APTINYX

Nasdaq: APTX

Innovative Therapies for Disorders of the Brain and Nervous System

Discovering and Developing Novel Small-Molecule NMDAr Modulators

June 2019

Forward-looking statements

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Clinical-stage biopharmaceutical company developing transformative NMDA receptor-modulating therapies

VALIDATED TECHNOLOGY
with differentiated science & mechanism

TARGETING RELEVANT DISEASE AREAS
with significant unmet need & commercial opportunity

POSITIVE HUMAN DATA
in Phase 1 & Phase 2 clinical studies

CLINICAL MILESTONES IN NEXT 12-18 MONTHS
across multiple compounds & indications

ROBUST IP
through internal innovation & proprietary platform

PRODUCTIVE COLLABORATION
with Allergan

WELL-FUNDED & BACKED
by highly regarded healthcare investors

PROVEN TEAM WITH EXPERTISE & SUCCESS
across pharma value chain

Chronic Pain

- Affects up to **100mm people** in the U.S.
- Current therapies have **limited efficacy** and substantial **side effects**
- Market leading therapies have significant drawbacks, yet have garnered **>$5bn** in annual revenues each
- Significant **abuse liability**

PTSD

- **~8.5mm** people suffering from PTSD in the U.S.
- Caused by **numerous trauma types** and **underdiagnosed**
- Elevated **suicide risk**
- Often with simultaneous **addiction or drug abuse**
- **Only 2 approved therapies,** both approved **10+ years ago**

Parkinson's Cognitive Impairment

- Affects up to **500k people** in the U.S.
- **50% of those with Parkinson's** have some cognitive impairment
- Significant disease burden on **patients and caregivers**
- **Only 1 approved therapy** with limited efficacy in PD

Aptinyx is developing innovative therapies in large therapeutic areas with significant unmet need

Multiple clinical-stage development programs across various CNS indications

	Indication	Phase 1	Phase 2	Phase 3	Est. U.S. Prevalence	Next Milestone
NYX-2925	Painful Diabetic Peripheral Neuropathy				~5.5mm	Phase 2b in advanced DPN patients
	Fibromyalgia				~5mm	Phase 2b in fibromyalgia patients
NYX-783	Post-Traumatic Stress Disorder				~8.5mm	Phase 2 data expected 1H 2020
NYX-458	Parkinson's Disease Cognitive Impairment				~500k	Phase 2 in PD cognitive impairment

Additional Program from Our Discovery Platform

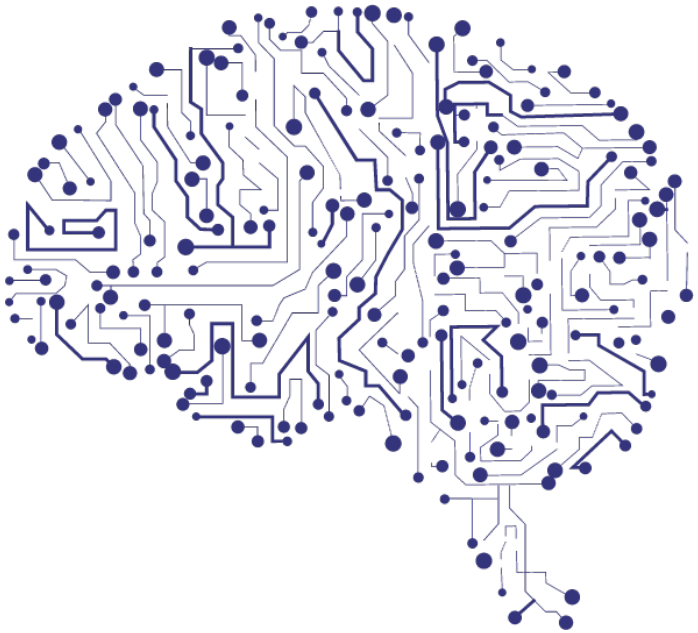
	Indication	Partner	Details
AGN-241751	Major Depressive Disorder	Allergan	Acquired by Allergan via exercise of option under ongoing research collaboration. No further economic consideration to Aptinyx associated with future development.

Three product candidates in clinical development by Aptinyx for various CNS disorders – with INDs in all three CNS divisions of FDA

NMDA receptor has been a target of interest to drug developers for decades

NMDA receptors are vital to normal brain physiology and abnormal NMDAr function underpins numerous CNS diseases

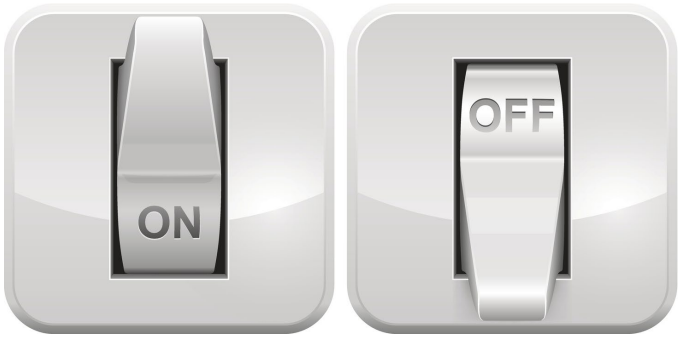
- Chronic Pain
- Alzheimer's Disease
- Depression
- PTSD
- Traumatic Brain Injury
- Autism Spectrum Disorders



- Dementia
- Schizophrenia
- Huntington's Disease
- Cerebral Ischemia
- Cognitive Impairment
- Anti-NMDAr Encephalitis
- Parkinson's Disease

<u>But</u>, NMDAr-targeted drugs discovered to date (largely inhibitors, e.g., PCP, ketamine) have significant limitations

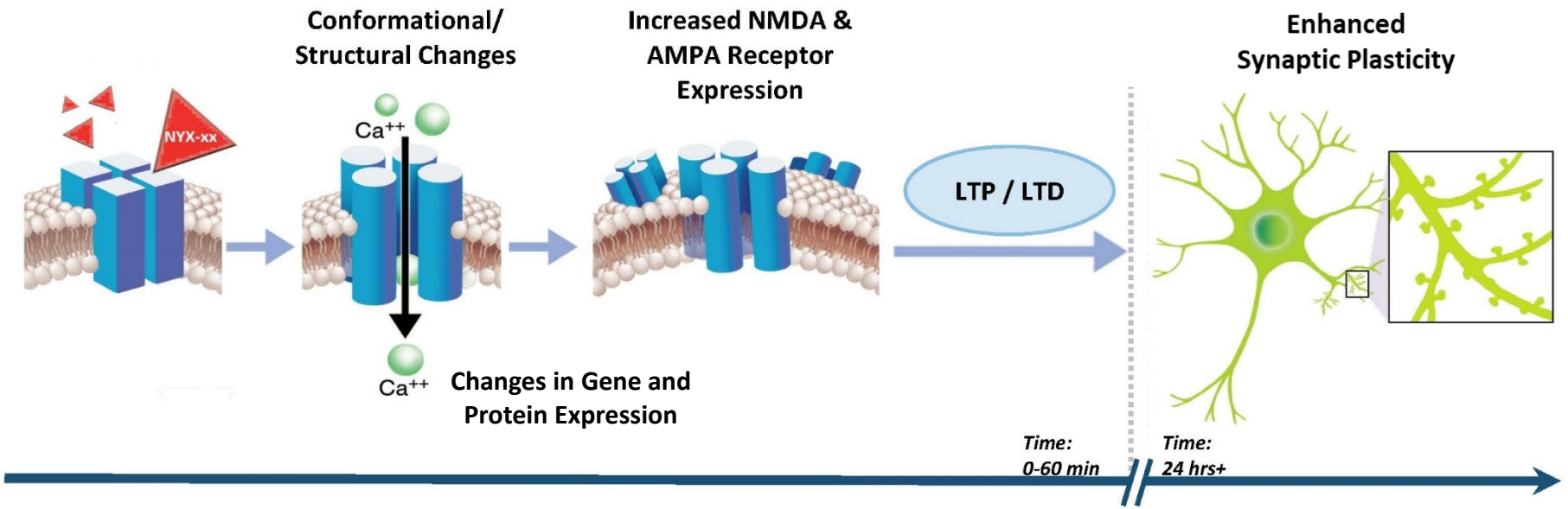
Modulation: a differentiated approach to targeting the NMDA receptor



VS.

Modulation of NMDAr enhances synaptic plasticity, the foundation of neural cell communication

NMDAr modulation triggers neurobiological cascade



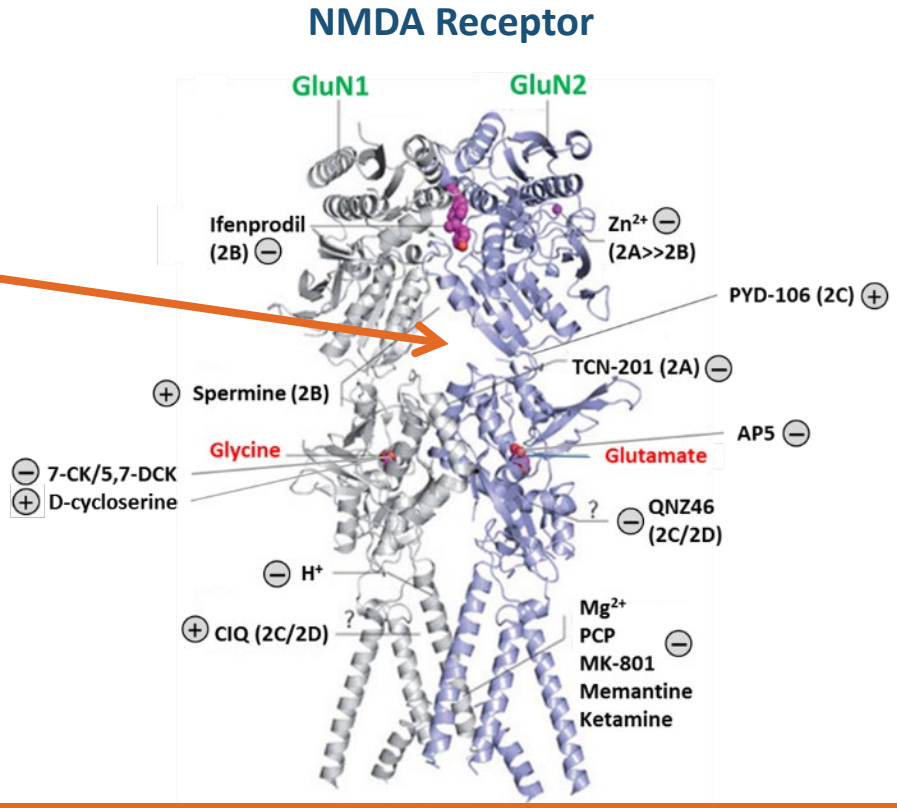
LTP = long-term potentiation
LTD = long-term depression

