Poster 69

Summary of the Preclinical Pharmacology of NTM-006 (formerly JNJ-10450232): A Novel Orally-Active Non-Opioid Analgesic

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ABSTRACT

JNJ-10450232 (now NTM-006), a structural analog of acetaminophen (paracetamol), was designed to retain the good analgesic efficacy, but not have the usual AEs associated with opioid and other classes of analgesics–or opioid abuse potential. Its clinical analgesic efficacy was demonstrated recently in a dental pain model (see companion poster). Its full potential of efficacy and possible therapeutic use in chronic/neuropathic pain continues in development as NTM-006. We summarize the basic preclinical pharmacology of this new non-opioid analgesic.

JNJ-10450232 was screened in a variety of *in vitro* assays and in animal models of acute pain, thermal hyperalgesia, a postsurgical model, and was tested for antipyresis. *In vivo* safety pharmacology studies were conducted in several species and in *in vitro* assays for toxicology. It had no significant affinity at any of more than four-dozen receptor types or sub-types (including opioid MOP, DOP, KOP; CB1 and CB2); enzymes (*e.g.*, kinases, COX-1 and COX-2), or neurotransmitter reuptake site (norepinephrine). It displayed concentration-related effect on binding at adenosine A_3 receptors (A_3R), and demonstrated antinociceptive, anti-hyperalgesic, and antipyretic activity in animal models suggestive of efficacy in acute and possibly chronic and/or neuropathic pain conditions.

CONCLUSIONS

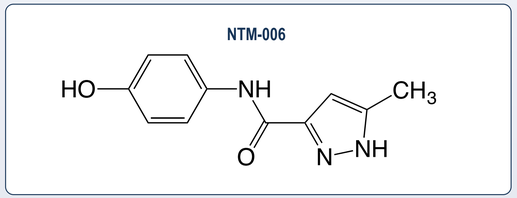
JNJ-10450232 demonstrated oral non-opioid, non-NSAID antinociceptive activity and antipyretic activity in several animal models that are predictive of analgesic efficacy against acute and chronic pain. Its preclinical pharmacologic profile is consistent with its efficacy and safety in the clinical testing. Future work as NTM-006 is aimed at elucidation of its full efficacy potential and possible use for chronic/neuropathic pain conditions with/without an inflammatory component.

INTRODUCTION

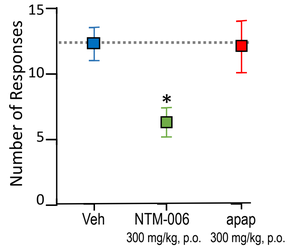
The impetus for drug-discovery efforts from which NTM-006 was identified was the desire to bring to patients an alternative analgesic and antipyretic that has an improved benefit-risk profile relative to the common current therapies.

NTM-006 is a structurally unique (inset), orally active antinociceptive and antipyretic agent in a variety of animal models with potential to relieve pain and reduce fever in human patients.

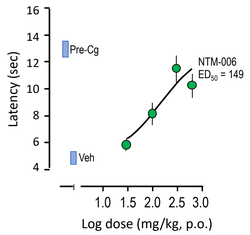
Based on preclinical studies (*in vitro* radioligand binding assays and *in vivo* animal models), NTM-006 is a novel non-opioid non-NSAID(it does not bind to opioid receptors, and does not inhibit cyclooxygenase). Although the molecule bears some similarity to acetaminophen, it significantly differs in overall *in vitro and in vivo* pharmacologic profile, metabolism, pharmacokinetics, and lack of hepatotoxicity.



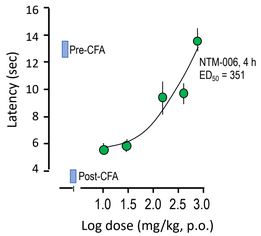
RESULTS



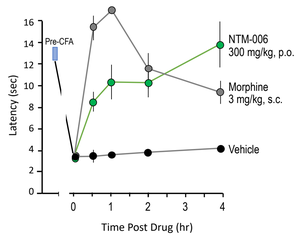
Antinociceptive effect in phenylquinone-induced abdominal irritant model. * P < 0.05. Mice



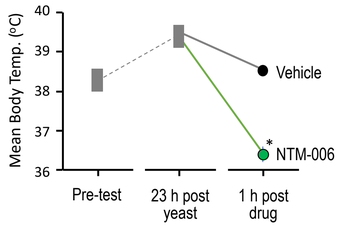
Antihyperalgesic effect in carrageenan(Cg)-induced thermal hyperalgesia. Rats.



Antihyperalgesic effect (4 hr) in model of thermal hyperalgesia induced by i.pl. injection of complete Freund's adjuvant (CFA). Rats.



Time-course of antihyperalgesic effect in model of complete Freund's adjuvant-induced thermal hyperalgesia. Rats.



Antipyretic evaluation at 600 mg/kg, p.o. in a yeast-induced pyresis model. Rats.

- NTM-006 exhibited little or no inhibition of ligand binding in a panel of receptor, enzyme, ion-channel, or neurotransmitter transporter, except for concentration-related inhibition at human adenosine A_3 receptors at concentrations attained in brain following active *in vivo* dose.
- NTM-006 did not display agonist or antagonist activity, suggesting a modulatory role.

SUMMARY & CONCLUSION

1. NTM-006 was designed to differ from opioids and NSAIDs.
2. In animal models, it was antinociceptive and antihyperalgesic, and had antipyretic activity.
3. Taken together, the results obtained in the *in vitro* and *in vivo* preclinical investigation of NTM-006 suggest that it has the potential to become an alternative, differentiated non-opioid, non-NSAID analgesic and antipyretic agent that should have a favorable clinical benefit-risk profile compared to currently available therapies. Study of relative efficacy compared to other classes of analgesics is ongoing, as is examination of its efficacy against a variety of pain types.
4. Given the importance of adenosine A_3 receptors along pain-transmitting pathways in the periphery, spinal cord, and brain, efficacy against additional pains might be possible, including against neuropathic pain, which would not be an unexpected property of an A_3 receptor modulator (A3RM). Use in combination with other drugs offers additional possibilities in pain and other therapeutic areas.
5. Ongoing studies will investigate the analgesic efficacy of NTM-006 compared to other classes of analgesics, as well as antiinflammatory action or efficacy vs neuropathic pain.

JVP and RBR disclose investment or management positions with Enalare and CaRafe, and recent consultant/speaker and/or researcher relationships with BDSI, Grünenthal, Lilly, Pfizer, Redhill, Regeneron, Salix, Scilex, Teva, US World Meds, and others. RBR is a past employee of J&J; JRC, EEC, and JJM were part of the discovery and development of JNJ-10450232.