JNX1001 – A novel neurotrophic factor modulator in development for ALS

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Sept 10th 2015

3rd European Neurotech Investing & Partnering Summit 2015

Junaxo Inc.

- Focussed on neurodegenerative disorders
- Develop compounds through initial Proof-of-Concept studies
- Multiple licensing opportunities

Product	Indication	2015	2016	2017	2018
JNX1001	ALS	Biomarker studies	Phase II proof-of-concept clinical trials		
JNX3001	Parkinson's Disease	In vivo PoC	Phase I and II clinical trials		
JNX4001	Dyskinesia	Preclinical evaluation		Phase II PoC trial	

Amyotrophic Lateral Sclerosis (ALS)

- Amyotrophic lateral sclerosis
  - Characterised by degeneration of cholinergic motor neurons
  - Most common form of Motor Neuron Disease.
  - Life-expectancy from diagnosis of ~14 months.
  - Prevalence of 40,000 in US – one of the more common orphan diseases.

- Market size
  - Only FDA-approved treatment is Rilutek® (riluzole)
    - Modest effect (increased survival of 3-6 months).
    - Global sales of $300m (2010). Now off-patent.
  - If a drug extended life expectancy by 24 months the market size would be similar to Multiple Sclerosis ($2-4Bn)

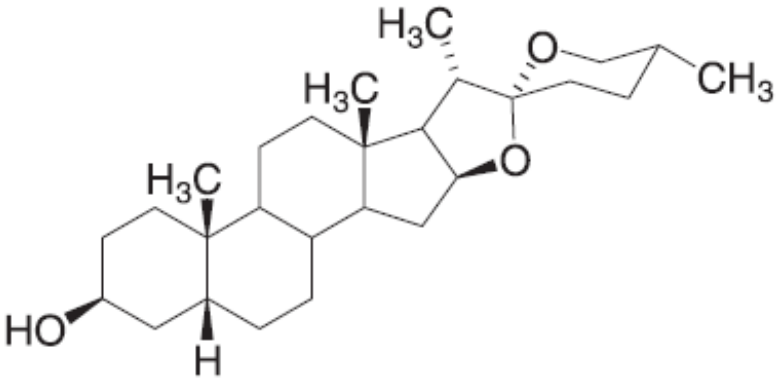
An effective drug will drive the ALS market

ALS - Challenge

- Many Phase II clinical trials in ALS have been performed. Most have been negative.
  - Incorrect dosage selection (too high and too low)
  - Poor drug delivery
  - Inadequate sample size
  - Lack of pharmacodynamic marker of drug effect
- A pharmacodynamic marker allows:
  - Correct patient selection/ post-hoc responder analysis
  - Determine dosage
  - Studies powered to see pharmacodynamic effect

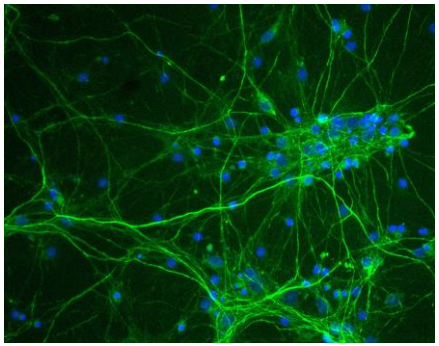
JNX1001 - a small molecule drug with potential to stimulate endogenous neurotrophic factor actions