Rapid acting → **Long lasting**

Prolific output from Aptinyx small-molecule NMDAr modulator discovery platform

Molecules from the Aptinyx chemistry platform…

- stem from dozens of **novel chemical** scaffolds
- bind at a **novel, distinct, newly characterized binding domain**
- demonstrate **high oral bioavailability** and stability
- **are protected through 2034 and beyond** by Aptinyx **composition of matter patents** and patent applications
- have **diverse** potency, activity, subtype selectivity, and pharmacology/biology profiles



Over 1,000 unique, small-molecule NMDAr modulators designed and synthesized

Chronic pain represents a major healthcare and societal challenge

Current therapies have limited efficacy and significant drawbacks

Large market:
100 million people with chronic pain in the U.S.

Substantially underserved:
40-60% do not achieve even partial pain relief with current NP therapies

Cymbalta and **Lyrica** each have achieved **$5B+** in peak annual sales despite major limitations:

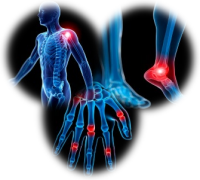
- Significant side effects
- Variable and marginal efficacy
- Compliance challenges due to burdensome dosing regimens

Significant **abuse liability**

NYX-2925 in Phase 2 clinical development for treatment of chronic pain

Synaptic plasticity mechanism targeting centralized chronic pain

Acute



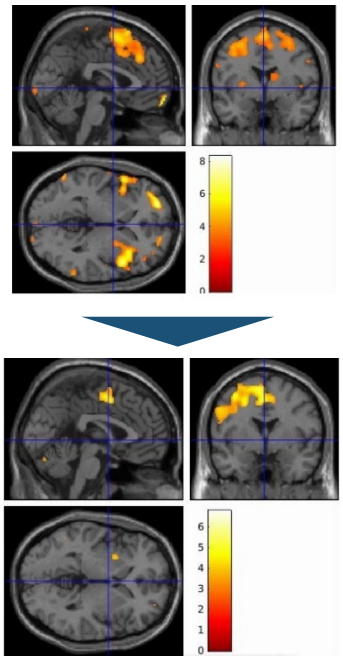
- Physiological
- Protective
- Externally caused
- Tissue damage
- Normal response
- Resolves with tissue healing

Centralization

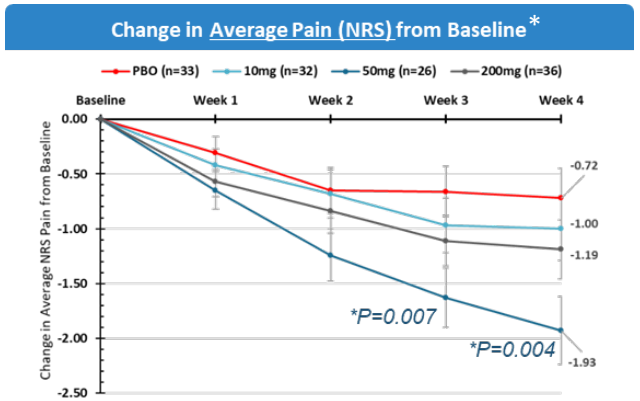
Chronic

- Pathological
- Non-protective
- Internally caused/less-clear insult
- CNS changes
- Abnormal response
- Broad range of enduring symptoms

Objective imaging demonstrates CNS activity on central pain processing



Clinical evidence of effects on patient-reported symptoms of chronic pain



- Mood
- Sleep
- Pain

NYX-2925 acts centrally to enhance synaptic plasticity…

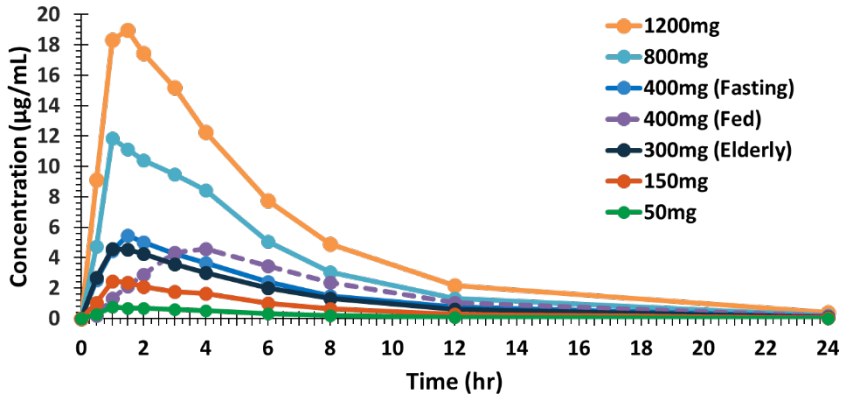
…has confirmed activity on pain processing biomarkers…

…and addresses numerous symptoms of chronic pain disorders

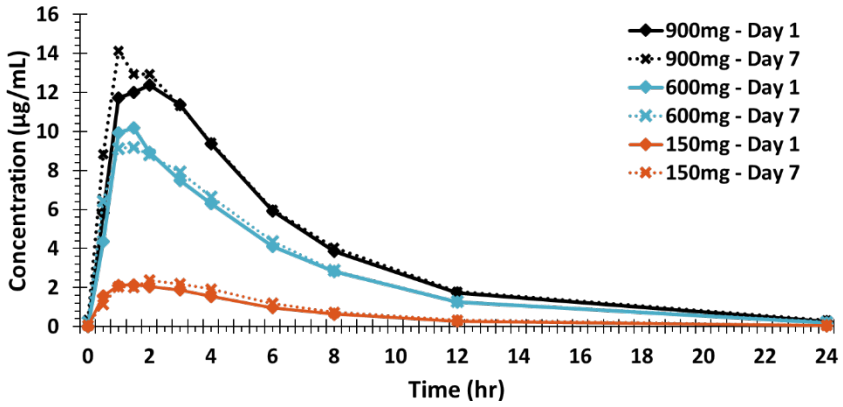
*Graph showing results from post-hoc analysis of Phase 2 DPN study in patients with advanced DPN (≥ 4yrs)

Favorable tolerability and dose-proportional PK of NYX-2925 observed in 84-subject Phase 1 study

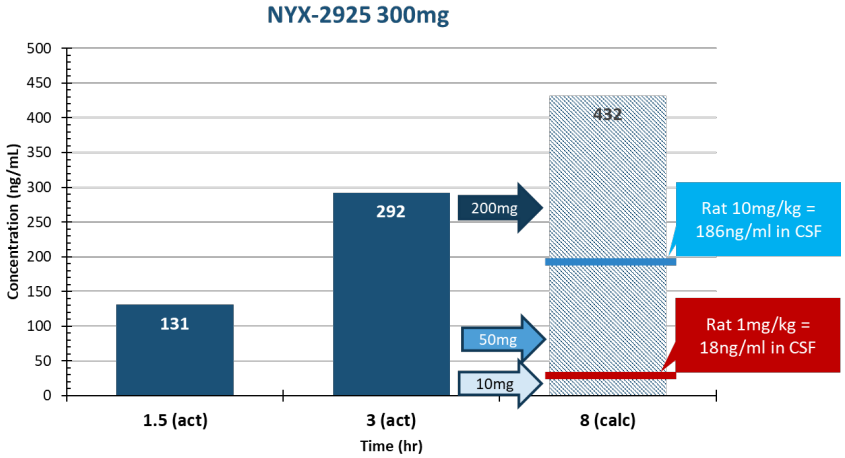
Single Ascending Dose Plasma PK



Multiple Ascending Dose Plasma PK



CSF Exposure



With single and repeat dosing…

- drug is cleared within 24 hours
- no significant accumulation after 7 daily doses
- AUC and Cmax are directly proportional to unit dose
- no impact on AUC in fed vs. fasted state
- brain exposure is ample and predictable
- no drug-related SAEs, even at very high doses
  - ✓ no dissociative side effects
  - ✓ no clinically significant changes in safety ECGs
  - ✓ no clinically significant changes in laboratory values

NYX-2925 has rapid, persistent, NMDAr-mediated pharmacodynamic effects in humans

Two exploratory studies in healthy volunteers:

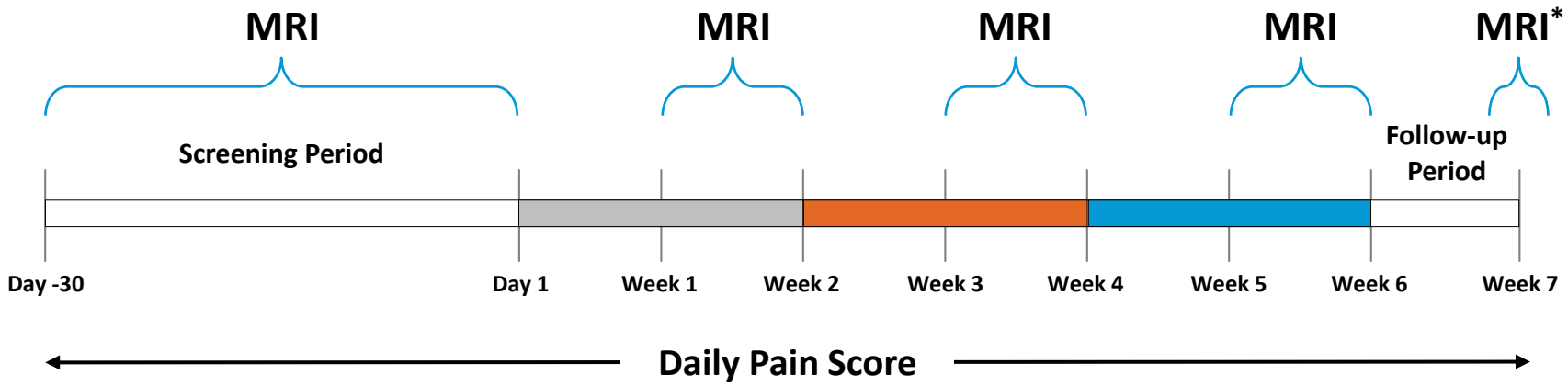
- Using EEG readings to measure NMDAr-mediated brain activity in response to auditory/sensory stimuli
- Using polysomnography to measure sleep parameters following sleep disruption

