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NTM-001: A Novel, Alcohol-free Formulation of Ketorolac Tromethamine in a Pre-Mixed Bag for Intravenous Continuous 24h Infusion: A Potential Alternative to Opioids to Treat Acute Moderately Severe Post-Operative Pain

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PURPOSE

Efforts to address issues related to inappropriate or excess use of opioid analgesics include restricting their use in the postoperative period. This has resulted in a pressing need for alternative effective options for the short-term management of moderately severe acute pain that requires analgesia at the opioid level.

Ketorolac tromethamine is a well-known and extensively-studied non-steroidal anti-inflammatory and analgesic drug which was approved by the FDA in 1989, "For short-term (up to 5 days) management of moderately severe acute pain that requires analgesia at the opioid level, usually in a post-operative setting."

Previous clinical studies and clinical experience have shown that parenteral ketorolac, perhaps uniquely among NSAIDs, is as effective as morphine in treating moderate-to-severe postoperative pain (Brown, Mazzulla et al. 1990). While it is often used as part of a multimodal analgesia and opioid-sparing strategy (White, Raeder et al. 2012), efficacy results have been mixed, perhaps due to insufficient control of dose exposure using products that rely on periodic parenteral injections. This could result from fluctuating peak and trough plasma exposures from an injected product that might be corrected with a product that provides more continuous levels of exposure.

There is broad evidence that patients may benefit from a continuous infusion regimen of ketorolac, considering that several aspects of current bolus dosing regimens are suboptimal and may result in unnecessary drug exposure and consequent adverse effects.

We addressed this deficit by:

1) establishment of an evidence-based selection of loading dose and infusion rate using modern PK/PD modeling that identified an improved exposure profile, reduced maximum daily dose, and a provided a 50% reduced-dosing regimen for at-risk populations in line with the generic reference label

2) designing an alcohol-free IV formulation of ketorolac at approximately pH 7.4 that is readily available for use without further dilution in a pre-mixed bag and applied by pre-programmed infusion pumps (as in regular hospital use).

FIGURE 1: EXAMPLE OF A PRE-MIXED BAG WITH NTM-001 FROM CLINICAL TRIAL USE (NOT REPRESENTING FINAL PRODUCT)

METHODS AND RESULTS

PK/PD modeling was employed to design a product that delivers a continuous IV infusion of ketorolac tromethamine following controlled IV delivery of a loading dose delivered from the same pre-mixed bag.

IMPROVED EXPOSURE PROFILE AND REDUCED MAXIMUM DAILY DOSE

Exposure Profile and Efficacy

As outlined earlier it is a target of the development of NTM-001 to overcome fluctuating peak and trough plasma exposures from an injected product with a product that provides more continuous levels of exposure.

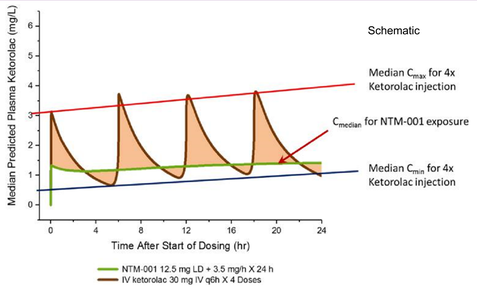
- The current ketorolac bolus dosing regimen results in a high peak exposure (Cmax) that, from a pharmacological perspective, increases safety-related risks without providing evidence of increased analgesic efficacy.
- Furthermore, the trough (Cmin) between repeat i.v. or i.m. doses of ketorolac tromethamine may provide insufficient analgesia for many patients.

Both of these issues could be mitigated through a continuous infusion with NTM-001, providing a relatively constant exposure to effective dose levels of ketorolac during the first 24 hr following surgery with a lower total daily dose (96.5 mg) compared to the indicated dosing with generic ketorolac tromethamine injection (120 mg).

PK/PD Modeling

Based on a population PK/PD model describing reduction in pain scores after ketorolac tromethamine injection (Mandema and Stanski 1996), Neumentum used deterministic and stochastic simulations to predict the time courses of drug exposure and the analgesic effect for a series of candidate IV loading dose/24-hour constant-rate (LD/CR) infusion regimens. These were compared to the exposure and effect time courses from a reference regimen of 30 mg bolus IV ketorolac q6h for 24 hours. The reference regimen was selected based on the FDA-approved ketorolac label. The candidate LD/CR infusion regimens were investigated via simulations according to the goals of achieving equal analgesic efficacy, fewer unsafe or ineffective ketorolac exposures, and lower 24-hour total ketorolac exposure. Regimens consisting of various combinations of ketorolac tromethamine loading doses and infusion rates were simulated and the predicted PK and PD vs. time profiles were compared to the reference regimen.

