A Double-Blind, Placebo-Controlled, Phase 2 Study to Assess the Safety and Efficacy of NYX-2925 in Subjects with Painful Diabetic Peripheral Neuropathy

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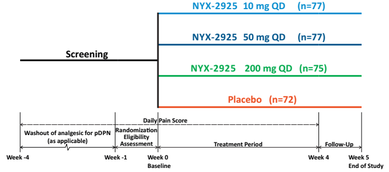
INTRODUCTION

- NYX-2925 [(2S,3R)-3-hydroxy-2-((R)-5-isobutyryl-1-oxo-2,5-diazaspiro[3.4] octan-2-yl)butanamide] is a novel, oral, N-methyl-D-aspartate receptor (NMDAR) modulator that enhances NMDAR activity. NYX-2925 is in clinical development for the treatment of chronic pain conditions, including chronic painful diabetic peripheral neuropathy (DPN).
- NMDARs are primarily found in the central nervous system,[1,2] and chronic pain involves central signaling pathways.[3] In pathology such as diabetic neuropathy, disease progression is associated with transition of underlying pain mechanisms from peripheral to central sensitization.[4,5] Recent evidence suggests that the central component of chronic neuropathic pain relies on changes in NMDAR-dependent plasticity within the corticolimbic circuitry, including the medial prefrontal cortex (mPFC).[6,7]
- Preclinical data have determined that the analgesic effects of NYX-2925 are achieved by direct administration of NYX-2925 into the mPFC, but not into the spinal cord.[8] Thus, it is hypothesized that the analgesic effect of NYX-2925 in chronic pain conditions is centrally mediated (supraspinal).
- NYX-2925 has been evaluated at doses of 0.1–100 mg/kg in rodents, and data indicate an inverted U-shaped dose response, with maximal effects at 1–10 mg/kg.[8,9] In a rodent model of streptozotocin-induced diabetic neuropathy, a single oral dose of NYX-2925 (3 or 10 mg/kg) produced a significant ($p<0.05$), long-lasting (up to 1 week post dose) analgesic effect compared to control.[8] Additionally, a single in vivo dose of NYX-2925 (1 mg/kg, oral) induced structural metaplasticity (at 24 hours post dose) and enhanced LTP for up to 1 week post dose.[9]
- The safety of NYX-2925 has been demonstrated at single doses up to 1200 mg/day and multiple doses up to 900 mg/day for 7 days in healthy volunteers, with no dose limiting adverse events.[10]
- The study presented here was the first-in-patient evaluation of the safety and efficacy of NYX-2925 in subjects with painful DPN. Three doses (10, 50 and 200 mg) were selected for evaluation based on estimated cerebrospinal fluid exposure within the most efficacious range of preclinical doses (1–10 mg/kg). The 4-week duration of the study was selected based on available toxicology data.[11]

Figure 1. Study Schematic



QD=once daily; pDPN=painful diabetic peripheral neuropathy

OBJECTIVES

- To evaluate in patients with DPN the effects of multiple dose levels of NYX-2925 vs. placebo on
  - treatment of neuropathic pain associated with DPN
  - pain characteristics and sleep interference
  - safety and tolerability

METHODS

Study Design and Masking

- Phase 2, randomized, double-blind, placebo-controlled study
- Dosing was once daily x 4 weeks
- One allowable concomitant analgesic medication for DPN-associated neuropathic pain was permitted; dose must have been stable for ≥30 days before screening, with no change during the study.
- In addition to customarily used blinding principles, to reduce potential bias, study personnel and study subjects were masked to treatment assignment, number of active treatment arms, NYX-2925 dose levels, and randomization criteria with regard to pain scores and diary compliance requirements.
- Daily pain scores and diary compliance data were transferred into an interactive response technology system for eligibility determination using a protocol-defined proprietary algorithm. Using masked, pre-set criteria, subjects were either randomized or determined to be screen failures.

Key eligibility criteria

- Adults (18–75 years of age) with a diagnosis of type 2 diabetes
- Diabetic peripheral neuropathy, of symmetrical nature and in lower extremities for ≥6 months to ≤10 years, with a score of ≥3 on the Michigan Neuropathy Screening Instrument
- Score of ≥4 and ≤9 on the 11-point numerical rating scale (NRS) over the 24 hours prior to the Screening visit
- Mean daily average pain intensity score during the 7 (±1) days prior to randomization within the protocol-defined proprietary algorithm and adequate compliance with daily diary
- No concurrent major cardiovascular, renal, hepatic, psychiatric, or neurologic disorders

Pre-defined Endpoints

Primary: Change in NRS score assessing average (avg) pain intensity over the past 24 hours from baseline (avg Days -7 to -1) to Week 4 (avg Days 22–28)

Key Secondary:

- Change in NRS score from baseline (avg Days -7 to -1) to each treatment week (avg Days 1–7, 8–14, 15–21, 22–28) assessing:
  - average pain intensity
  - worst pain intensity
  - average pain upon walking intensity
  - average pain intensity for subjects not taking concomitant analgesic medication
- Change in Daily Sleep Interference Scale (DSIS) score from baseline to each treatment week