Studies demonstrated that, relative to placebo, a single dose of NYX-2925:

- ☑ Enhanced synaptic plasticity within 2 hours and enhanced stimulus processing for at least 7 days
- ☑ Enhanced overall sleep duration and non-REM sleep duration, without adversely affecting REM sleep

Human studies reinforced preclinical observations, demonstrating NYX-2925 target engagement and activity at doses consistent with those under evaluation in Phase 2

Phase 2 neuroimaging biomarker study of NYX-2925 in fibromyalgia patients



- Functional MRI conducted:
  - During screening period
  - During 2nd week of each phase of treatment
  - Optionally at follow-up visit

Legend:
- Placebo q.d.
- NYX-2925 20 mg q.d.
- NYX-2925 200 mg q.d.

Neuroimaging biomarker changes directly and objectively measure drug activity

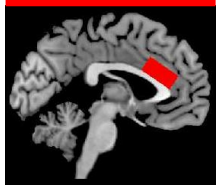
**MRI at follow-up visit was optional*

NYX-2925 significantly reduced connectivity and Glx levels in key pain-processing brain regions

Top-line fMRI Findings

- **NYX-2925 at 20mg and 200mg clearly reduced level of connectivity in the dorsal anterior cingulate cortex (dACC) and the posterior insular cortex (pINS)**

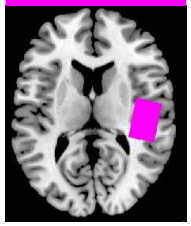
dACC:



Significantly reduced connectivity to:

- Right superior temporal gyrus ($P_{FWE} < 0.05$)
- Left premotor/ Primary somatosensory cortex ($P_{FWE} < 0.05$)
- Right precuneus – part of the DMN ($P_{FWE} < 0.05$)
- Left precentral gyrus/premotor cortex ($P_{FWE} < 0.05$)
- Right insula and left insula ($Uncorr.\ p < 0.001$)

pINS:



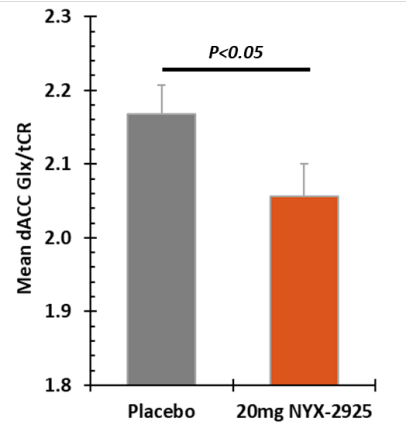
Significantly reduced connectivity to:

- Left dorsal acc ($SVC\ P_{FWE} < 0.05$)
- Right dorsal acc ($SVC\ P_{FWE} < 0.05$)

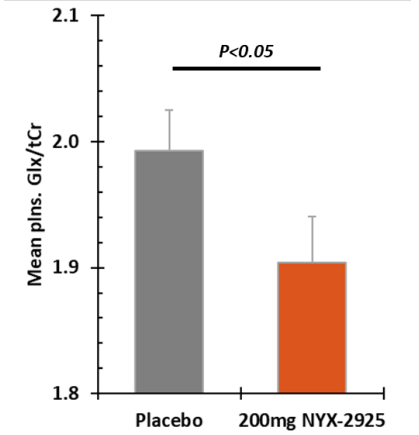
Top-line Glx/^{1}H-MRS* Findings

- **Increased Glx levels are associated with higher pain perception**
- **NYX-2925 reduced Glx levels, leading to pain alleviation**

dACC Glx Levels (Resting State)



pINS Glx Levels (Post-Evoked Pain)



Effects on objective biomarkers demonstrated clear activity on central pain processing in patients with chronic pain and were strongly correlated with effects on patient-reported measures

* ^{1}H-MRS = Proton magnetic resonance spectroscopy

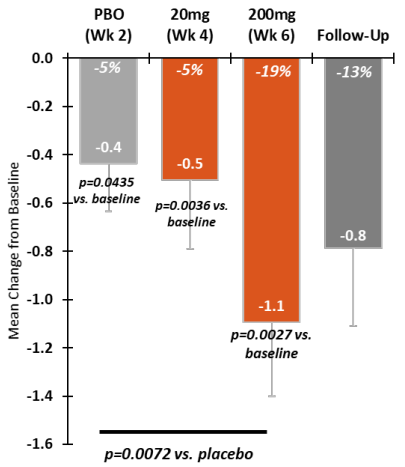
Notes: *p-values calculated using paired-t test based on individual changes from placebo (week 2) to 20mg (week 4) or 200mg (week 6)*
Error bars reflect standard error of mean
Glx/tCR = glutamate + glutamine normalized over total creatine

NYX-2925 had significant effects on patient-reported outcomes across broad spectrum of fibromyalgia symptoms

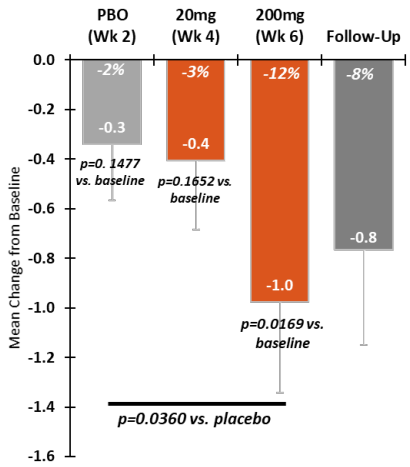
Pain Endpoints

Key QoL/Function Endpoints

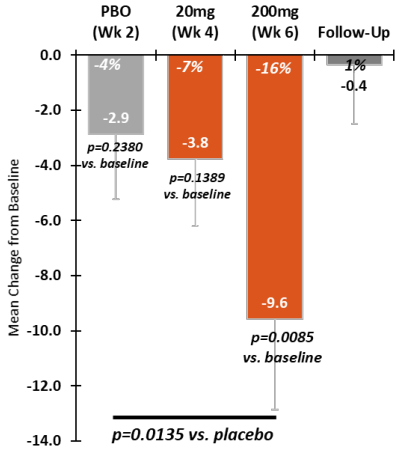
Average Daily Pain



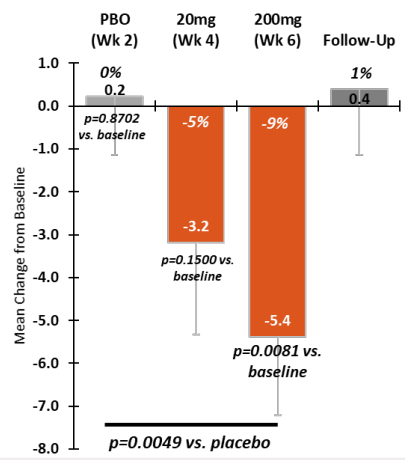
Worst Daily Pain



Total FIQR Score*



PROMIS$_{FM}$ Total Fatigue Profile Score**

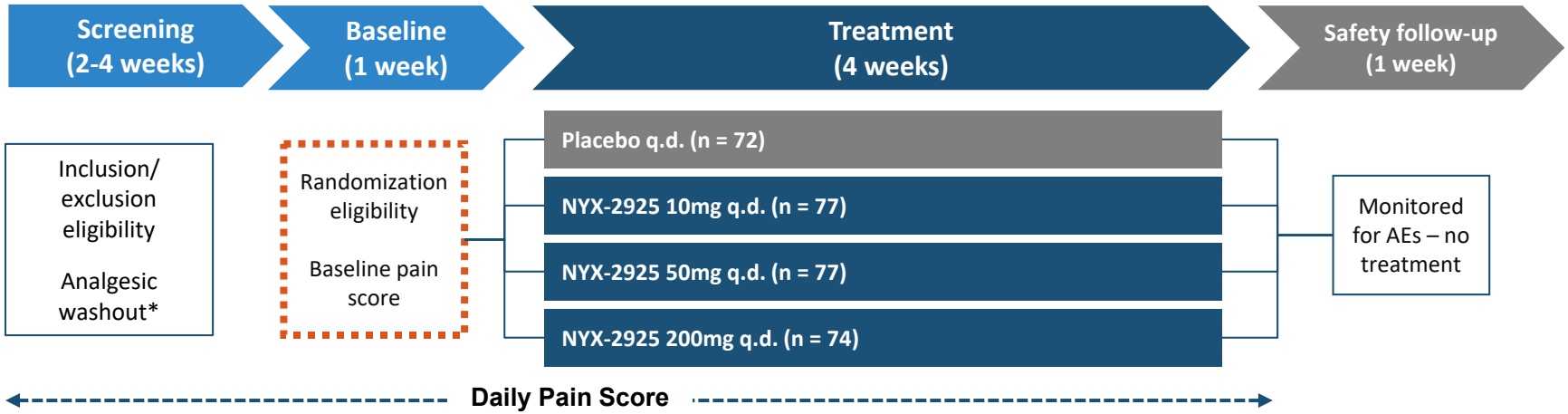


*Total FIQR reflects composite of Function, Overall Impact, and Symptom domain Scores