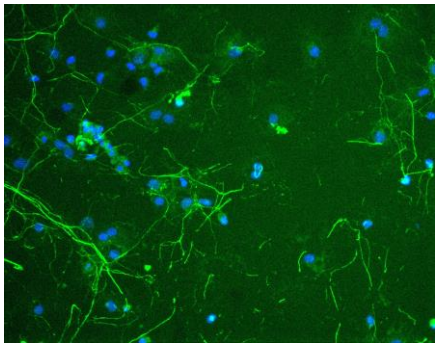
JNX1001

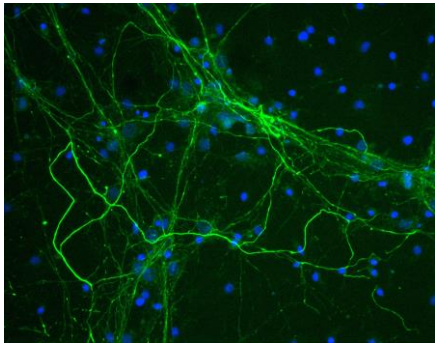


- Synthetic, small molecule chemical entity
- Increases GDNF and BDNF synthesis
- Mimics neurotrophic factor actions *in vitro* and *in vivo*
- Orally active, for once daily dosing
- Toxicology and safety pharmacology studies completed
- Phase I and II studies performed – good emerging safety profile
  - 28 weeks dosing in man performed in a Phase II study in PD

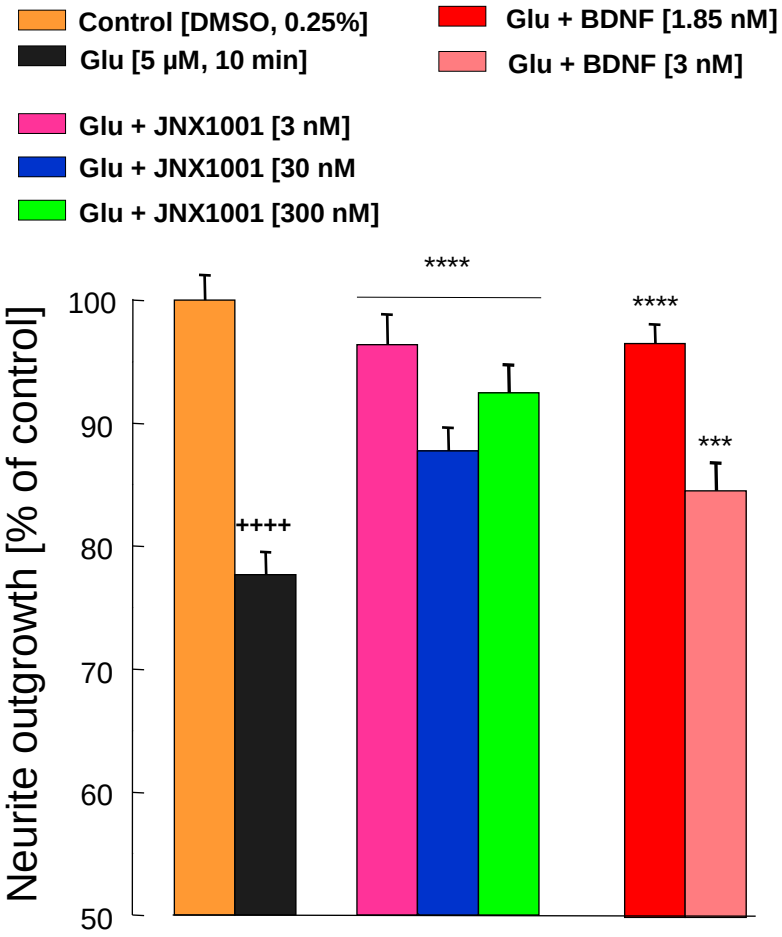
Neurotrophic effects in spinal motor neurons







Reverses Neuronal Atrophy



- Primary cultured rat spinal motor neurons
- Neurons exposed to glutamate (5 µM) for 10 min
- Cultures then washed and placed in fresh medium containing JNX1001 for 48 h
- Cells then fixed, stained and neurite outgrowth measured

