Poster 22

Efficacy and safety of NTM-006 in a randomized, double-blind, placebo- and active-controlled trial in moderate to severe pain after third molar extraction

Meaningful and sustained analgesia over 24h demonstrated for a single dose (1000 mg) of NTM-006, an NCE with a novel non-opioid/non-NSAID mechanism of action

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PURPOSE

NTM-006 (formerly JNJ-10450232) was discovered as part of a research program to identify a novel analgesic with an enhanced safety and efficacy profile vs. acetaminophen. Despite structural similarity to acetaminophen (APAP), it is notably different with respect to overall in-vitro and in-vivo pharmacologic profile, metabolism and pharmacokinetics, and the targeted lack of acetaminophen-induced hepatotoxicity. It is also targeted to positively differ from other classes of analgesics/co-analgesics like opioids, NSAIDs, cannabinoids and gabapentinoids with their shortfalls (*i.e.*, gastrointestinal, cardiovascular, respiratory, CNS and renal safety or abuse potential). In preclinical models, NTM-006 exhibited clear antinociceptive and antipyretic effects but little inhibition of ligand binding in a panel of receptor, enzyme, ion-channel, and neurotransmitter transporters, except for a concentration-related inhibition of radiolabelled ligand at the human adenosine A3 receptor, at concentrations attained in the brain following administration of an active *in vivo* dose (Raffa et al., Painweek 2020).

The development program comprised two phase 1 studies with NTM-006 apart from the reported phase 2a study: In a first-in-human double-blind study exploring SD and MD kinetics, NTM-006 administered up to 6000 mg as a single dose and up to 2500 mg twice daily (5000 mg/day) for eight days was well tolerated by 102 healthy male subjects (data on file). An open-label, multiple-dose, safety, and pharmacokinetics study assessed the tolerability of NTM-006 under a 10 days MD treatment regimen (500 mg bid) in male and female volunteers (data on file).

Since the original target profile for NTM-006 was as an OTC analgesic with APAP as a comparator, dose strengths selected for the reported phase 2a study (ie 250 mg and 1000 mg) were targeted to assess the potentially lowest and comparably effective single doses of NTM-006 vs 1000 mg APAP (relating to the maximum daily dose of APAP of 4000 mg). The current development of NTM-006 as a prescription analgesic for moderate to severe acute and chronic pain indications (including neuropathic and nociplastic pain) aims to explore a wider dose range and more potent comparators from other classes of analgesics including opioids and gabapentinoids.

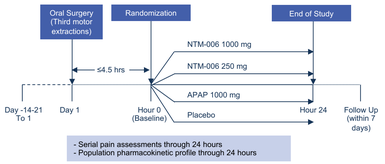
NTM-006 was licensed to Neumentum, Inc. in October. 2019, for further development.

METHODS

This was a single-center, randomized, double-blind, placebo- and active-controlled, parallel group study to evaluate the efficacy, safety and pharmacokinetic profile of a single dose of NTM-006, over a 24-hour on-site period in moderate to severe pain after third molar extractions in up to 280 male subjects.

Healthy male subjects, ages 18 to 45 years, were screened by medical history, vital signs, electrocardiogram (ECG), and clinical laboratory tests. Eligible subjects returned to the clinic on the day of surgery and completed baseline vital signs and clinical laboratory tests.

Fig. 1: Study Flowchart



Study Objectives

The primary study objective was to evaluate the efficacy and safety over 24 hours following a single dose of NTM-006 (250 or 1000 mg) compared with placebo in the dental pain model following third molar extractions.

The secondary study objectives were to evaluate NTM-006 analgesia relative to a single dose of 1000 mg acetaminophen over 24 hours and to evaluate individual and population pharmacokinetics of NTM-006.

Extraction of a minimum of three third-molars was required:

- Mandibular extractions without a trauma rating of "severe" (on a scale of mild, moderate, severe) including
  - A. Two full or partial bony impactions or
  - B. One full bony impaction in combination with a partial bony or soft tissue impaction.
- Maxillary third molar extraction regardless of impaction level.

