Preclinical Through Early-Stage Clinical Development of a Novel NMDA Receptor Modulator, NYX-2925

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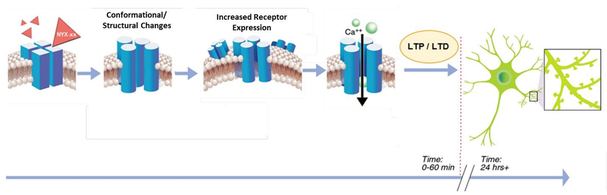
Poster Number: 15

NYX-2925 Mechanism of Action

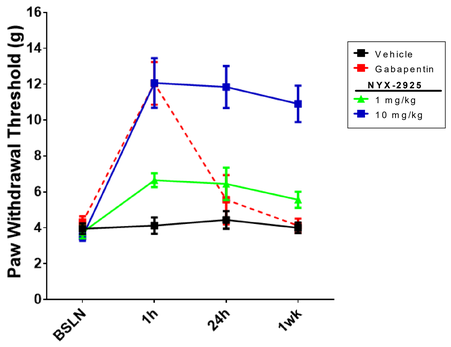


INTRODUCTION

N-methyl-D-aspartate receptors (NMDAR) are one member of a family of ionotropic glutamate receptors that play a pivotal role in synaptic plasticity processes associated with learning and have become attractive therapeutic targets for CNS disorders such as depression, neuropathic pain, and cognitive impairment among others. NYX-2925, a new chemical entity, acts as a co-agonist to glutamate at the NMDAR. NYX-2925 is being developed for the treatment of chronic pain conditions, including diabetic peripheral neuropathy and fibromyalgia. The presentation provides data from pivotal nonclinical studies and a first-in-human clinical study. NYX-2925 has demonstrated robust effect in various measurements across multiple nonclinical animal models of neuropathic pain.

A Phase 1 study evaluated the safety, tolerability, and pharmacokinetics in 84 healthy adult volunteers, following single doses ranging from 50 to 1200 mg, and multiple doses ranging from 50 to 900mg daily for 7 days. NYX-2925 exhibited dose-proportional pharmacokinetics and minimal accumulation following once-daily dosing for 7 days. NYX-2925 reached the CNS and was safe and well-tolerated in healthy volunteers, and the study results support the continued clinical development for neuropathic pain conditions.

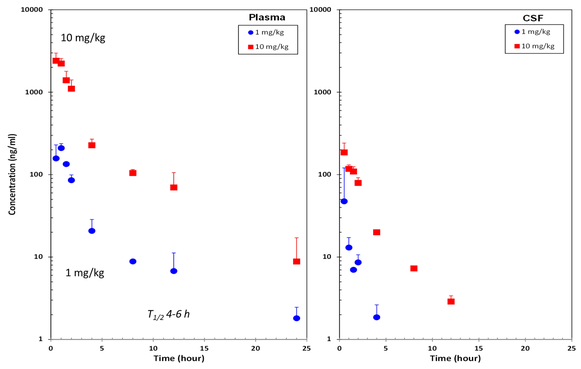
NYX-2925 Produces Long-lasting Analgesia in the STZ Model of Diabetic Peripheral Neuropathy



Treatment	1 h	24 h	1 wk
Gabapentin 150 mg/kg	*	NS	NS
NYX-2925 1.0 mg/kg	NS	NS	NS
NYX-2925 10.0 mg/kg	*	*	*

Rats were injected with streptozotocin at 20 mg/kg ip daily for 5 consecutive days after which they were given drinking water supplemented with sucrose (15 g/L) for 48 h to limit early mortality. Blood glucose levels were assessed weekly to evaluate hyperglycemia and the rats with fasting blood glucose of over 15 mmol/L (280 mg/dL) were selected to be included in the studies of diabetic neuropathy. Animals were tested 3 month post-STZ. Testing occurred 1 h, 24 h and 1 wk post-dosing with NYX-2925 (0.1-10 mg/kg PO), gabapentin (150 mg/kg PO), or 0.5% Na-CMC in 0.9% sterile saline. Mechanical analgesia was measured using Von Frey filaments and Dixon's up-down method (Chaplan et al., 1994).

PK in Rats at Analgesic Doses



Plasma and CSF exposure ranges resulting in analgesia in rodent models

NYX-2925 Has Potential for Wide Therapeutic Index

- No off-target activity when tested against 80 receptors
- No inhibition of CYP450 enzymes, and no induction of CYP3A4
- Negative in patch-clamp hERG test.
- No clinical or laboratory adverse findings in neurobehavioral and cardiovascular study in telemetered dogs (600 mg/kg).
- Ketamine-like drug discrimination: NYX-2925 does not share discriminative stimulus effects with ketamine
- Negative in the three regulatory-GLP genetic toxicology assays
- 6-Week Toxicology: No adverse findings (organ weight, macroscopic, or microscopic changes) following daily doses in rats and dogs at >50-fold the projected therapeutic dose (480 mg/kg in rats and 180 mg/kg in dogs).