**Total Fatigue Profile Score reflects composite of Experience, Social Impact, Motivational Impact, and Cognitive Impact domain Scores

Notes: p-values calculated using paired-t test based on individual changes from baseline to each week or from placebo (week 2) to 200 mg (week 6)
Error bars reflect standard error of mean

Phase 2 study of NYX-2925 in patients with painful diabetic peripheral neuropathy (DPN)



*Patients were allowed to maintain stable dosing of 1 allowable concomitant analgesic

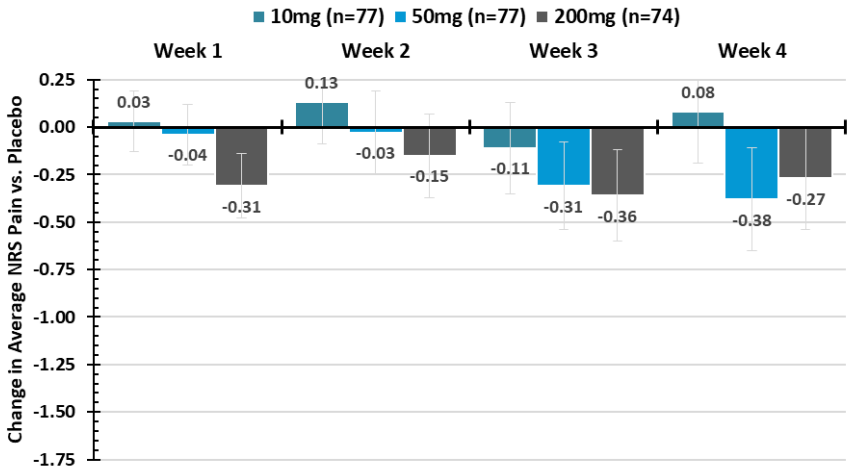
Key objectives of the study:

- Evaluate safety and tolerability of NYX-2925 in a DPN patient population
- Assess the most active dose level across a 20-fold dose range
- Assess activity of NYX-2925 across multiple endpoints relevant to chronic pain
- Identify key patient characteristics to inform inclusion/exclusion criteria for future studies

NYX-2925 showed numeric, but not statistically significant, separation from placebo on primary endpoint

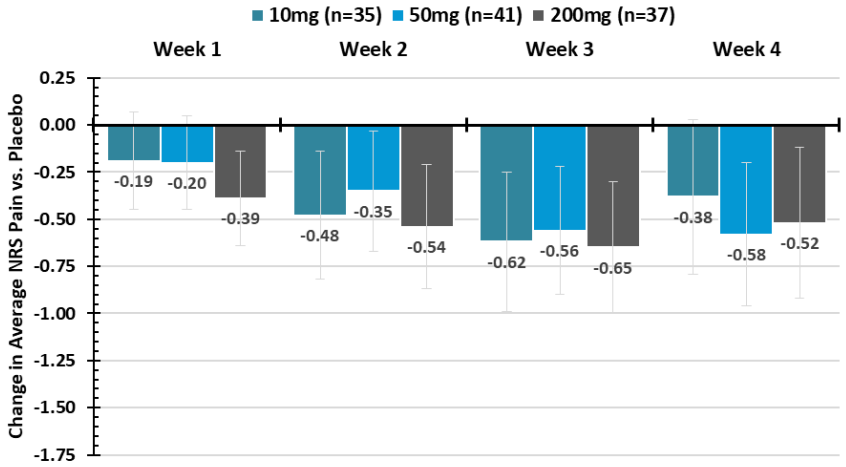
Change in average daily pain vs. placebo (primary efficacy endpoint)

Total efficacy population (N=300)



P-value vs. Placebo	Week 1	Week 2	Week 3	Week 4
10mg	0.853	0.562	0.655	0.770
50mg	0.787	0.895	0.188	0.159
200mg	0.064	0.487	0.132	0.315

Patients not using a concomitant analgesic med. (N=148)



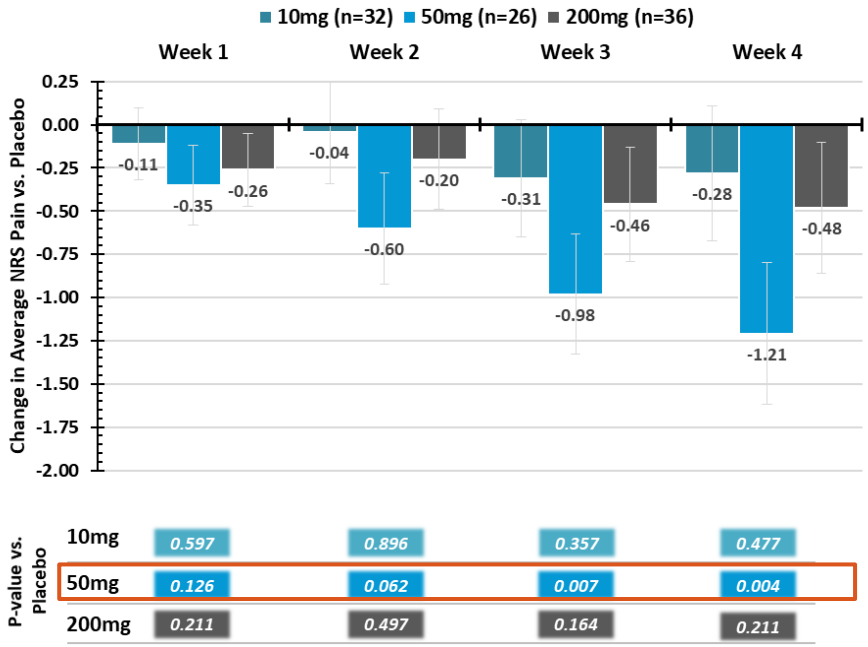
P-value vs. Placebo	Week 1	Week 2	Week 3	Week 4
10mg	0.459	0.164	0.094	0.351
50mg	0.413	0.281	0.104	0.131
200mg	0.120	0.109	0.069	0.198

Did not achieve statistically significant separation on primary endpoint in total study population; patients not using a concomitant analgesic showed much greater separation from placebo

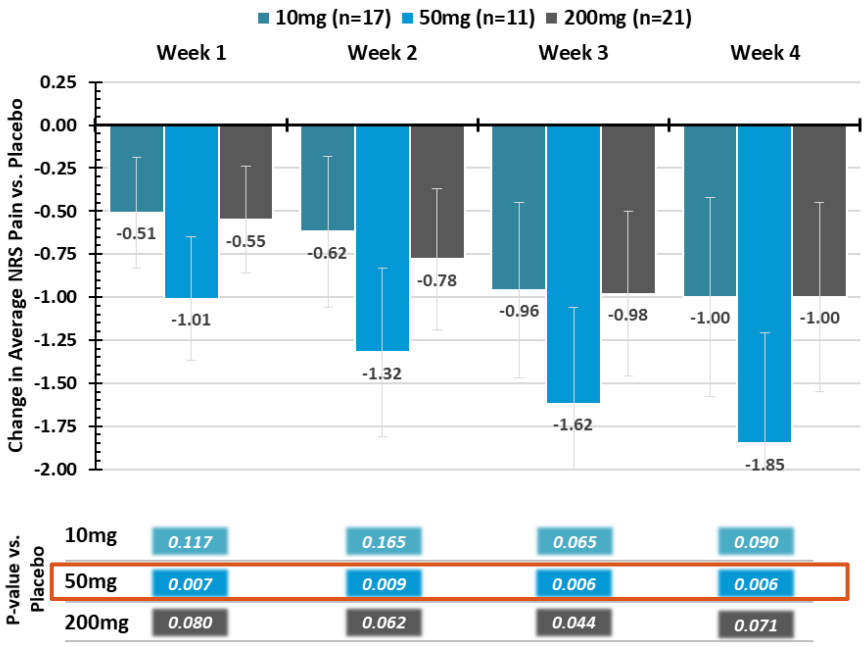
NYX-2925 showed significant effects in patients with advanced DPN, a large and mechanistically relevant patient sub-population

Change in average daily pain vs. placebo (primary efficacy endpoint)

Advanced DPN population (N=127)*



Advanced DPN population – No con. med. (N=64)*



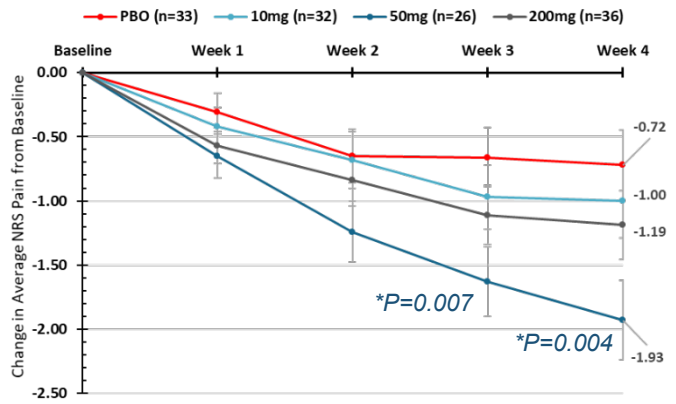
NYX-2925 exhibited robust and consistent effects across primary and secondary endpoints in patients with advanced DPN

*Post-hoc analysis of advanced DPN population includes patients who had DPN for ≥ 4 years

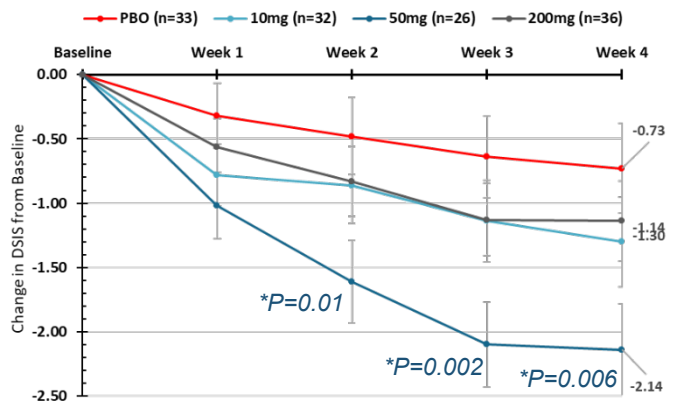
NYX-2925 showed consistent significant improvements, without plateau, across endpoints in advanced DPN population