Subjects had to meet **randomization criteria:**

- Post-surgical pain of moderate or severe intensity on the 4-point categorical pain scale
- At least a score of 5 on the 11-point [0-10] pain intensity numerical rating scale [PI-NRS] at baseline within 4.5 hours after the last surgical stitch

Qualified subjects were **randomized 1:1:1:1 to four treatment groups**:

- **NTM-006 250 mg**
- **NTM-006 1000 mg**
- **Acetaminophen 1000 mg**
- **Placebo**

Assessments: Pain intensity/pain relief were collected at 0.25, 0.5, 0.75, 1, 1.5, 2, hourly up to 12, 16, 24 hours post-dose and at time of first rescue medication.

Efficacy Endpoints

Primary:

Analgesic efficacy 0-6h after dosing using the time-weighted Sum of Pain Intensity Difference (SPID 0-6).

Secondary/Tertiary

- Pain intensity difference from baseline (PID) scores and pain relief (PAR) scores at each time point
- Duration of pain relief after dosing (time to rescue medication)
- Subject Global Evaluation
- Time-weighted SPID and TOTPAR at 0-4, 0-8, 0-12, 0-24 hours
- Times to confirmed first perceptible / meaningful pain relief (2-stopwatch technique)
- Amount of rescue medication (oral ibuprofen) at all evaluation time intervals.

Safety: Assessed by results from ECGs, vital signs, clinical laboratory, additional hepatic aminotransferase/bilirubin measurements and subject-reported adverse events.

A follow-up phone call was scheduled within 7 days after surgery.

Pharmacokinetic samples were taken linked to population pharmacokinetic model development and analysis (results not presented on this poster)

Statistical Methods (Selected)

A sample size of 66 subjects by treatment group was needed to detect a treatment difference at an alpha level of 0.05 (two-sided) with approximately 90% power, assuming an effect size of 0.57 for SPID 0-6.

The primary endpoint, SPID 0-6, was analyzed with an analysis of variance with baseline pain (moderate or severe) score and treatment group in the model. A model that included the interaction term of treatment and baseline pain was also examined for the primary endpoint. PID and PAR scores were analyzed at each time point with an analysis of variance with baseline pain score (moderate or severe) and treatment group in the model. Time-weighted SPID from 0-4, 0-8, 0-12, and 0-24 and TOTPAR from 0-4, 0-6, 0-8, 0-12, and 0-24 were each analyzed with an analysis of variance with baseline pain (moderate or severe) and treatment group in the model. Summary statistics (mean, standard deviation, median, minimum and maximum, least squares mean, standard error of the least squares mean) were tabulated by treatment group.

RESULTS

Population/Demographics

Overall, 269 subjects were randomized to IMP:

N= 66	**NTM-006 1000 mg**
N= 69	**NTM-006 250 mg**
N= 67	**Acetaminophen 1000 mg**
N= 67	**Placebo**

Three subjects withdrew from the study, one for personal reasons, two for TEAEs (under placebo and NTM-006 250 mg), not related to study treatments (details: safety section).

Demographic/baseline characteristics were comparable among treatment groups:

All subjects were male with an average age of 19.1 years and a mean BMI of 23.56 kg/m^2, N=251 (93.3%) were Caucasian, 92.6% not of Hispanic or Latino ethnicity.

Table 1: Third Molars Extracted and Most Frequent Bony Impactions

Third molears extracted (n=)	Subjects (%)		Bony impactions	Subjects (%)
3	7.4		2 full	65.4
4	91.8		2 partial	16.7
>4	<1		1 full and 1 partial	16.4

At baseline, 51.3% (138/269) reported severe pain with a mean PI-NRS score of 7.6.

Efficacy

Primary efficacy endpoint: SPID 0-6 was significantly greater (p<0.001) for subjects treated with 1000 mg NTM-006 (20.56) and acetaminophen 1000 mg (20.75) but not 250 mg NTM-006 (8.95) when compared with placebo (4.37).

