#39

Phase 1 Trial Results for NTM-001 (Novel Alcohol-free Formulation for Continuous 24h IV Infusion of Ketorolac from a Pre-Mixed Bag) Meet Predictions of PK/PD Modeling: *Preliminary Results for Elderly Subjects with/without Renal Impairment of a Randomized, Controlled Pharmacokinetic Study of NTM-001 Compared with an IV Bolus Regimen of 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 applied by continuous intravenous infusion for 24 h 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.

Reduced Dosing Regimen in Patients at Risk

This paper reports results of a pharmacokinetic trial with NTM-001 related to cohorts with vulnerable populations (elderly, renally impaired) potentially at increased risk for NSAID use.

The approved IV ketorolac bolus regimen (15 mg q6h) for patients >/= 65 y of age or renally impaired (or </=50 kg of body weight) reflects a 50% reduction compared to doses in populations not at increased risk for NSAID use to mitigate safety risks in this vulnerable population.

The studied NTM-001 dosing regimen in adult patients >/= 65 y of age with no, mild or moderate renal impairment comprises

- A 6.25 mg **loading dose**
- Immediately followed by a **continuous infusion** of 1.75 mg/h

administered by pre-programmed, regular infusion pumps for up to 24 h.

In line with the bolus reference label as part of a 505(b)2 regulatory pathway doses are reduced by 50% compared to the regimen in younger patients with a normal renal function.

A more detailed description of NTM-001 and its dosing and development rational can be derived from 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 50% reduced regimen of NTM-001 comparing to a reference regimen of 15 mg bolus IV ketorolac q6h for 24 hours.

FIRST-IN-MAN STUDY NTM-001-HP001

This first-in-man study aimed to explore pharmacokinetics and safety of NTM-001 in a data-informed, model-based investigation of a candidate dosage regimen in populations at risk, consistent with current ketorolac labeling, and to assess suitability for use in further development and practice.

Preliminary results are reported for cohorts 2-4 (healthy elderly, elderly with mild and moderate renal impairment) 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.

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

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

METHODS-CONT

Cohorts 1 and 2 were dosed sequentially followed by a parallel conduct of cohorts 3 and 4 informed by an independent DSMB evaluations of safety and exposure data of cohorts 1 and 2, respectively. **Preliminary cohort 2-4 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 2/3/4 subjects were randomized to receive:

- a half dose regimen of NTM-001(6.25 mg loading dose, 1.75 mg/h continuous infusion)
- an intravenous (IV) bolus regimen of KETO-BOLUS (15 mg q 6 h)

over 24 h, in a cross-over design with a 7-day washout period between doses.

PK/PD

The overall goal of this exploratory assessment was to determine whether the reduced NTM-001 regimen is suitable for further clinical development in subjects 65+ years old with/without renal impairment, or if regimen adjustment is warranted.

A) Graphical Overlay Comparisons:

Observed ketorolac concentration-time profiles from each treatment of each subject were plotted over the corresponding model-predicted ketorolac target profile according to 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. 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.

SAFETY

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

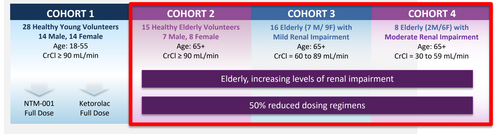
- Reporting and severity assessment by the principal investigator
- The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers (2007)

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 safety and exposure data with trial progress.

RESULTS

FIGURE 1. OVERVIEW TRIAL NTM-001-HP001 – FOCUS ON COHORTS 2-3-4

- **OL, randomized, controlled trial of NTM-001 vs. IV bolus Q6H for 24 hours for a total of 4 doses.**
- **Each cohort was studied in a randomized crossover design with a 1-week washout between doses.**



Sample size: Safety population

Goal of NTM 001 Program: Demonstrate that stable pain relief by continuous infusion for up to 24 hours with ketorolac provides pain relief at opioid levels

RESULTS-CONT.