Advanced DPN population (N=127)†

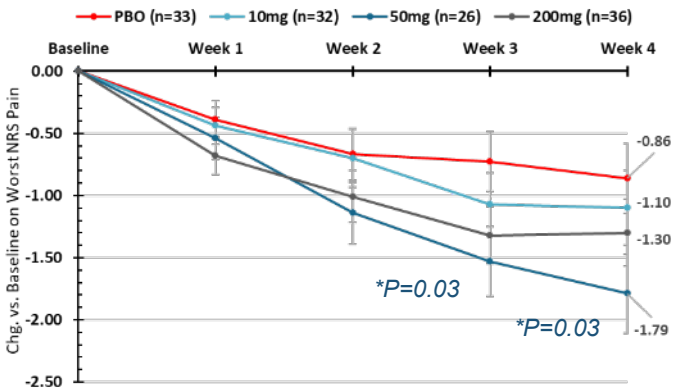
Change in Average Pain (NRS) from Baseline



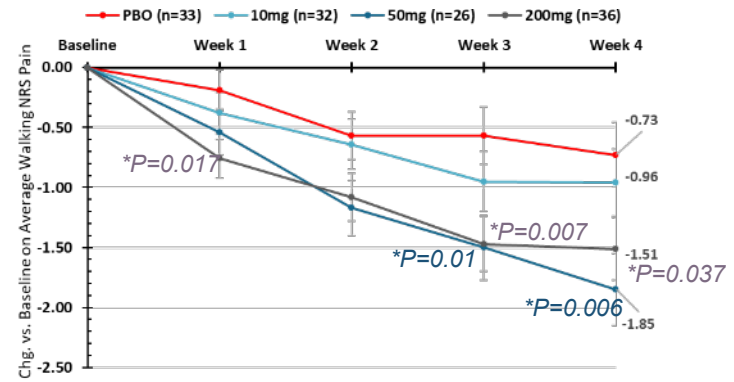
Change in Daily Sleep Interference Scale Score from Baseline



Change in Worst Pain (NRS) from Baseline



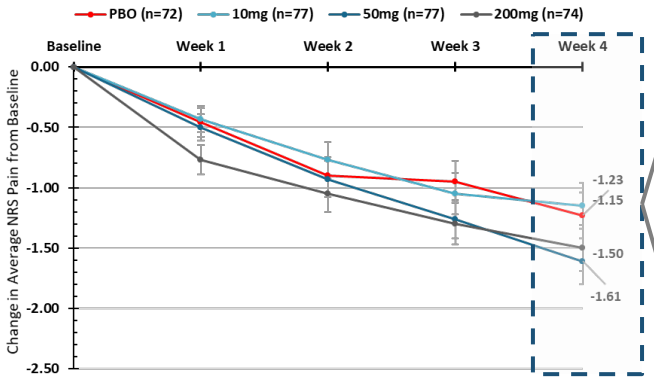
Change in Pain on Walking (NRS) Score from Baseline



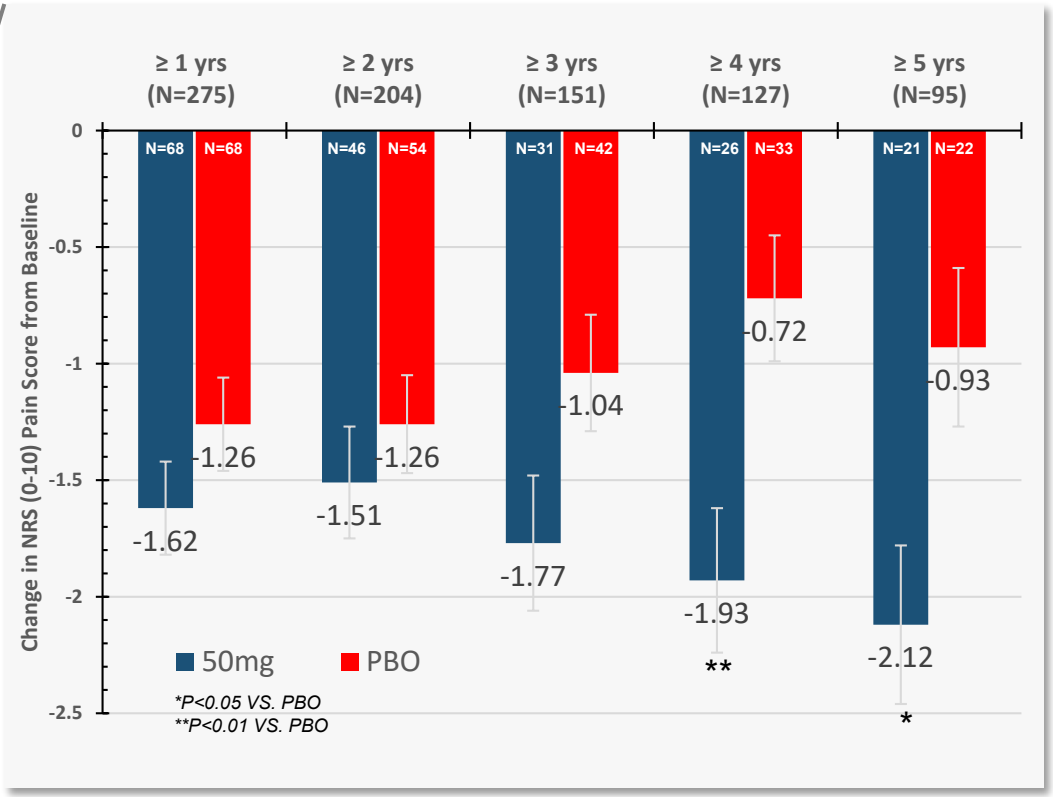
†*Post-hoc analysis of advanced DPN population includes patients who had DPN for ≥ 4 years*

Large and highly relevant sub-population identified based on mechanistic understanding and time-course of "chronification"

Change in Average Daily Pain – Total Study Pop.



Change in Average Daily Pain (Bsln to Wk 4) by Painful DPN Duration



In increasingly chronic patients, pain shifts from primarily peripheral sensory processing to more pronounced central manifestation – and NYX-2925 had increasingly greater effects

Note: Pain reduction by DPN duration is post-hoc analysis

Key study findings provide foundation for further development of NYX-2925 for painful DPN

- NYX-2925 was safe and well tolerated in the study no SAEs and an overall AE profile comparable to placebo
- Patients with advanced DPN showed the greatest treatment benefit
  - Mechanism of NYX-2925 addresses the increasing central manifestation of pain perception and processing associated with the prolonged chronic pain these patients experience
  - Patients with advanced DPN represented nearly half of the entire study population (N = 127)
- 50 mg identified as the most active dose level among the three doses tested
  - Evidence of inverted-U-shaped dose response, consistent with previous preclinical and clinical data with this mechanism
- In patients with advanced DPN, effect of 50 mg dose was robust and clinically meaningful
  - Week 4 change vs. baseline in average daily pain (on 10-point NRS) = 1.93 points ($p<0.0001$)
  - Week 4 change vs. placebo in average daily pain (on 10-point NRS) = 1.21 points ($p=0.004$)
- Robust improvements were consistent across primary and secondary endpoints
- Use of concomitant analgesic appears to confound treatment benefit of NYX-2925
  - Effects were even more pronounced in patients not on a concomitant analgesic medication
  - ~50% of patients were not on a con. med. → a study not allowing con. med use can likely be recruited

Based on study results, Aptinyx plans to initiate a Phase 2b study in advanced DPN patients in 2019

PTSD affects millions, is likely underdiagnosed, and is commonly associated with self-medication and substance abuse

Large market

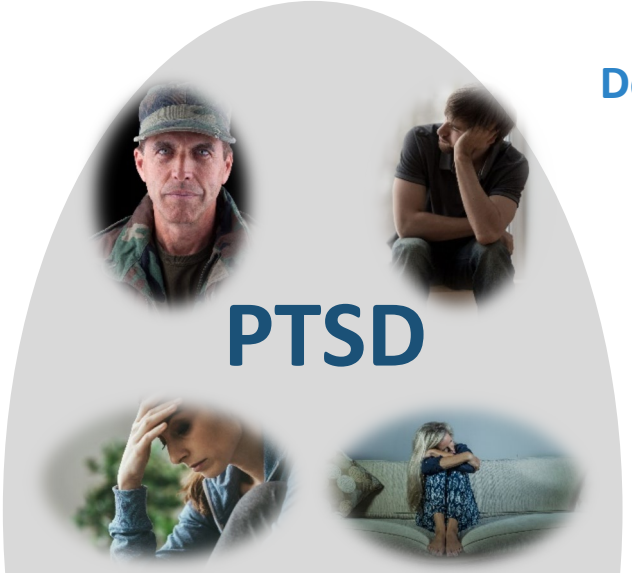
~8.5 million people suffering from PTSD in the U.S.

with an estimated lifetime prevalence of 4.7%

Limited effective therapy options

Only 2 currently approved therapies

both SSRI antidepressants with limited utility that were approved 10+ years ago



Numerous causes of PTSD

Car accidents

Criminal assault

War combat

Natural disaster

Sexual trauma

Detrimental comorbidities compound the medical and societal costs

Elevated suicide rates among PTSD suffers

~20 veterans or servicemembers die from suicide daily

50-66 % also battle simultaneous addiction

to alcohol and other drugs

NYX-783 in Phase 2 clinical development for the treatment of PTSD

Clear Mechanistic Rationale

- Learning and memory dysfunction is at the root of PTSD symptomatology
- D-cycloserine (DCS), an NMDAr modulator, has demonstrated effect in PTSD