Secondary endpoints: statistically significantly greater PID and PAR scores were observed for both 1000 mg NTM-006 and acetaminophen compared to placebo beginning at 45 min and 30 min, respectively, while continuing through 24h on a stable level for NTM-006 and only 7h for acetaminophen. Accordingly, subjects treated with NTM-006 1000 mg had significantly greater PID scores compared with subjects treated with acetaminophen 1000 mg beginning at seven hours and continuing through 24 hours (p≤0.004), consistent with respective PAR scores (p≤0.003).

The median time to first perceptible pain relief was 45.2 and 28.3 minutes for the 1000 mg NTM-006 and acetaminophen groups, respectively. The median time to meaningful pain relief was 115.2 minutes for the NTM-006 1000 mg group and 52.9 minutes for the acetaminophen 1000 mg group.

Fig. 2: Pain Intensity Difference from Baseline at Each Time Point (Intent-to-Treat Set)

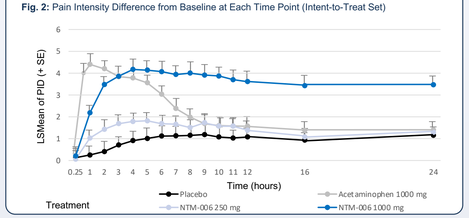
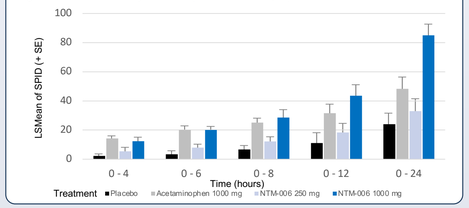


Fig. 3: Bar Chart of SPIDs by Treatment (Intent-to-Treat Set, All)



For both SPID 0-12 and 0-24, 1000 mg NTM-006 had statistically significantly greater scores than 1000 mg acetaminophen while SPID 0-4 and 0-8 were similar between these treatment groups (and TOTPAR for these periods.) Although superior to placebo for PID and PAR from 1.5 to three hours, NTM-006 250 mg generally did not provide statistically significant pain relief compared with placebo in the overall study population.

Fig. 4: NTM-006: Pain Intensity Difference from Baseline at Each Timepoint – Moderate Baseline Pain (Intent-to-Treat Set)

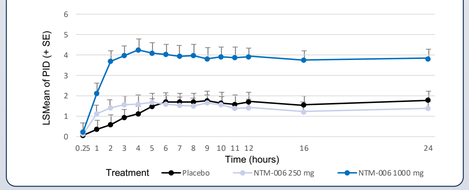
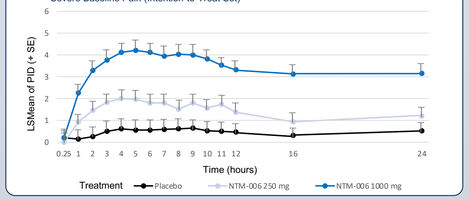


Fig. 5: NTM-006: Pain Intensity Difference from Baseline at Each Timepoint: Severe Baseline Pain (Intention-to-Treat Set)



For subjects with moderate baseline pain, the placebo response was greater than for subjects overall while for subjects with severe baseline pain, the placebo response was less than for subjects overall. NTM-006 1000 mg provided a stable analgesic effect over the 24h period on both moderate and severe pain. NTM-006 250 mg showed a better and prolonged effect vs. placebo in subjects with severe baseline pain than in the moderate pain subset.

Time/PD	Placebo	Acetaminophen	Ntam-006 250 mg	NTM-006 1000 mg
2 hours	0.41 (0.31)	4.20 (0.31)*	1.43 (0.31)*,†	3.48 (0.31)*
6 hours	1.12 (0.37)	3.04 (0.37)*	1.69 (0.37)†	4.07 (0.38)*
8 hours	1.15 (0.36)	1.99 (0.36)	1.51 (0.35)	4.00 (0.36)*,†
12 hours	1.08 (0.36)	1.57 (0.36)	0.39 (0.35)	3.61 (0.36)*,†
24 hours	1.15 (0.39)	1.41 (0.39)	1.29 (0.38)	3.47 (0.39)*,†

*p≤0.05 vs placebo; †p≤0.05 vs acetaminophen 1000 mg

Over the 24h study period, less subjects treated with NTM-006 1000 mg rescued (45.45%) compared with those treated with NTM-006 250 mg (73.53%), acetaminophen (72.73%), or placebo (71.86%).