Select Post-hoc Endpoints

- Change in NRS score assessing average pain intensity over the past 24 hours from baseline to each treatment week in subjects with a ≥4-year history of DPN
- Change in DSIS score from baseline to each treatment week for subjects:
  - not taking concomitant analgesic medication
  - with a ≥4-year history of DPN

Statistical Analysis

- Efficacy population (primary analysis population), defined as all randomized subjects in the safety population with at least 4 post-baseline daily NRS scores assessing average pain intensity or at least 1 post-baseline visit
- Safety population, defined as all subjects who were dispensed study drug and did not return all study drug at their next visit
- A mixed model repeated measures analysis of variance was used to assess treatment differences. The model included factors for study site, treatment, week, and the treatment-by-week interaction, with baseline value as a covariate.
- All statistical tests were two-sided and tested at the 5% level, and data were analyzed using SAS version 9.4.

RESULTS

Table 1. Baseline Demographics and Characteristics (Efficacy Population)

	NYX-2925 10 mg N=77	NYX-2925 50 mg N=77	NYX-2925 200 mg N=74	Placebo N=72
Age, yrs	58.0 (8.4)	59.1 (8.4)	59.5 (7.5)	56.6 (9.2)
Males, n (%)	45 (58.4)	40 (51.9)	44 (59.5)	35 (48.6)
Race, n (%)				
White	55 (71.4)	53 (68.8)	54 (73.0)	53 (73.6)
African-American	18 (23.4)	20 (26.0)	17 (23.0)	15 (20.8)
Other	4 (5.2)	4 (5.2)	3 (4.1)	4 (5.6)
Not Hispanic or Latino, n (%)	50 (64.9)	47 (61.0)	44 (59.5)	44 (61.1)
Weight, kg	90.0 (13.9)	88.0 (14.3)	90.8 (14.4)	90.6 (17.6)
BMI, kg/m^2	31.0 (3.4)	30.9 (3.9)	31.0 (4.3)	30.9 (4.5)
History of type 2 diabetes, yrs	10.6 (7.2)	11.4 (7.9)	11.0 (7.2)	11.0 (7.5)
History of DPN, lower extremities, yrs	3.9 (2.5)	3.5 (2.6)	4.0 (2.7)	3.9 (2.4)
Pain intensity NRS score[a]	6.4 (1.0)	6.5 (1.0)	6.5 (1.0)	6.2 (0.9)
DSIS score[a]	5.9 (1.6)	6.0 (1.8)	5.8 (1.7)	5.5 (1.8)
Concomitant Analgesic Medications, n (%)[b]	42 (54.5)	36 (46.8)	38 (50.7)[c]	36 (50.0)
Gabapentin	31 (40.3)	28 (36.4)	30 (40.0)[c]	31 (43.1)
Pregabalin	7 (9.1)	3 (3.9)	5 (6.7)[c]	3 (4.2)
Duloxetine	1 (1.3)	3 (3.9)	1 (1.3)[c]	2 (2.8)
Other	5 (6.5)	4 (5.2)	2 (2.7)[c]	0

Data are mean (standard deviation), unless otherwise noted. BMI=body mass index; DPN=diabetic peripheral neuropathy; DSIS=11-point daily sleep interference scale (where 0=did not interfere with sleep and 10=completely interfered with sleep/unable to sleep due to pain); NRS=11-point numerical rating scale (where 0=no pain and 10=worst pain imaginable).
[a]Baseline scores shown are the average of Day -7 to Day -1.
[b]Data are from the safety population; N=75 for the NYX-2925 200 mg group.

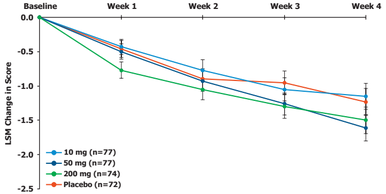
Table 2. Most Common Treatment-Emergent Adverse Events (TEAEs)[a] (Safety Population)

	NYX-2925 (Pooled) N=229	Placebo N=72
	Number of Subjects (%)	
At least one TEAE	49 (21.4)	15 (20.8)
At least one related TEAE	11 (4.8)	5 (6.9)
At least one serious TEAE	0	1 (1.4)
TEAEs leading to study discontinuation	1 (0.4)	2 (2.8)
Preferred Term		
Headache	6 (2.6)	3 (4.2)
Diarrhoea	5 (2.2)	1 (1.4)
Upper respiratory tract infection	4 (1.7)	0
Alanine aminotransferase increased[b]	3 (1.3)	0
Back pain	3 (1.3)	0
Arthralgia	2 (0.9)	0
Hypertension	2 (0.9)	0
Nasopharyngitis	2 (0.9)	0
Urinary tract infection	2 (0.9)	0

[a]TEAEs reported in at least 2 subjects for the pooled NYX-2925 group.
[b]All events were of mild intensity and none caused study discontinuation.