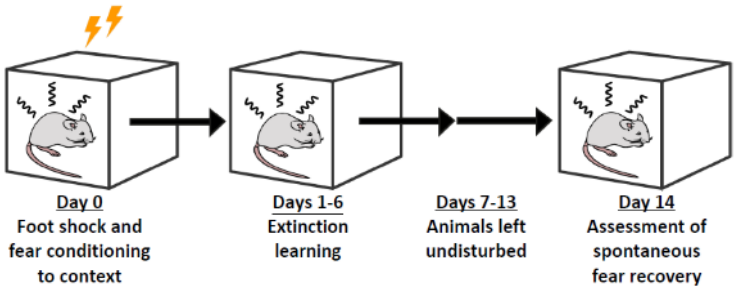
Significant Unmet Need

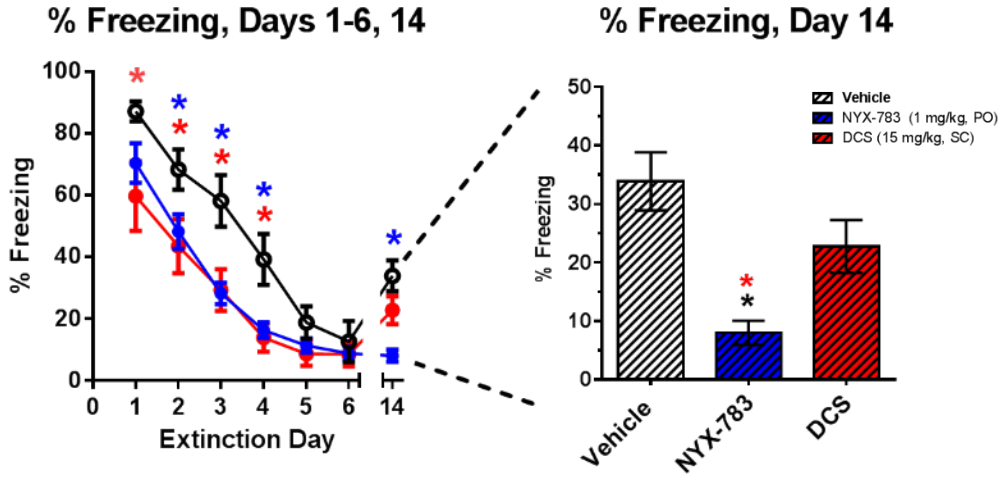
- Currently, only 2 FDA-approved therapies for PTSD: both SSRI antidepressants with limited efficacy
- Current therapies only target symptoms of PTSD
- Side effects limit utilization of some effective therapies

Strong Preclinical Evidence

Robust and long-lasting activity observed in model of fear extinction

Contextual Fear Conditioning Model

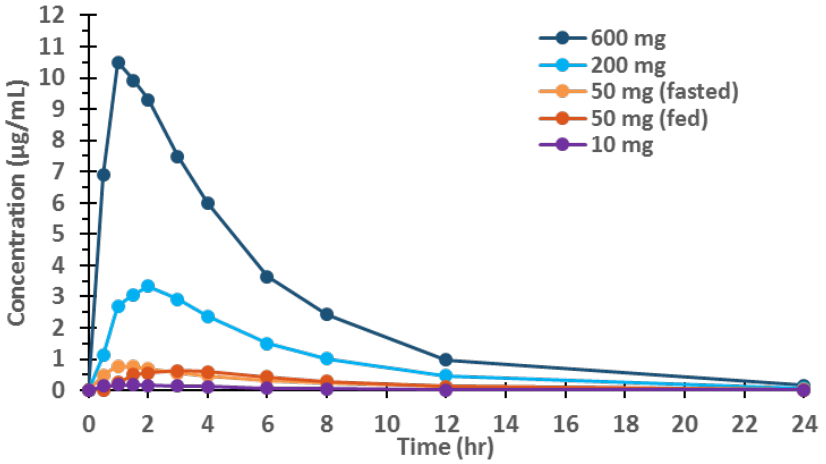




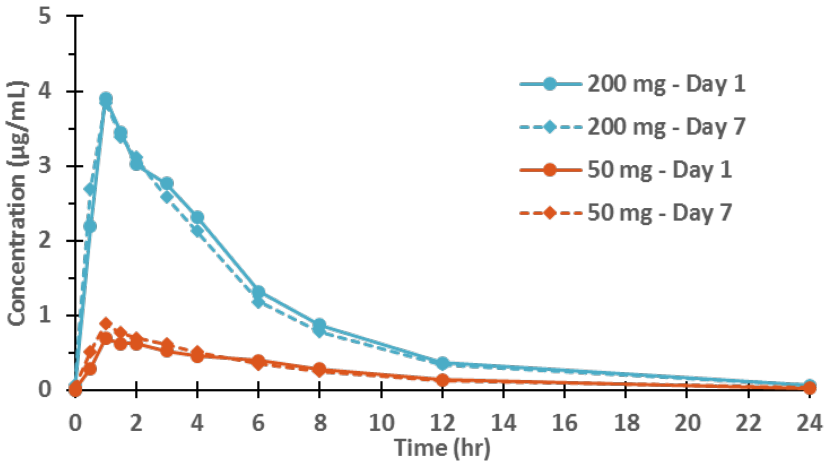
Preclinical evidence and clinical safety profile indicate the potential for NYX-783 to address significant unmet needs in the treatment of PTSD

Favorable safety and tolerability and dose-proportional PK of NYX-783 observed in 62-subject Phase 1 study

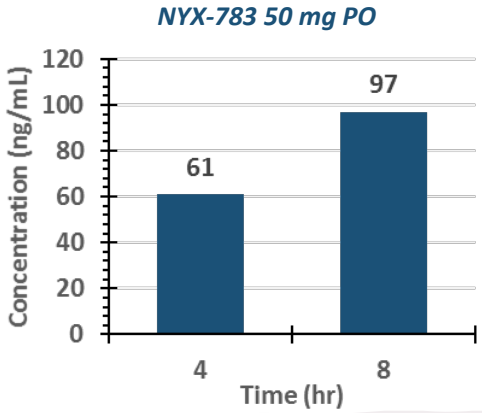
Single Ascending Dose Plasma PK



Multiple Ascending Dose Plasma PK



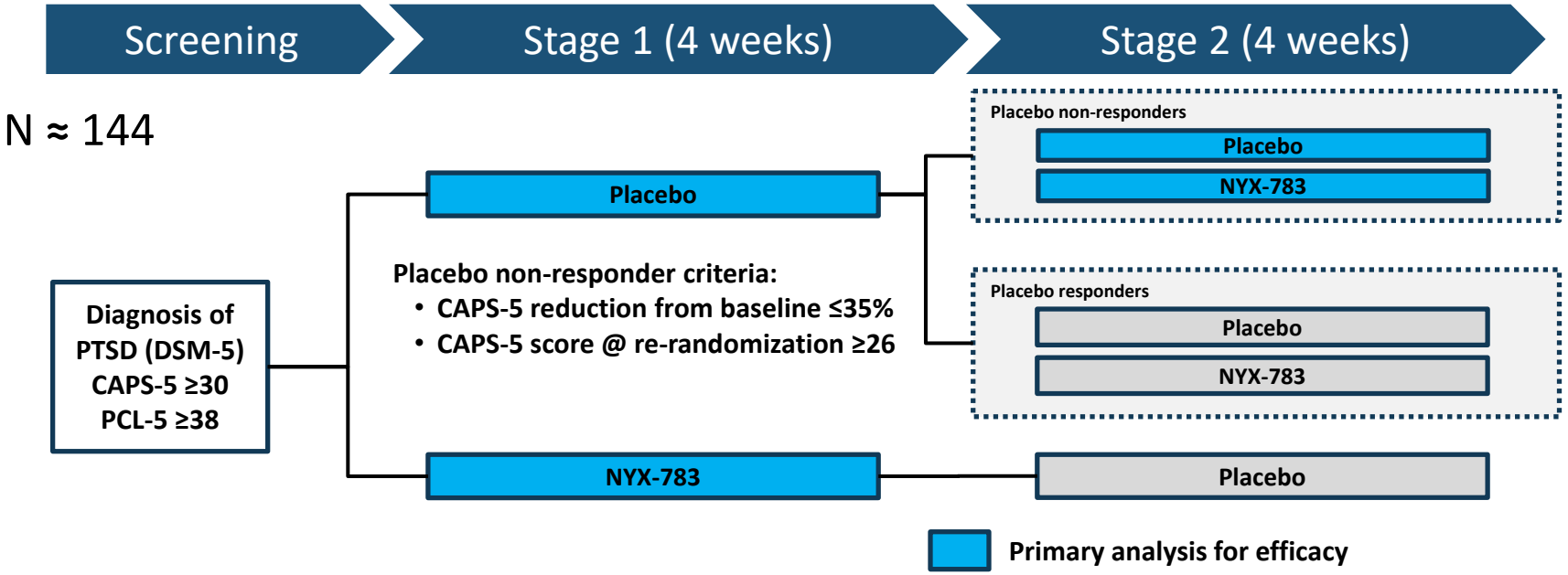
CSF Concentration



NYX-783 exhibits favorable tolerability and PK properties:

- Predictable and dose-proportional PK
- Cleared from plasma in 24 hrs.
- No accumulation with repeat dosing
- No apparent impact on AUC in “fed” state
- Ample, predictable brain exposure
- No SAEs at any dose tested

First-in-patient Phase 2 study of NYX-783 in patients with post-traumatic stress disorder



- Evaluating effects of NYX-783 on PTSD symptoms using multiple endpoints
- Outcome of study to inform most appropriate enrollment criteria and endpoints for future studies

Data from this first-in-patient Phase 2 study expected 1H 2020

CAPS-5 (Clinician Administered PTSD Scale – DSM 5th Edition)
PCL-5 (PTSD Checklist – DSM 5th Edition)

Vast unmet need in Parkinson's disease cognitive impairment despite significant disease burden

~1 million

people suffering from Parkinson's disease in the U.S.