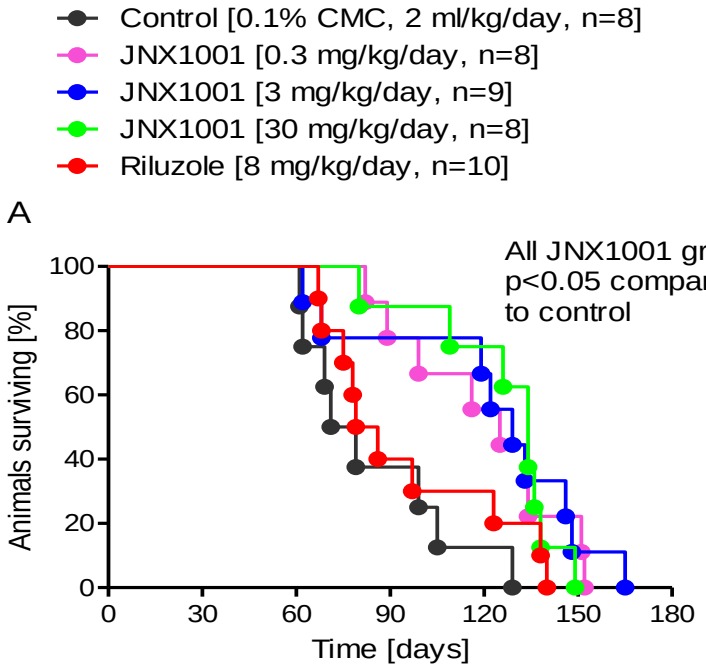
JNX1001 in mSOD1 mice

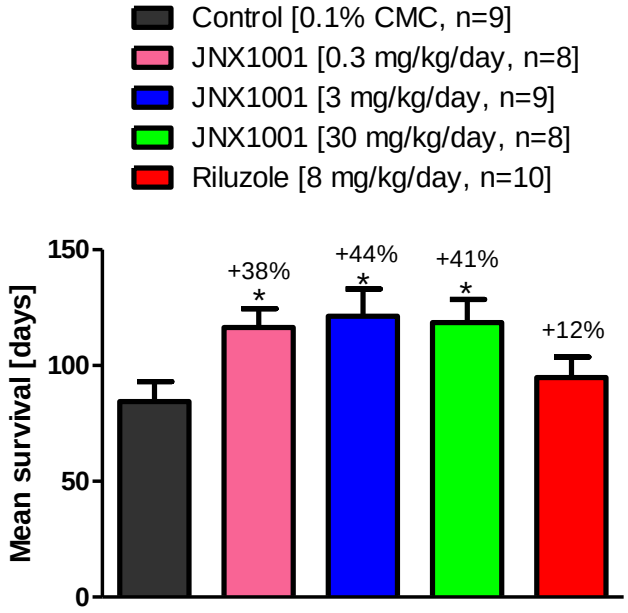
- Two studies performed in different laboratories using mSOD1^{G93A} mice

- Study 1: Survival study
  - Mice administered JNX1001 from day 60 until death or unable to feed themselves
  - Survival, motor performance and CMAP characteristics examined

- Study 2: Effect on motor neuron study
  - Mice administered JNX1001 for 50 days starting on day 70
  - Motor neuron survival, motor unit survival, muscle contraction force, muscle contraction characteristics and muscle phenotype examined

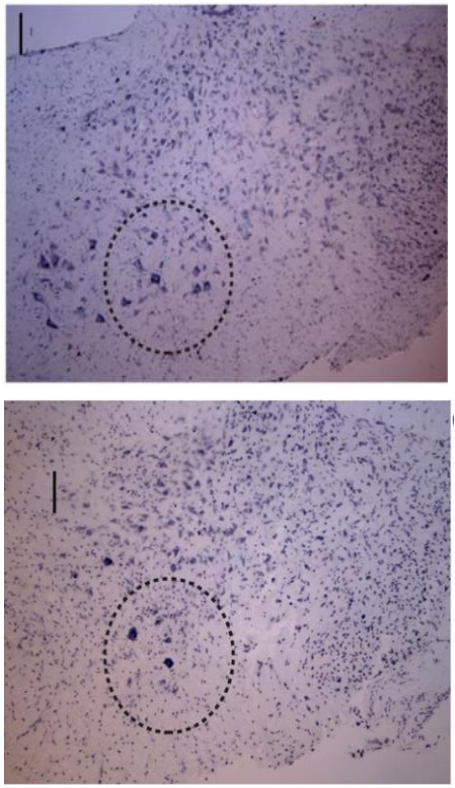
Study 1: JNX1001 increases survival and maintains motor performance