NYX-2925-1001: First in Human Clinical Study

Phase 1, randomized, double-blind (sponsor-open), placebo-controlled, healthy volunteer trial evaluating safety, tolerability, and pharmacokinetics (PK): Single-center / 84 subjects dosed

Two phases

- Single Ascending Dose (SAD): evaluated 50 – 1200 mg QD po
- Multiple Ascending Dose (MAD): evaluated 150 – 900 mg QD po

Subsets evaluated

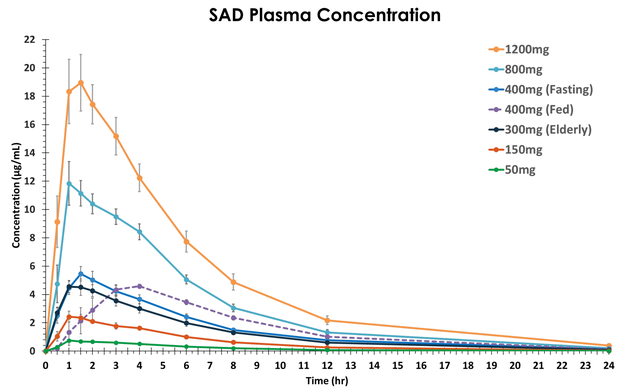
- One food-effect group at single-oral dose 400 mg
- One elderly group at single-oral dose of 300 mg
- Brain exposure evaluated by analyzing NYX-2925 concentrations after 50 and 300 mg doses

Endpoints

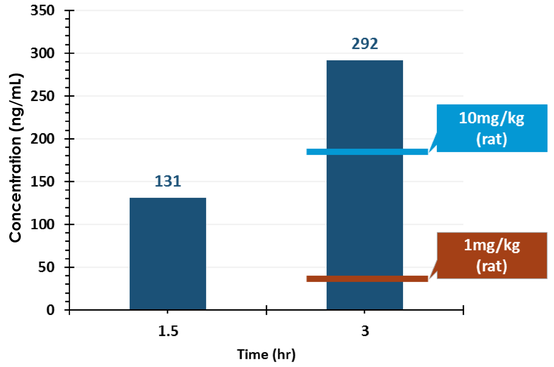
- Safety and tolerability
- Adverse events
- Vital signs, clinical labs, single intermittent 12-lead ECGs
- Psychiatric questionnaires (C-SSRS, BPRS+, CADSS)
- Thorough ECG analysis
- Pharmacokinetics
- Plasma Pharmacokinetics
- Food effect (1 dose cohort in SAD phase)
- Elderly (1 dose cohort in SAD phase)

Phase 1 PK Data

SAD Plasma Concentration



Human CSF Concentration Following a 300mg Dose of NYX-2925



PK Conclusions

- Mean NYX-2925 plasma concentrations increased in a dose-dependent manner; minimal accumulation across groups with repeat dosing.
- Cmax was achieved within 2 h post-dosing and declined in a roughly monophasic manner over 24 h; most subjects had measurable plasma concentrations at 24 h post-dose on Day 1 and at 48 h post-dose on Day 7.
- Half-life was approximately 4 hrs, but trended higher after repeat dosing, with geometric mean estimates of 4.8 – 7.3 h.
- The mean amount NYX-2925 excreted in the urine over 24 h suggested the majority (60% to 70%) of the administered dose was eliminated via the kidneys as unchanged drug.
- Data indicate that NYX-2925 cold be orally administered with or without food.
- NYX-2925 crosses the blood brain barrier, with maximum CSF concentration of approximately 6 to 9% of plasma C_{max}.

Safety Findings

	All NYX-2925 (N=66)	All Placebo (N=18)
Treatment-related TEAE*	**Number of Subjects (%)**	
Any treatment-related TEAE	**3 (4.5)**	**1 (5.6)**
Abdominal distension	1 (1.5)	0
Fatigue	0	1 (5.6)
Flatulence	1 (1.5)	0
Headache	1 (1.5)	0
Lethargy	0	1 (5.6)
Procedural headache	**1 (1.5)**	**0**

* Events considered by the Investigator to be related to study drug treatment.

- 1 subject (600 mg dose group) reported abdominal distension and flatulence.
- Headache and procedural headache were reported in the CSF cohorts.
- 1 subject (150 mg QD x 7 dose group) reported urinary retention — considered unlikely related by the Investigator, but possibly related by the sponsor.

CONCLUSIONS

- The NYX-2925 analgesic effect in neuropathic pain is rapid and long lasting in well characterized rodent models.
- NYX-2925 is highly bioavailable, and reaches the CNS in humans
- NYX-2925 is safe and tolerated following single doses of 1.2 g and 7-daily doses of 0.9 g
- No SAEs at any dose. No clinically significant changes in lab values or ECGs. No dissociative side effects
- The therapeutic index is likely > 100, based on PK in nonclinical-safety studies and the PK of potentially-therapeutic doses in humans

REFERENCES

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(2) Khan, M.A., et al, 2017. NYX-2925 Is a Novel NMDA Receptor-Specific Spirocyclic-β-Lactam That Modulates Synaptic Plasticity Processes Associated with Learning and Memory. *International J. Neuropsychopharmacology* (in press)

AFFILIATION and FINANCIAL DISCLOSURES

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