FIGURE 2. MODELED NTM-001 VS. KETOROLAC TROMETHAMINE INJECTION DATA



Real World Administration Pattern

The generic regimen also depends on timely application of the boli every 6 hours. If, in clinical hospital practice, subsequent boli were applied too early due to nursing time constraints, it might lead to overexposure and increased safety-related risks, while a delayed administration might cause insufficient analgesia.

A real-world **hospital chart audit** by Outcomes Insights (Neumentum, data on file), commissioned by Neumentum provides an analysis of

- 1,005 patient charts
- collected from 119 hospitals
- nationally distributed across the U.S.
- The data looked at a real-world hospital-based postsurgical use of ketorolac IV bolus treatment regimens (total daily dose, duration of treatment, total dose over treatment duration, dosing interval).
- The treatment setting included the operating room, PACU and nursing floor.

After the initial bolus dose of ketorolac injection, results of the chart audit data showed that only 25% of patients received subsequent bolus doses within a time window of 5.5 to 6.5 hours, while 14.0 % received a repeated bolus between less than 4.5 and 5.5 hours after the previous one (and 11% after less than 4.5 hours), exposing patients to an increased risk of excessive dosing and increased side effects.

The audit also showed that 48% were re-dosed only after 6.5 with a high probability of insufficient pain relief due to the prolonged dosing intervals.

FIGURE 3. CHAR AUDIT: DEMOGRAPHICS, PATIENT DISTRIBUTION, TYPES OF SURGERIES

Based on a total of 1,005 charts, three-quarters (76%) of ketorolac patients are under the age of 65 and have most typically undergone orthopedic, general, or obstetric/gynecological surgeries.

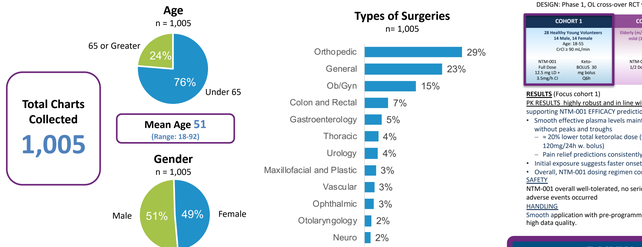
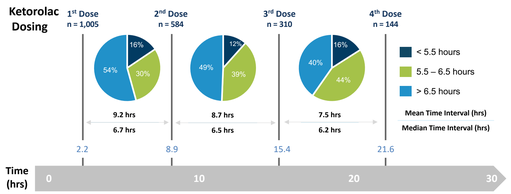


FIGURE 4. CHART AUDIT: KETOROLAC ADMINISTRATION PATTERN

Approximately one-third of patients receive their ketorolac dose between 5.5 - 6.5 hours. Of note, some patients (12-16%) receive their ketorolac dose within 5.5 hours of their initial dose.



The loading dose and continuous infusion regimen of NTM-001 is expected to overcome those exposure-related disadvantages and to actually provide a comparable level of analgesia as with the bolus regimen at a clearly lower total daily (24-hour) dose.

Modeling Predictions and Results in Humans

Neumentum has conducted extensive PK/PD modeling to define an optimal regimen for loading dose and infusion dose to rapidly reach and maintain stable and effective plasma levels for 24 hr. AUC analyses related to PK/PD modeling suggest a comparable or improved level of analgesia for NTM-001 vs. the 30 mg bolus regimen at clearly lower maximum exposure levels. Upper exposure margins of the bolus regimen are not exceeded by NTM-001 at any time (**Figure 5**).

The proposed loading dose is lower than a generic ketorolac bolus single dose. In line with literature and modeling suggesting this, it is designed to ensure rapid achievement of therapeutic plasma concentrations and smooth (peak- and trough-free) establishment and maintenance of efficacious levels of analgesia. This has been confirmed in a Phase-1 trial in healthy human subjects. The selected loading dose also avoids excessive exposure within the initial six hours of application in combination with the infusion.