The median time to rescue was not estimable for the NTM-006 1000 mg group, since fewer than 50% of subjects rescued. It was 109.0/129.0/468.5 minutes for placebo/NTM-006 250 mg/acetaminophen groups, statistically significant vs placebo for NTM-006 1000 mg and acetaminophen (p≤0.042) and for NTM-006 1000 mg vs. acetaminophen (p</= 0.006)

Fig. 6: Cumulative Percentage of Subjects Using Rescue Medication (Kaplan -Meier Estimates, Intent-to-Treat Set)

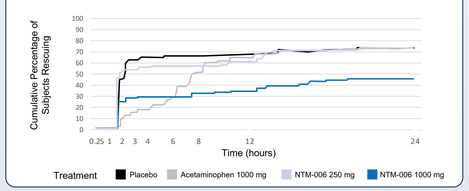
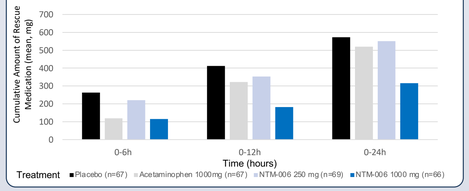


Fig. 7: Mean Cumulative Amount of Rescue Medication (mg) Per Subject By Time (Hours, Intent-to-Treat Set)



The **Subject Global Evaluation (0-12h)** was recorded 12 hours after start of treatment only. The percentage of subjects who rated their overall impression of study medication as "very good" or "excellent" was 42.4% for the NTM-006 1000 mg group, 18.8% for the NTM-006 250 mg group, 47.8% for the acetaminophen 1000 mg group, and 10.4% for the placebo group. Since the full 24h treatment period was not assessed, the prolonged effect of NTM-001 (1000 mg) could not be evaluated vs. acetaminophen from 0-24 h or 12-24 h.

Safety

Overall, 13.4% of subjects reported TEAEs (Treatment-Emergent Averse Events) with similar incidences among treatment groups: 7 (10.6%) - 1000 mg NTM-006, 7 (10.1%) - 250 mg NTM-006, 10 (14.9%) - acetaminophen, and 12 (17.9%) placebo. No serious TEAEs or deaths were reported.

Two subjects withdrew from the study due to TEAEs (one with pyrexia under placebo and one NTM-006 250 mg-treated subject with nausea, dizziness, and headache exacerbation, not rated as related to IMP). There were no clinically important differences among treatment groups for hematology and chemistry laboratory measurements.

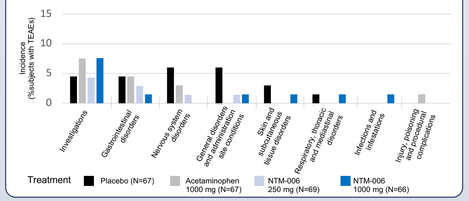
All TEAEs were of mild or moderate intensity with the exception of one case of syncope considered severe, not related to IMP (placebo). The severity and nature of adverse events were similar among groups. There were no clinically relevant differences among groups for vital signs and ECGs.

While not rated as clinically important, there were increases in indirect bilirubin in all treatment groups and increased bilirubin was reported as the most frequent TEAE by 5.9% of subjects. Increases in bilirubin at 4 hours for both the NTM-006 1000 mg group and the NTM-006 250 mg group were thought to be due to competition of NTM-006 with bilirubin for conjugation. Increases in bilirubin at 24 hours were hypothesized to be a result of subjects swallowing blood during the dental surgery. Elevations in liver function test values of AST and/or ALT after study treatment were observed only in subjects who had elevations at baseline before treatment was administered. Elevations in AST and/or ALT after baseline were in general always the same or lower than at baseline.