~500k

~250k with MCI
~250k with dementia

50%+

of those with Parkinson's Disease have some form of cognitive impairment

1

therapy approved to date, Exelon®, which is minimally efficacious in PD patients

NYX-458 in clinical development for the treatment of cognitive impairment associated with Parkinson's disease

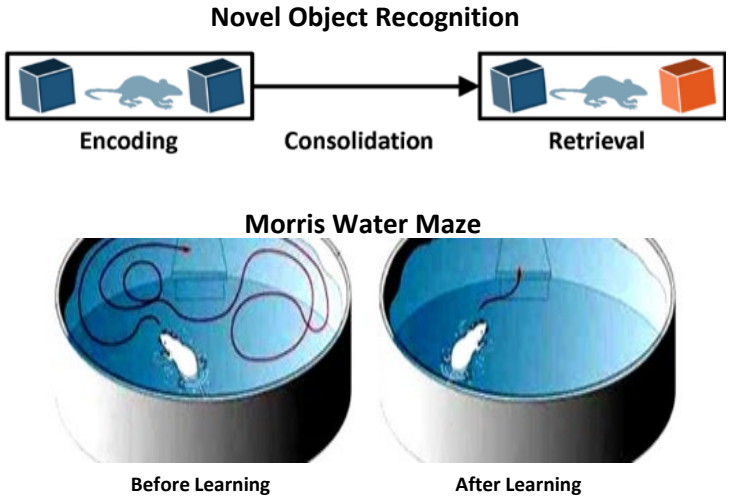
Clear Mechanistic Rationale

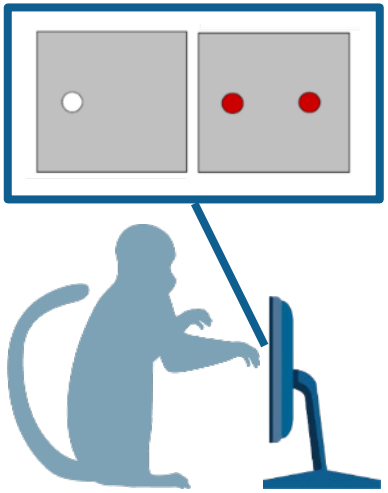
- Synaptic plasticity and LTP – both enhanced by NYX-458 – play key roles in learning and memory
- NMDAr dysregulation and dysfunction caused by neuronal loss (dopamine neurons in Parkinson's)

Substantial Opportunity

- Significant unmet need
- Concentrated patient and prescriber base
- Attractive potential follow-on indications in a number of cognitive disorders

Strong Preclinical Evidence

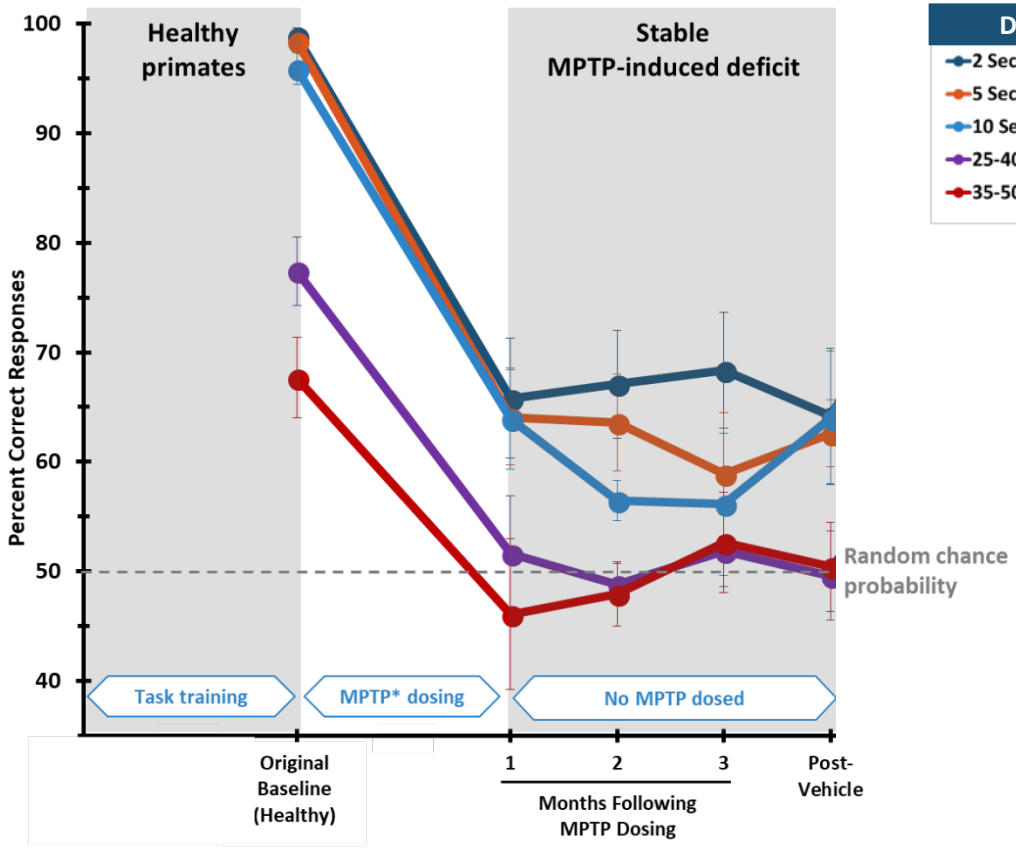




Robust effects on cognition in preclinical models support development in Parkinson's disease cognitive impairment

NYX-458 demonstrated long-lasting activity in non-human primate model of Parkinson's cognitive impairment

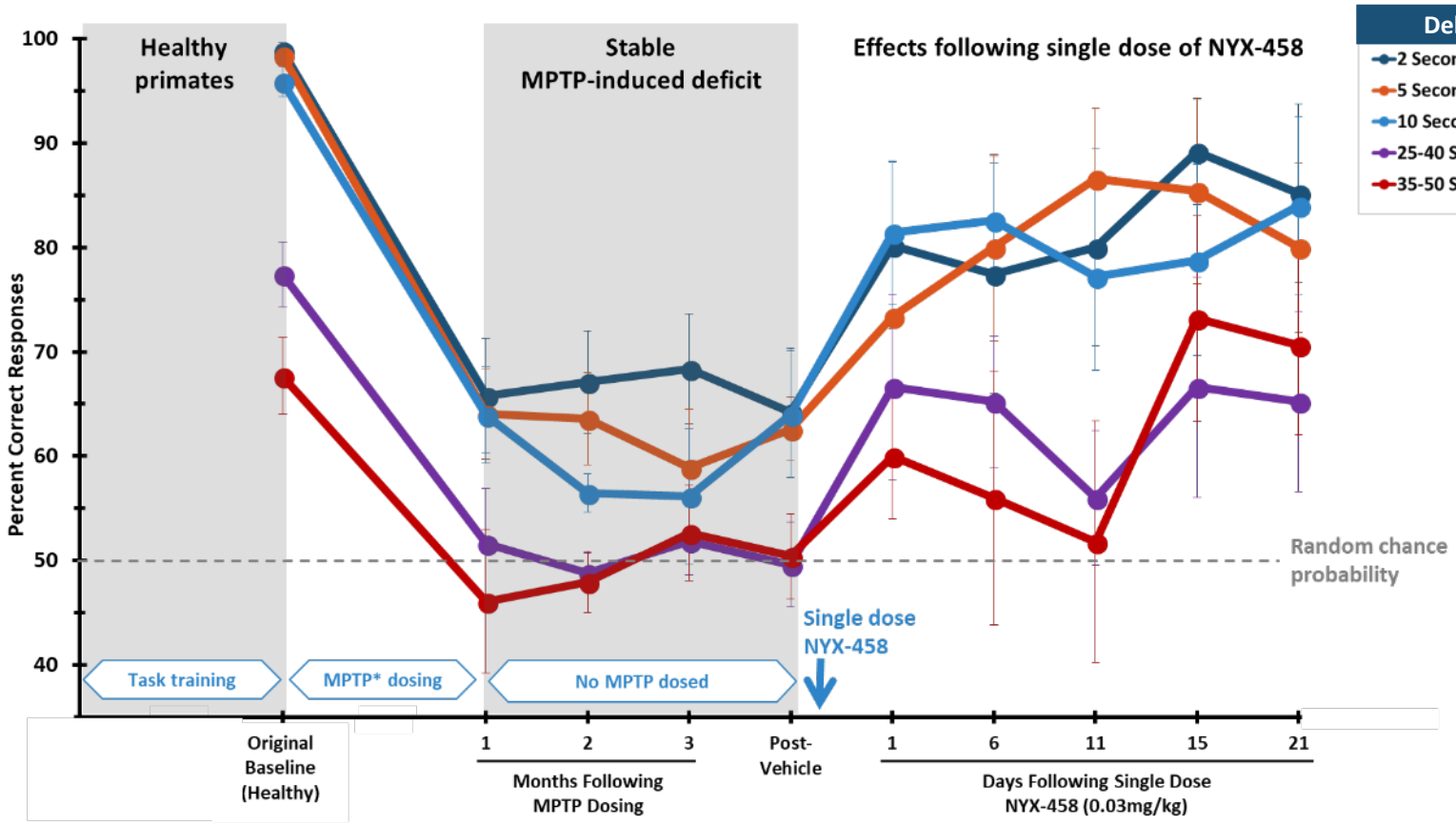
Variable Delayed Response



*MPTP is a neurotoxin employed to deplete dopamine-related neural cells -- similar to the way Parkinson's disease does in humans

NYX-458 demonstrated long-lasting activity in non-human primate model of Parkinson's cognitive impairment