- The majority of all subjects with TEAEs had events that were mild or moderate in severity (98.0% [48/49] for NYX-2925 and 93.3% [14/15] for placebo).

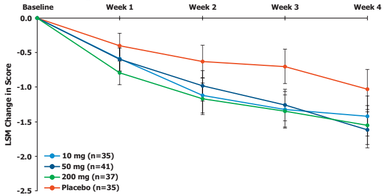
Figure 2. Mean Change in NRS Score Assessing Average Pain Intensity in the Past 24 Hours from Baseline to Each Treatment Week (Efficacy Population)



LSM=least squares mean; error bars represent standard error of the mean.

- There were no significant differences in average pain intensity between NYX-2925 and placebo at any measured timepoint, including Week 4 (primary endpoint).
- In addition, there were no significant differences in worst pain intensity or pain on walking between NYX-2925 and placebo at any measured timepoint.

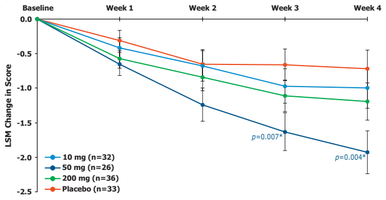
Figure 3. Mean Change in NRS Score Assessing Average Pain Intensity in the Past 24 Hours from Baseline to Each Treatment Week in Subjects not Taking a Concomitant Analgesic Medication



LSM=least squares mean; error bars represent standard error of the mean.

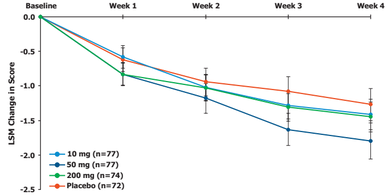
- Larger effect seen in all NYX-2925 dose groups for subjects not taking a concomitant analgesic medication vs. total efficacy population
- 50% of subjects were taking a concomitant analgesic medication, and of these approximately 79% was gabapentin.

Figure 4. Mean Change in NRS Score Assessing Average Pain Intensity in the Past 24 Hours from Baseline to Each Treatment Week in Subjects with DPN ≥4 Years (Post-Hoc Endpoint)



LSM=least squares mean; error bars represent standard error of the mean.
* p-value indicates significance vs. placebo

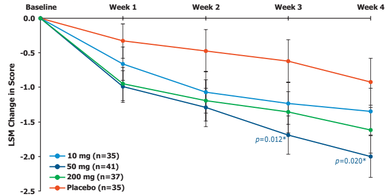
Figure 5. Mean Change in Daily Sleep Interference Scale Score from Baseline to Each Treatment Week (Efficacy Population)



LSM=least squares mean; error bars represent standard error of the mean.

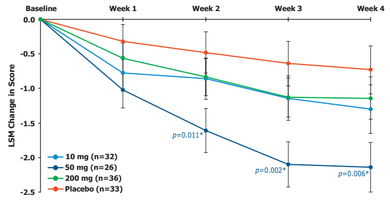
- Sleep interference due to pain showed a trend toward improvement for NYX-2925 50 mg.

Figure 6. Mean Change in Daily Sleep Interference Scale Score from Baseline to Each Treatment Week in Subjects not Taking a Concomitant Analgesic Medication (Post-Hoc Endpoint)



LSM=least squares mean; error bars represent standard error of the mean.
* p-value indicates significance vs. placebo

Figure 7. Mean Change in Daily Sleep Interference Scale Score from Baseline to Each Treatment Week in Subjects with DPN ≥4 Years (Post-Hoc Endpoint)



LSM=least squares mean; error bars represent standard error of the mean.
* p-value indicates significance vs. placebo

SUMMARY

- This first-in-patient study in subjects with DPN explored a wide (20-fold) dose range.
- The overall adverse event rate was similar between NYX-2925 and placebo. TEAEs were mild or moderate in 98% of NYX-2925 subjects, and no subjects receiving NYX-2925 reported any serious adverse events.
- In general, differences between NYX-2925 and placebo with regard to the changes in pain scores over the 4-week treatment period across the efficacy population did not achieve statistical significance.
- Certain pre-specified and post-hoc subgroups demonstrated clinical improvements in average daily pain intensity as well as nighttime pain causing sleep interference, and significant findings were most consistently limited to the NYX-2925 50 mg dose group:
  - subjects not taking concomitant analgesic medication
  - subjects with ≥4 years of DPN
- The group of subjects who reported a longer duration of DPN exhibited a better response to treatment, which aligns with the hypothesized mechanism of action of NYX-2925.

CONCLUSIONS

- NYX-2925 was safe and well-tolerated in this first-in-patient, proof-of-concept study in subjects with DPN.
- Although the pre-specified primary endpoint was not met, post-hoc analyses indicate that NYX-2925 has antinociceptive potential and may alleviate neuropathic pain in patients with advanced disease.
- Future studies would employ a longer treatment period, and focus on patients with advanced DPN who have persistent complaints of neuropathic pain and are not using concomitant analgesic medications.

References

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