolac concentration-time profiles and PK parameter values observed in Study NTM-001 – HP-001 to those predicted using the NTM-001 Base Model
- To update the NTM-001 Base Model (the "Updated Model") if warranted, using observed NTM-001 plasma ketorolac concentrations
- To predict post-operative analgesia using the Updated Model for comparison to the target analgesia vs. time profiles predicted using the Base Model, and to recommend modifications of the NTM-001 regimens if warranted

**Matching clinical objectives**

- Confirm that human PK data match PK/PD modeling
  - Efficacy target profile
  - Safety exposure profile
- Finetune/adjust the model with real data (where applicable)
- Predict postoperative analgesia based on real exposure data
- Decide if dosing regimen can be maintained without changes

## METHODS

### GENERAL

The study comprised **4 cohorts:**

- Cohort 1 healthy young subjects (18-55 y)
- Cohort 2 healthy elderly subjects (>/= 65y)
- Cohort 3 elderly subjects with mild renal impairment
- Cohort 4 elderly subjects with moderate renal impairment

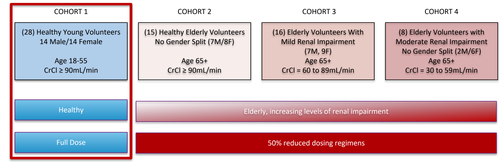
Cohorts 1 and 2 were dosed subsequently followed by a parallel conduct of cohorts 3 and 4 as determined by an independent DSMB evaluating safety and exposure data of cohorts 1 and 2, respectively. **Preliminary cohort 1 results are reported.**

Per cohort the study consisted of

- Screening Period (up to 28 days)
- Baseline Assessments (1 day)
- Treatment Periods (24 h each)
- Washout Period (7 days)

Blood sampling was continued for up to 96 h post dosing. Cohort 1 healthy young subjects (age 18-55) were randomized to receive a full dose regimen of NTM-001 (12.5 mg loading dose, 3.5mg/h continuous infusion) and an intravenous (IV) bolus regimen of KETO-BOLUS (30 mg q 6 h) over 24 h, in a cross-over design with a 7-day washout period between doses.

### FIGURE 2. OVERVIEW OF COHORTS TRIAL NTM-001-HP001 – FOCUS ON COHORT 1




Cohort 1: Testing a **full dose regimen** of NTM-001 vs. ketorolac bolus

Confirming

- Consistency of modeling vs. clinical reality (PK and PD)
- Adequacy of the full dosing regime of NTM-001
  - To achieve early onset of efficacy via loading dose
  - To maintain stable level of efficacy over 24 h
  - To maintain exposure margins related to safety
- Clinical feasibility and ease of use (pre-programmed infusion pumps)
- Safety of NTM-001 in the trial population

### PK/PD

Observed ketorolac concentration-time data were assessed using **(a) graphical overlay comparisons (b) model-based comparisons.**

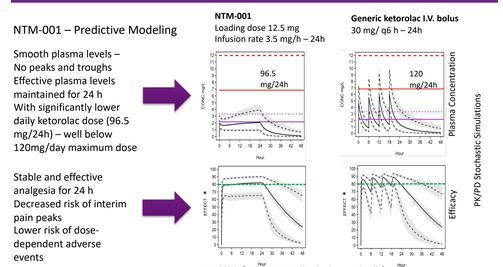
**(a)Graphical Overlay Comparisons:**

Observed ketorolac concentration-time profiles from each treatment of each subject were plotted over the corresponding stochastic ketorolac target profile predicted using the pharmacokinetic Base Model and inspected visually.

**(b)Model-based Comparison:**

Concentration-time data from the NTM-001 and KETO-BOLUS treatments of each cohort were fitted with the Base Model using NLME modeling implemented in Monolix 3.2 and the resultant median predicted plasma ketorolac concentration vs. time profiles with associated 95% population prediction intervals, were plotted over the corresponding target median and prediction interval profiles established using the Base Model.

### FIGURE 3. SUMMARY: PK/PD MODELING FOR NTM-001 VS. A BOLUS REGIMEN OF IV KETOROLAC




### SAFETY

In the trial, two systems of safety data reporting and assignment of severity were used in parallel:

- Reporting and severity assessment by the principal investigator
- The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers (2007)

Events of special interest regarding NSAID use and continuous infusion as well as stopping criteria for individual subjects and the overall trial were pre-defined. An independent DSMB reviewed interim safety and exposure data after cohort 1 and 2 to determine trial progress. As planned for the interim analyses, preliminary safety data are summarized by each Cohort for all subjects who receive at least one dose of study drug.