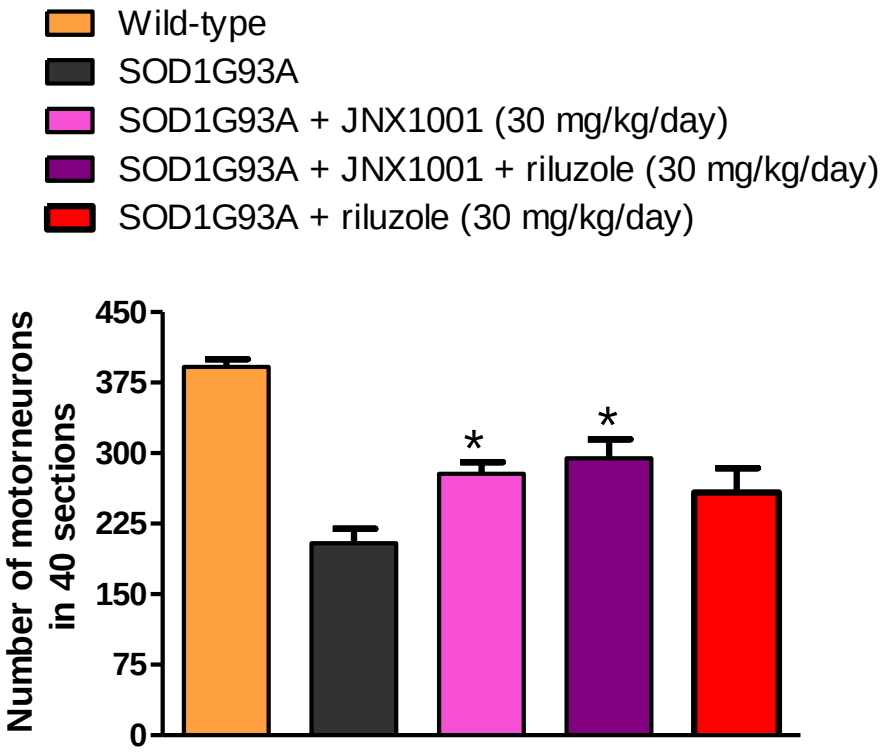




Group	Rotarod test (s)	Grid test (no. of stumbles)	Hanging test (s)	CMAP amplitude (mV)	Survival time (days)
Control [0.1% CMC]	31.6 ± 5.8	23.6 ± 1.1	50.8 ± 1.8	6.3 ± 1.1	84.4 ± 8.6
JNX1001 [0.3 mg/kg/day]	70.0 ± 6.9****	14.7 ± 1.2****	44.5 ± 1.9***	12.9 ± 1.2****	116.4 ± 8.2*
JNX1001 [3 mg/kg/day]	66.0 ± 6.7****	15.0 ± 1.2****	42.3 ± 2.1****	14.9 ± 1.3****	121.3 ± 11.7*
JNX1001 [30 mg/kg/day]	64.2 ± 6.9****	15.5 ± 1.4****	42.4 ± 2.2****	12.9 ± 1.2**	118.6 ± 9.9*
Riluzole [8 mg/kg/day]	42.7 ± 5.8	21.2 ± 1.1	46.3 ± 1.9*	9.6 ± 1.2**	94.8 ± 8.9

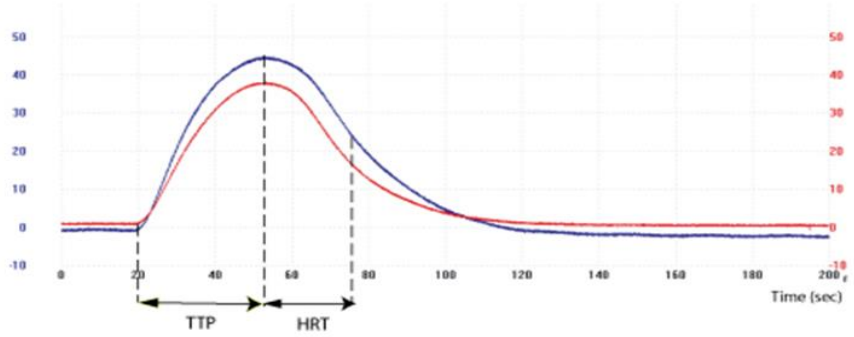
Study 2: JNX1001 reduces loss of spinal motor neurons