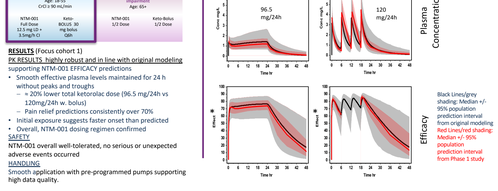
TABLE 1. CHARACTERISTICS OF THE NTM-001 LD/CR INFUSION REGIMEN VS. TO THOSE OF THE REFERENCE 30 MG BOLUS IV KETOROLAC Q6H REGIMEN

Characteristic	NTM-001 LD/CR Regimen	Reference IV Bolus Regimen
24-hour total dose	96.5 mg	120 mg
Predicted fraction of reference regimen efficacy*	0.963	1

*Estimated as the ratio of NTM-001/Reference regimen pain relief areas under the effect curves from time 0 to 24

Interim pharmacokinetic modeling results and model-predicted pain relief for both NTM-001 and KETO_BOLUS have been reported from the recently completed Phase 1 study. A high degree of similarity to the previously established targets was demonstrated and no modification of the NTM-001 dosing regimen were required in healthy patients with normal renal and hepatic function (Cohort1).

FIGURE 5. PHASE 1 TRIAL RESULTS FOR NTM-001 MEET PREDICTIONS OF PK/PD MODELING (2019 PAINWEEK ABSTRACT #40)



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Safety and Exposure

In an earlier review of ketorolac safety from March 1990 to June 1994, (Reinhart 2000) indicated that GI bleeding and perforation, platelet inhibition, and renal impairment were among the most frequently encountered adverse events in a survey. However, Reinhart also indicated that the incidence of serious adverse effects has declined since dosage guidelines were revised to restrict the duration of treatment; the risk for adverse events increases with high doses, with prolonged therapy (>5 days) or in vulnerable populations (e.g. elderly).

Reinhart concluded that, "Ketorolac should be prescribed at the lowest dosage necessary to control pain; the duration of therapy should also be limited to as few days as possible."

The current generic US label clearly reflects the dose-dependency of the incidence of serious gastro-intestinal events, with even more increased risk for the elderly (≥65 years of age) and a dose reduction for other patients in special risk populations.

All this evidence has been taken into account for the doses and dosage schedule for NTM-001. With a loading dose of 12.5 mg and an infusion rate of 3.5 mg, the total 24 hr dose of NTM-001 will be 96.5 mg vs. the respective dose of the bolus regimen of 30 mg q6h or 120 mg/24 hr, so almost a 20% dose sparing.

TABLE 2. COMPARISON OF KETOROLAC TROMETHAMINE DOSING SCHEDULES

Formulation	Generic ketorolac tromethamine injection	Proposed Neumentum Formulation (NTM-001)
Treatment Duration up to	5 days	24 hours
24 hr Dosing (patients < 65 yr/age, ≥ 50 kg body weight, normal renal function) †	30 mg IM/IV injection every 6 hours; not to exceed 120 mg/day	Loading dose: 12.5 mg IV from NTM-001 infusion solution. Maintenance dose: 3.5 mg/hr as a continuous infusion x 24 hours. (total maximum dose 96.5 mg/24 hr)

†A 50% reduced dosing regimen is proposed for risk patient populations (≥65 years old, renally impaired and/or less than 50 kg (110 lb) body weight), in line with the current label and in patients with moderate hepatic impairment.

The target dosing regimen, confirmed by recent Phase 1 PK data, is proposed to be independent of dosing intervals, to avoid peaks and troughs in exposure and allow for stable efficacy over 24 hr with an almost 20% reduced daily dose of ketorolac tromethamine vs. a standard q6h bolus regimen.

Reduced Duration of Application (24 h)

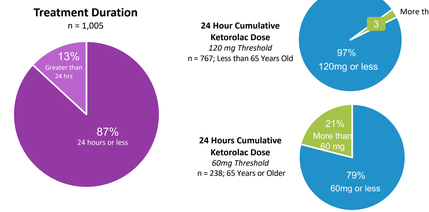
NTM-001 is proposed for a continuous infusion of 24 hr, largely in line with current practice in hospitals.

This is fully in line with developments in recent years targeting early mobilization and discharge of patients like the ERAS (Enhanced Recovery After Surgery) initiative that has been implemented with increasing frequency in hospitals internationally including the US (Ljungqvist, Scott et al. 2017). The target is to get patients off their i.v. lines to trigger mobilization and gut function usually 24 hr after surgery or the morning after major surgery (Johns Hopkins 2017).