Standard methods for the full safety analyses in line with the SAP are applied for the final analyses. Preliminary (topline) interim safety reports focus on a by subject-centered presentation of data of special interest and related surrogates:

- Gastro-intestinal (GI) events
- Infusion/injection site reactions
- Renal function /Signs of renal injury
- Hemoglobin levels /Signals of bleeding

There are limitations related to interim data presented that will be replaced by a more detailed final analysis.

## RESULTS

Preliminary PK and safety results are reported for cohort 1 (healthy young volunteers) of a phase 1, randomized, open-label, crossover, pharmacokinetic study of Intravenous NTM-001 compared with a bolus regimen of ketorolac tromethamine (KETO-BOLUS) in healthy subjects and subjects with impaired renal function.

### TRIAL POPULATION

#### Demographics

In Cohort 1, 28 subjects were randomized and received IMP - 14 males and 14 females (safety population).

**TABLE 1. COHORT 1-DEMOGRAPHICS-GENDER-RACE-ETHNICITY**

| Race/Ethnicity | N= (%) |
|---|---|
| White | 14 (50) |
| Black | 8 (28.6) |
| Hispanic or Latinos | 3 (10.7) |
| Native Hawaiian or Pacific Islander | 3 (10.7) |
| Asian | 2 (7.1) |
| **Total** | 28 (100) |

#### Premature Discontinuations

- Three subjects discontinued early (1 NTM-001, 2 KETO-BOLUS) due to personal/family matters.

### PHARMACOKINETICS

#### (a) Graphical Overlay Comparison Results

Plasma ketorolac concentration-time profiles displayed relatively low between-subject variability falling within their respective concentration-time targets (original modeling) with only a small proportion (for NTM-001) falling below. Initial plasma concentrations for the IV bolus loading dose were somewhat higher than predicted. No extreme concentrations and no "outlier" subjects were observed.

### FIGURE 4. OBSERVED VS. PREDICTED PLASMA CONCENTRATION-LOW BETWEEN SUBJECT VARIABILITY




#### (b) Model-Based Comparison Results

Fitting the original pharmacokinetic Base Model to PK data from both regimens was successful;

Plots of

- observed vs. predicted data were distributed symmetrically around the line of identity indicating good fit of equations and error models and actual data.
- median plasma ketorolac concentration-time profiles and 95% prediction limits fell within exposure targets created with the original model

NTM-001 exposure based on median ketorolac AUC was approximately 13% below target.

#### (c) Prediction of Pain Relief based on Pharmacokinetic Results

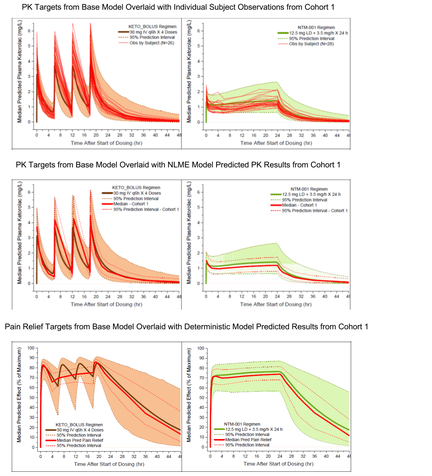
Pain relief scores vs. time were imputed using the Cohort 1 predicted median plasma ketorolac concentration-time profiles and 95% prediction limits and the effect compartment and pharmacodynamic models described by the original model. Results fell within the pain relief targets, consistent with observed ketorolac exposure patterns.

Predicted initial pain relief scores for the IV bolus loading dose of NTM-001 were somewhat higher, consistent with observed somewhat higher initial plasma ketorolac concentrations.

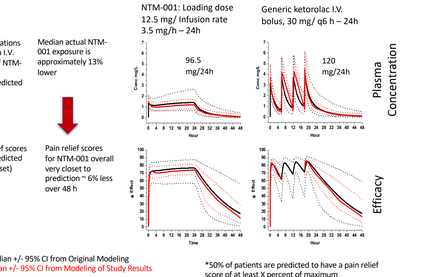
NTM-001-predicted 24-hr pain relief based on AUC of the median ketorolac pain relief was approximately 6% less vs. original target.

Treatment with NTM-001 maintains plasma concentrations greater than trough values for KETO-BOLUS, always greater than the target EC50 value for pain relief. (Reference is made to poster 39, PAINWeek 2019.)