Table 2: Summary of Treatment-Emergent Adverse Events By System Organ Class (SOC) and MEDDRA Preferred Term (Safety Analysis Set)

	Placebo (N=67)		Acetaminophen 1000 mg (N=67)		NTM-006 250 mg (N=69)		NTM-006 1000 mg (N=66)	
SOC/Preferred Term	Subjects with at least one TEAE (n, %)							
	n	(%)	n	(%)	n	(%)	n	(%)
ALL	12	(17.9%)	10	(14.9%)	7	(10.1%)	7	(10.6%)
Investigations	3	(4.5%)	5	(7.5%)	3	(4.3%)	5	(7.6%)
Blood bilirubin increased	3	(4.5%)	5	(7.5%)	3	(4.3%)	5	(7.6%)
Gastrointestinal disorders	3	(4.5%)	3	(4.5%)	2	(2.9%)	1	(1.5%)
Hypoaesthesia oral	1	(1.5%)	1	(1.5%)	1	(1.4%)	0	
Nausea	0		1	(1.5%)	1	(1.4%)	1	(1.5%)
Diarrhoea	2	(3.0%)	0		0		0	
Vomiting	0		1	(1.5%)	0		1	(1.5%)
Abdominal pain upper	1	(1.5%)	0		0		0	
Nervous system disorders	4	(6.0%)	2	(3.0%)	1	(1.4%)	0	
Headache	2	(3.0%)	1	(1.5%)	1	(1.4%)	0	
Dizziness	1	(1.5%)	1	(1.5%)	0		0	
Paraesthesia	1	(1.5%)	0		0		0	
Syncope	1	(1.5%)	0		0		0	
General disorders and administration site conditions	4	(6.0%)	0		1	(1.4%)	1	(1.5%)
Pyrexia	2	(3.0%)	0		0		1	(1.5%)
Chills	1	(1.5%)	0		0		0	
Feeling hot	1	(1.5%)	0		0		0	
Malaise	1	(1.5%)	0		0		0	
Suprapubic pain	0		0		1	(1.4%)	0	
Skin and subcutaneous tissue disorders	2	(3.0%)	0		0		1	(1.5%)
Pruritus	1	(1.5%)	0		0		1	(1.5%)
Hyperhidrosis	1	(1.5%)	0		0		0	
Respiratory, thoracic and mediastinal disorders	1	(1.5%)	0		0		1	(1.5%)
Oropharyngeal pain	1	(1.5%)	0		0		1	(1.5%)
Infections and infestations	0		0		0		1	(1.5%)
Oral infection	0		0		0		1	(1.5%)
Injury, poisoning and procedural complications	0		1	(1.5%)	0		0	
Mouth injury	0		1	(1.5%)	0		0	

Fig. 8: Summary of Treatment-Emergent Adverse Events By System Organ Class (Safety Analysis Set)



CONCLUSIONS

NTM-006, an analgesic NCE with a novel mechanism of action (non-opioid, non-NSAID) provided sustained pain relief throughout a 24 h time interval in moderate to severe pain following third molar extraction with a single oral dose of 1000 mg. It exerted significantly superior efficacy over 1000mg of acetaminophen after 7 h and decreased use of rescue medication over the observation period. NTM-006 appeared overall safe and well-tolerated.

The natural properties of NTM-006 with sustained efficacy may qualify it further as an important asset for the treatment of chronic in addition to acute pain. The full analgesic potential of NTM-006 has yet to be explored, in more severe pain conditions, at different doses, vs. opioids or gabapentinoids in chronic and neuropathic pain. Being devoid of opioid-related side effects (CNS, GI, respiratory), apparent abuse potential as well as potentially serious NSAID-related side effects (GI, cardiovascular, renal) and considering a favorable metabolic profile, NTM-006 may work as a monotherapy and also become a suitable combination partner in multimodal analgesic regimens.

These opportunities will be explored during the continued development of NTM-006 in moderate to severe acute and chronic pain indications including musculoskeletal, nociplastic and neuropathic pain.

Disclosures

Ilona Steigerwald, MD is an employee (Chief Medical Officer) of Neumentum, Inc.
Joseph V Pergolizzi, Jr, MD: Consultant/ Speaker and Researcher for US World Meds, BDSI, Salix, Enalare, Scilex, Pfizer, Lilly, Teva, Regeneron, Redhill, Grünenthal, Neumentum.
Charles Argoff, MD is consulting Neumentum on NTM-006 and its development