Variable Delayed Response

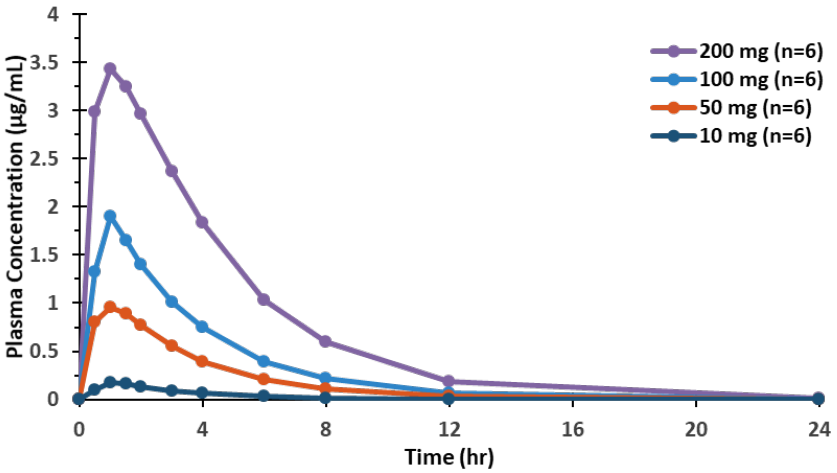


Results demonstrated robust effects on cognitive function and support development in PD and a number of other cognitive disorders

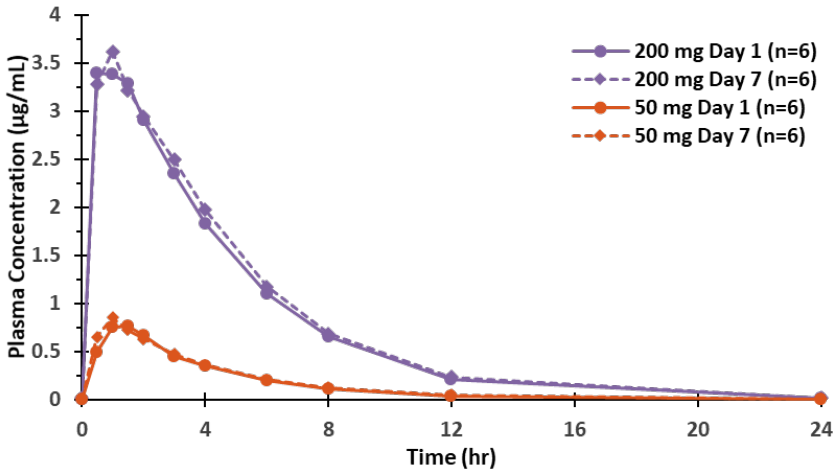
**MPTP is a neurotoxin employed to deplete dopamine-related neural cells -- similar to the way Parkinson's disease does in humans*

Favorable safety and tolerability and dose-proportional PK of NYX-458 observed in 62-subject Phase 1 study

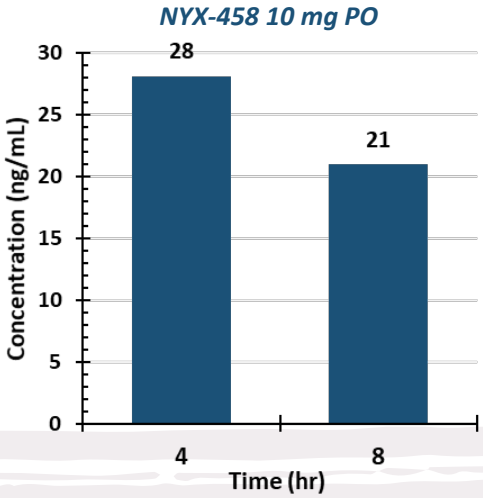
Single Ascending Dose Plasma PK



Multiple Ascending Dose Plasma PK



CSF Concentration



NYX-458 exhibits favorable tolerability and PK properties:

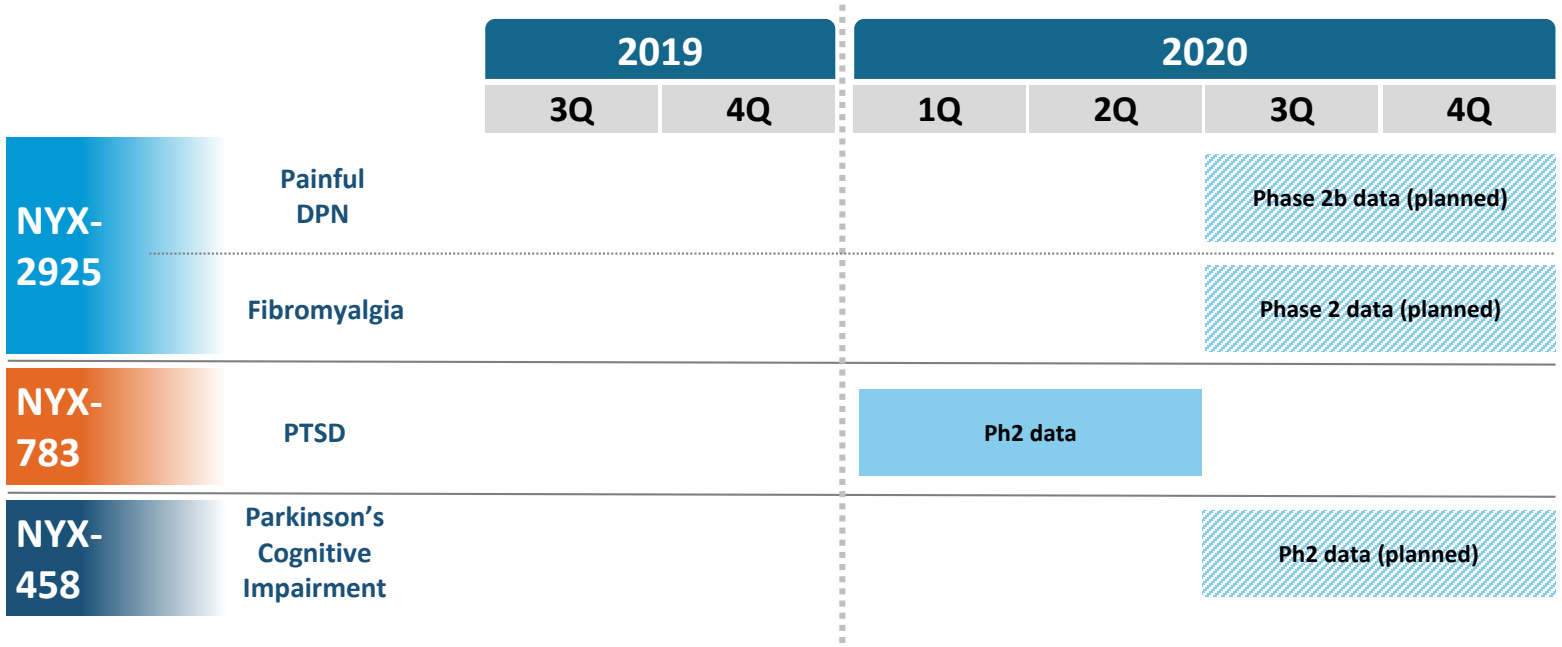
- Predictable and dose-proportional PK
- Cleared from plasma in 24 hrs.
- No meaningful accumulation with repeat dosing
- Ample, predictable brain exposure
- No SAEs at any dose tested

Mechanism of action and biological activity validated extensively through preclinical and clinical studies conducted to date

	Preclinical	Phase 1 (safety and mechanistic studies)	Phase 2
NYX-2925 *Chronic Pain*	☑ Robust effects across numerous pain models	☑ Favorable safety & PK with no SAEs ☑ Ample BBB penetration ☑ Enhances NMDAr mediated plasticity ☑ Increases non-REM sleep	☑ Significant effects on pain processing biomarkers and patient-reported symptoms in fibromyalgia neuroimaging study ☑ Significant pain reduction in patients with advanced DPN ☐ Advanced DPN – planned (2020) ☐ Fibromyalgia – planned (2020)
NYX-783 *PTSD*	☑ Robust effects across numerous psychiatric models ☑ Significant reduction in fear behavior in conditioned fear model	☑ Favorable safety & PK with no SAEs ☑ Ample BBB penetration	☐ PTSD – ongoing (1H 2020)
NYX-458 *Cognitive Impairment*	☑ Robust effects across numerous rodent cognition models ☑ Reversal of cognitive deficits in non-human primate Parkinson's model	☑ Favorable safety & PK with no SAEs	☐ PD-MCI – planned (2020)

Positive findings across preclinical and clinical studies to date inform development across pipeline programs

Aptinyx is well-funded into 2021, enabling multiple clinical milestones



Current cash supports four planned Phase 2 data readouts

Cash and Cash Equivalents	**$137mm** (as of March 31, 2019)
Operating Expenses	**$18mm** (Three months ended March 31, 2019)

Experienced management team and a board of highly regarded healthcare investors

Leadership Team

Patricia Adams *VP of HR & Administration*	naurex, DURATA THERAPEUTICS, BioSante Pharmaceuticals, Lundbeck, Takeda
Cassia Cearley, PhD *VP of Research*	naurex, Takeda, L.E.K. Consulting
Juan Estupinan *VP of Finance and Accounting*	naurex, DURATA THERAPEUTICS, Abbott, Deloitte.
Betty Jang *VP of Legal Affairs*	bioscrip, axiom, CVS Health,
M. Amin Khan, PhD *VP of Chemistry R&D*	naurex, Northwestern University, élan, GLIATECH
Ashish Khanna *CFO & Chief Business Officer*	naurex, VANDA PHARMACEUTICALS INC., Johnson & Johnson, Capgemini
Andy Kidd *Chief Operating Officer*	Baxter, BCG The Boston Consulting Group
Kathryn King, PhD *SVP of Clinical Development*	levo, abbvie, Takeda, Veeva, Abbott
Joseph Moskal, PhD *Chief Scientific Officer*	naurex, Northwestern University, Einstein Albert Einstein College of Medicine, NIH National Institutes of Health
Norbert Riedel, PhD *President & CEO*	naurex, Baxter, Hoechst Marion Roussel, Boston University School of Medicine

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Patrick Enright *Founder & Managing Director*	Longitude Capital
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Norbert Riedel, PhD *President & CEO*	APTINYX