### FIGURE 5. GRAPHICAL AND MODEL-BASED COMPARISONS OF COHORT 1 PK AND PD RESULTS WITH PK/PD MODEL PREDICTED KETOROLAC EXPOSURE AND PAIN RELIEF TARGETS




### FIGURE 6. NTM-001 PK AND PAIN RELIEF MODELING RESULTS IN LINE WITH PREVIOUSLY ESTABLISHED POPULATION PK MODEL TARGETS




### SAFETY

#### Exposure

- The target exposure profile for NTM-001 was confirmed without any signal for excessive exposure vs. KETO-BOLUS (AUC, Cmax)

#### Adverse events

- No stopping criteria for individuals or the trial overall were met (DSMB supervision).
- No serious, unexpected events or deaths occurred.
- Regarding events of special interest for NSAID or infusion use, no signals of an increased risk with NTM-001 were observed:
  - ❑ Only few gastro-intestinal (GI) events were reported, all of mild intensity
  - ❑ No signs of renal injury

#### EVENTS OF SPECIAL INTEREST

**TABLE 2. COHORT 1: TREATMENT EMERGENT GASTRO-INTESTINAL EVENTS**

| Gastrointestinal disorders (at least 1event) | Severity | NTM-001 | KETO-BOLUS |
|---|---|---|---|
| Abdominal Pain | Mild | 0 | 1 |
| Constipation | Mild | 1 | 0 |
| Nausea | Mild | 1 | 0 |
| Vomiting | Mild | 1 | 0 |

**TABLE 3. COHORT 1: TREATMENT EMERGENT ADMINISTRATION SITE EVENTS (INFUSION SITE REACTIONS - NTM-001)**

| # of Subjects | Description | Severity |
|---|---|---|
| 1 | Catheter Site Erythema | Moderate |
| 1 | Redness at IV site | Mild |
| 1 | Bruising at needle site | Mild |
| | Soreness at needle site | Mild |

**TABLE 4. COHORT 1: TREATMENT EMERGENT ADMINISTRATION SITE EVENTS (INJECTION SITE REACTIONS - KETO-BOLUS)**

| # of Subjects | Description | Severity |
|---|---|---|
| 1 | Injection site pain | Mild |

#### ADVERSE EVENTS LINKED TO RENAL FUNCTION

- Preliminary analysis shows that there was 1 subject in the Keto – Bolus arm with a serum creatinine change of ≥ 0.3 at 96 hours post-dose. This subject had a mild elevation in serum creatinine from 0.98 at baseline to a 1.29 at 96 hours.
- There were no subjects in cohort 1 with an >=30% reduction in creatinine clearance as a signal of acute renal injury.

#### SIGNS OF BLEEDING (SURROGATE: HEMOGLOBIN FLUCTUATIONS)

- There were 2 intra-subject fluctuations in hemoglobin values observed in Cohort 1 (of moderate intensity in line with criteria of the Toxicity Grading Scale), both in the KETO-BOLUS arm that were not associated with events of bleeding.

## CONCLUSION

- NTM-001 is a novel, alcohol-free continuous IV infusion product with ketorolac tromethamine administered from a pre-mixed bag in development for the treatment of moderately severe acute pain for up to 24 h.
- Preliminary results from this first-in-man PK study (Cohort 1 with healthy young volunteers) confirm the scientific product concept and dosing regimen (loading dose followed by continuous infusion) developed with the support of extensive PK/PD modeling:
- Cohort 1 pharmacokinetic results for both NTM-001 and the comparator KETO-BOLUS show a high degree of similarity to the previously established modeling targets requiring no update to the Base Model.
- Results appear highly robust without extreme values or outliers.
- Regarding predictions of pain relief, stable analgesia over 24h was confirmed while for the loading dose a somewhat better and possibly earlier onset of pain relief is anticipated.
- Administration with pre-programmed infusion pumps went smoothly contributing to high data quality.
- The NTM-001 dosing regimen as modeled and studied appears appropriate for use in the target population and further development.
- NTM-001 was well tolerated and safe in this cohort of healthy young volunteers.
- If confirmed in further clinical trials, NTM-001 can be a suitable alternative to opioids in the management of postoperative pain.

## REFERENCES


NTM-001 Briefing Document for FDA End-of-Phase 2 Meeting including related attachments and references, Neumentum, data on file; Mandema, J. W. and D. R. Stanski (1996). "Population pharmacodynamic model for ketorolac analgesia." Clinical Pharmacology & Therapeutics 60(6): 619-635.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