TRIAL POPULATION

Demographics

TABLE 1. SAMPLE SIZE, GENDER AND ETHNICITY BY COHORT

Cohort	Total	Gender N=		Ethnicity
Number	N=	Male	Female	N=
Cohort 2	15	7	8	13 White, 2 Black/African American
Cohort 3	16	7	9	12 White, 3 Black/African American, 1 Pacific Islander
Cohort 4	8	2	6	8 White

Premature Discontinuations

TABLE 2. PREMATURE DISCONTINUATION BY COHORT

Cohort	Total	Treatment Arm		Reason
	N=	NTM-001	Keto-Bolus	
Cohort 2	2	1	1	mild cellulitis (NTM-001) rated as not related to IMP; withdrawal of consent (KETO-BOLUS)
Cohort 3	1	1	0	Subject pulled accidentally spike from infusion bag (NTM-001)
Cohort 4	0	0	0	

Pharmacokinetics

(A) Graphical Overlay Comparison Results

Individual-subject plasma ketorolac concentration-time profiles displayed relatively low intersubject variability.

Median concentrations following administration of the reduced regimens for both KETO-BOLUS and NTM-001 (50% dose reductions) were approximately

50% (Cohort 2), 60% (Cohort 3), 75% (Cohort 4)

of the corresponding median concentration targets predicted using the full dose regimens.

Two subjects in Cohort 2 and 1 in Cohort 3 receiving KETO-BOLUS displayed obvious outlier values and were omitted from analyses.

(B) Model-Based Comparison Results

Fitting the pharmacokinetic Base Model to preliminary PK data from Cohort 1 for NTM-001 and KETO-BOLUS reduced regimens was successful; model equations were consistent with those used to construct the original model.

Plots of observed vs. predicted data were distributed symmetrically around the line of identity and the lack of systematic departure from the line indicated that the equations and error models used fit the data well. These findings were reinforced by inspection of additional modeling output for both treatments. No model updating was required.

The model-predicted concentration curves were approximately 50%, 40% and 25 % (Cohorts 2/3/4) lower than the target curves (full dose) in line with increasing levels of renal impairment.

Pain relief scores were not imputed for preliminary analyses for subjects in Cohorts 2-4.

FIGURE 2. NTM-001: RESULTS COMPARED AMONGST COHORTS – FOCUS COHORTS 2-3-4

COHORT 1	COHORT 2	COHORT 3	COHORT 4
(24) Healthy Young Volunteers 14 Male/14 Female Age 18-55 CrCl ≥ 90mL/min	(15) Healthy Elderly Volunteers 8 Male/7 Female Age 65+ CrCl ≥ 90mL/min	(16) Elderly Volunteers With Mild Renal Impairment 7 Male, 9 Female Age 65+ CrCl = 60 to 89mL/min	(8) Elderly Volunteers with Moderate Renal Impairment No Gender Split (2M/6F) Age 65+ CrCl = 30 to 59mL/min
NTM-001 and KETO_ Bolus PK results highly consistent with targets from modeling and simulation	NTM-001 and KETO_ Bolus PK results ~ 50% lower than healthy subjects in Cohort 1 • Matchs the 50% reduction in dose • No apparent change in PK based on age alone	NTM-001 and KETO_ Bolus PK results ~ 40% lower than healthy subjects in Cohort 1 • Reflects the 50% reduction in dose plus ~ 20% lower ketorolac clearance in this mildly impaired population	NTM-001 and KETO_ Bolus PK results ~ 25% lower than healthy subjects in Cohort 1 • Reflects the 50% reduction in dose plus ~ 40% lower ketorolac clearance in this moderately impaired population

NTM-001 in All Cohorts

- NTM-001 exposure per mg dosed comparable to KETO_BOLUS as expected for different IV regimens of the same drug.
- Early onset of efficacy expected from use of loading dose
- Maintainence of stable ketorolac exposure and thus level of efficacy over 24 h
- Maintainence of exposure margins related to safety throughout the 24-h dosing period
- Clinical feasibility and ease of use (pre-programmed infusion pumps)
- Safe and well tolerated in the studied cohort populations

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OVERLAY PLOTS OF NLME MODEL-PREDICTED MEDIAN PLASMA KETOROLAC CONCENTRATION VS. TIME CURVES FOR COHORT 2-4, BY TREATMENT