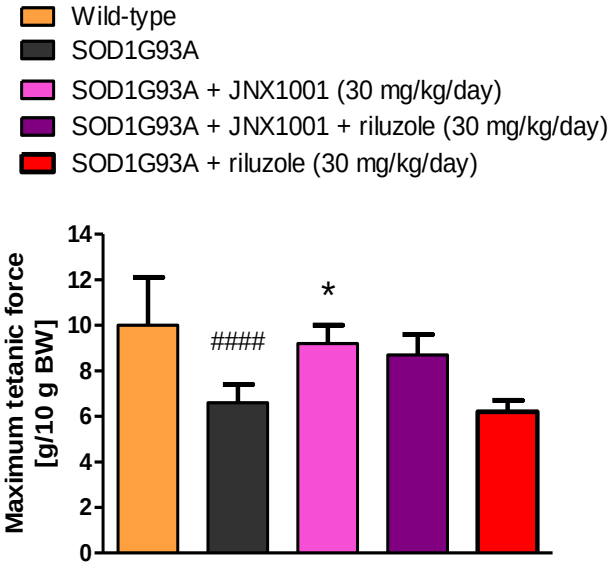


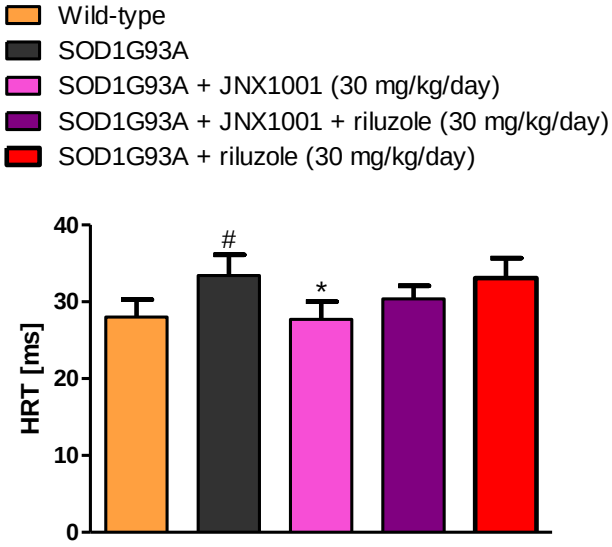


- JNX1001 significantly reduced motor neuron loss
  - JNX1001 also significantly increased the number of motor units