According to the hospital pharmacy chart review in 119 hospitals across the United States cited earlier with an analysis on 1005 patient charts across a large variety of surgical types related to use patterns of the current generic product, the IV ketorolac bolus regimen is used for no longer than 24 hours in 87% of postsurgical patients in hospitals (Neumentum, data on file, **Figure 6**)

FIGURE 6. CHART AUDIT – DURATION OF TREATMENT – KETOROLAC BOLUS REGIMEN

The majority of patients (87%) are treated with ketorolac for less than 24 hours. Virtually all patients (97%) receive 120 mg or less of ketorolac over 24 hours. Amongst the elderly (65 yrs or older), one-fifth of patients (21%) receive more than 60 mg over 24 hours.



Conclusion

The proposed shorter duration of exposure (24 hr) for NTM-001 vs. up to 5 days of treatment with generic i.v. ketorolac tromethamine suggest an improved safety profile for NTM-001.

The evidence on relationship of serious side effects of ketorolac to duration of exposure has in European countries like Italy - where ketorolac is a very popular analgesic- led to a restriction of use to 2 days maximum. In a recent publication evaluating 2 major safety databases and exploring the off-label use of ketorolac in Italy the authors concluded that "this use increases the risk of serious ADR, especially in case of prolonged duration of treatment and in elderly patients" (Viola, Trifirò et al. 2016).

These results were supported in a contemporary review of ketorolac safety in comparison to other postoperative analgesics (oxymorphone, tramadol, tapentadol; (Vadivelu, Chang et al. 2017)).

The practical use of NTM-001 as a continuous 24 hr infusion restricted to a supervised setting with a limited, tailored dose per bag (clearly separated, also by different bag size for full or 50% reduced dosing) further provides protection vs. off-label use including prolonged use of ketorolac tromethamine and use of unrestricted doses of ketorolac in elderly subjects that may lead to serious adverse drug effects.

In conclusion, limiting the proposed treatment period to 24 hours is in line with clinical practice and may improve the risk profile of NTM-001 vs. a 5 days application regimen.

CONCLUSION

- Neumentum has conducted extensive PK/PD modeling to define an optimal regimen for loading dose and infusion dose to rapidly reach and maintain an efficacious and safer regimen for 24 hr applied by pre-programmed infusion pumps.
- Extensive evidence shows continuous infusion of ketorolac provides postoperative pain control comparable to opioids (Schwinghammer, Isaacs et al. 2017).
- Modeling suggests a comparable level of analgesia for NTM-001 vs. the 30-mg bolus regimen at clearly lower maximum and without below-therapeutic trough exposure levels. Cmax exposures of the bolus regimen are not exceeded by NTM-001 at any time.
- The target dosing regimen, confirmed by recent Phase 1 PK data, is proposed to be independent of dosing intervals, to avoid significant peaks and troughs in exposure, and to allow for stable efficacy over 24 hr with an almost 20% reduced daily dose of ketorolac tromethamine vs. a standard q6h bolus regimen.
- Limiting the proposed treatment period to 24 hours is in line with clinical practice and may improve the risk profile of NTM-001 vs. a 5-day application regimen. In conclusion, NTM-001 may offer a safe and effective alternative to opioids for moderately severe post-operative pain.

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DISCLOSURES

Ilona Steigerwald, MD is an employee of Neumentum, Inc.. Joseph Pergolizzi, MD is a speaker/ consultant / researcher: BDSI, Daiichi, US World MEDS, Dompe, Salix, Neumentum, Enalare, Hikma. Equity owner Neumentum, NEMA and Enalare. Robert Raffa, PhD was a previous employee of Johnson & Johnson and has received research support or honoraria from multiple pharmaceutical companies involved in analgesics research and development (e.g., recently BDSI, CerSci, Grünenthal, Insys, NEMA, Salix, and US WorldMeds, etc.) – but he receives no remuneration based on sales of any product. He is a cofounder of CaRafe Drug Innovation and is CSO of Neumentum, both companies concentrate on non-opioid analgesic drug discovery and development. Frank Diana, PhD is a consultant to Neumentum, Inc. William Schmidt, PhD is a paid consultant to Neumentum, Inc. Technical editorial and medical writing assistance was provided under the direction of the authors and NEMA Research Inc, Naples, FL. NEMA Research received funding for this support from Neumentum Inc.