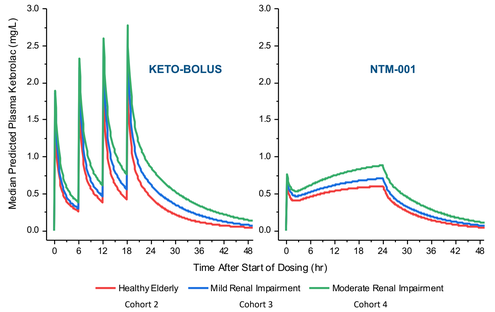
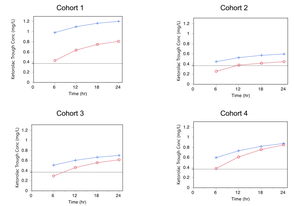


FIGURE 4 .NTM-001 CONCENTRATIONS EXCEED KETO-BOLUS TROUGHS IN ALL COHORTS – FOCUS ON COHORTS 2-3-4

- Treatment with NTM-001 maintains ketorolac concentrations that are greater than trough values for KETO-BOLUS, independent of dose level and subject renal function.
- Peak-trough fluctuation is expected to be greatly reduced with NTM-001.



SAFETY SUMMARY

Exposure

- Exposure profiles for a 50% reduced dosing regimen of NTM-001 did not show any signal for excessive exposure vs. KETO-BOLUS (AUC, Cmax) in elderly subjects, without/with mild or moderate renal impairment.

Adverse Events

- No stopping criteria for individuals or the trial overall were met.
- 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, of mild intensity
  - No signs of acute renal injury in this vulnerable population
  - Few injection site reactions were observed in the KETO-BOLUS group

Further analyses will be provided with the final trial results.

DETAILS: EVENTS OF SPECIAL INTEREST

TABLE 3. COHORTS 2-3-4: TREATMENT EMERGENT GASTRO-INTESTINAL EVENTS

Gastrointestinal Disorders (At least 1 event)	Severity	NTM-001	KETO-BOLUS
	Cohort 2		
N/A	-	0	0
	Cohort 3		
Diarrhea	Mild	0	1
	Cohort 4		
Abdominal pain upper	Mild	0	1
Diarrhea	Mild	0	1
Oral pain	Mild	1	0

TABLE 4. COHORTS 2-3-4: TREATMENT EMERGENT ADMINISTRATION SITE EVENTS

Administration Site Events (At least 1 event)	Severity	NTM-001	KETO-BOLUS
	Cohort 2		
Erythema	Mild	0	1
Induration	Mild	0	1
	Cohort 3		
Pain	Mild	0	1
	Cohort 4		
N/A	-	0	0

Administration Site Events

There were no administration site events for NTM-001 reported based on a preliminary evaluation of interim data.

Adverse Events linked to Renal Function

Changes in creatinine and creatinine clearance were assessed to determine a potential impact of IMP on renal function.

Preliminary analysis shows that there were no subjects in either cohort with a serum creatinine change of ≥ 0.3 or a reduction of creatinine clearance of ≥ 30% at 24- or 96-hours post-dose.

Signs of Bleeding (Surrogate Hemoglobin Level Fluctuations)

There were few intra-subject fluctuations in hemoglobin values observed across cohorts 2-4 (of moderate intensity in line with criteria of the Toxicity Grading Scale), more frequently 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 (Cohorts 2-4 with elderly volunteers without/with mild and moderate renal impairment) confirm the scientific product concept (loading dose followed by continuous infusion) developed with the support of extensive PK/PD modeling.
- Pharmacokinetic results in this vulnerable target population show a high degree of similarity to the modeling targets requiring no update to the Base Model.
- The 50% dose reduction implied by the generic ketorolac label (IV bolus) in the elderly and renally impaired suggests an effective level of analgesia while elderly patients with no or mild renal impairment might benefit from a dose reduction less than 50% for monotherapy.
- Administration with pre-programmed pumps went smoothly contributing to high data quality.
- NTM-001 was well tolerated and safe without any signs of excessive exposure with increasing renal impairment and no signal for acute renal injury.
- If confirmed in clinical trials, NTM-001 can be a suitable alternative to opioids in the management of postoperative pain, also in elderly and/or renally impaired patients.

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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