Study 2: JNX1001 preserves muscle function





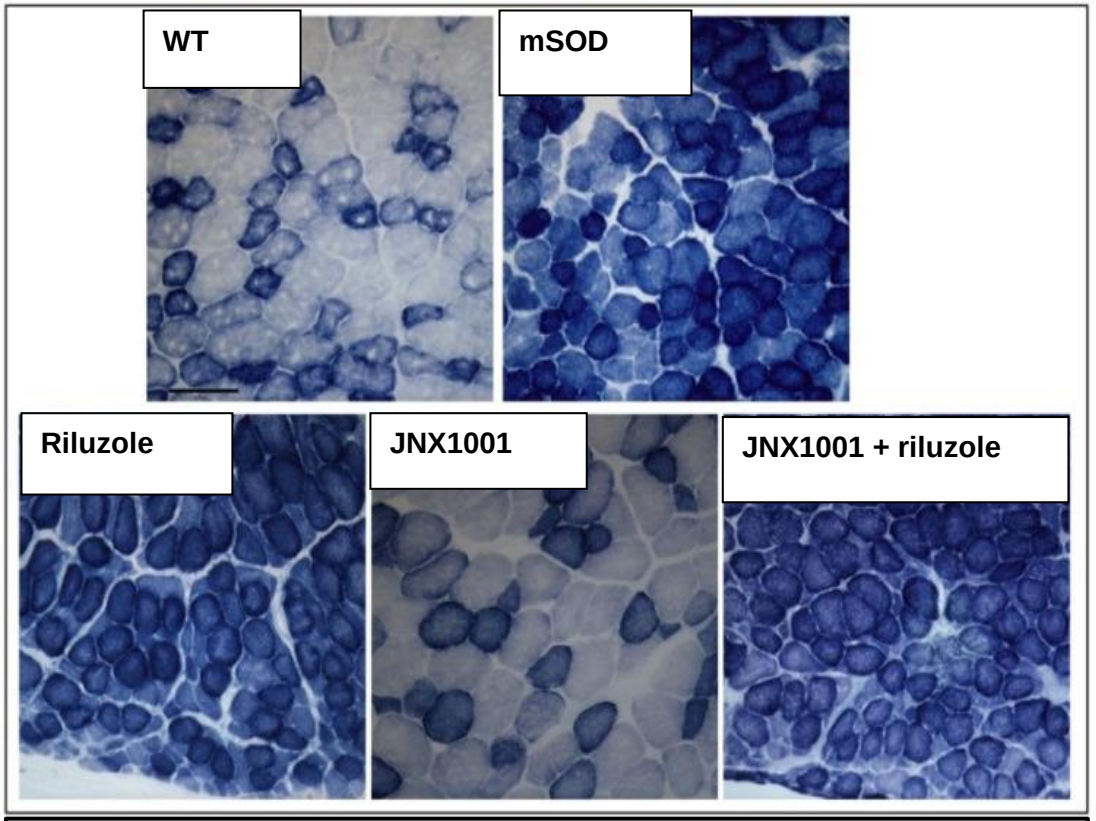


- JNX1001 preserved maximum tetanic force generated and muscle relaxation characteristics in a hindlimb (EDL) muscle

Study 2: JNX1001 preserves muscle phenotype

In mSOD1 mice, affected muscles undergo a characteristic metabolic change towards a more oxidative (SDH positive) phenotype. Thus, in untreated mSOD1 mice there is a higher proportion of muscle fibres staining strongly for SDH.

JNX1001 preserved the SDH staining pattern so that muscles from mice treated with JNX1001 was similar to staining pattern in wild-type mice.



Succinate dehydrogenase (SDH) is a marker for oxidative capacity of a muscle fibre

Dark stain = high SDH level

Light stain = low SDH level

Efficacy observed in additional models of motor neuron damage

- β-sitosterol-βD-glucoside (BSSG) is a toxin thought to be the cause of Guam type ALS-PDC.
  - JNX1001 prevented motor neuron loss, reduced microglia infiltration and prevented nitrosative damage as measured by 3-NT staining.
  - JNX1001 (1 and 10 mg/kg) also prevented the progressive decline in the gait of mice fed BSSG.

- Progressive motor neuropathy in *pmn* mice, model of SMA, possibly due to microtubule dysfunction
  - JNX1001 (3 mg/kg) significantly increased survival and reduced motor decline as measured by rotarod, grid and hanging tests.
  - Delayed the loss in neuronal function as measured by CMAP amplitude.

- In sciatic nerve crush mice
  - JNX1001 (0.3 and 3 mg/kg) significantly reduced the number of degenerating fibres and the number of hypomyelinated fibres in the sciatic nerve.
  - Improved nerve function as measured by CMAP amplitude.

GLP toxicology, safety pharmacology and clinical experience

Toxicology

- **Single dose toxicity**
  - Mouse, rat & dog
- **Repeat dose toxicity**
  - Mouse & Dog: 52 weeks
  - Rat: 26 weeks
- **Local tolerance**
  - Dermal irritation - rabbit
  - Ocular irritation - rabbit
  - Dermal sensitisation – guinea pig
- **Genotoxicity / mutagenicity**
  - Mutagenicity - Ames
  - Chromosomal damage - mouse micronucleus
  - Chromosomal aberration – CHO cells

Safety Pharmacology

- Irwin test - mouse
- Motor coordination - mouse
- Body temperature - rat
- Spontaneous locomotor activity - mouse
- Analgesia - mouse
- Convulsant effect - mouse
- CV and respiratory function - anaesthetised dog
- Respiration - conscious rat
- hERG channel blockade - HEK-293 cells

Clinical

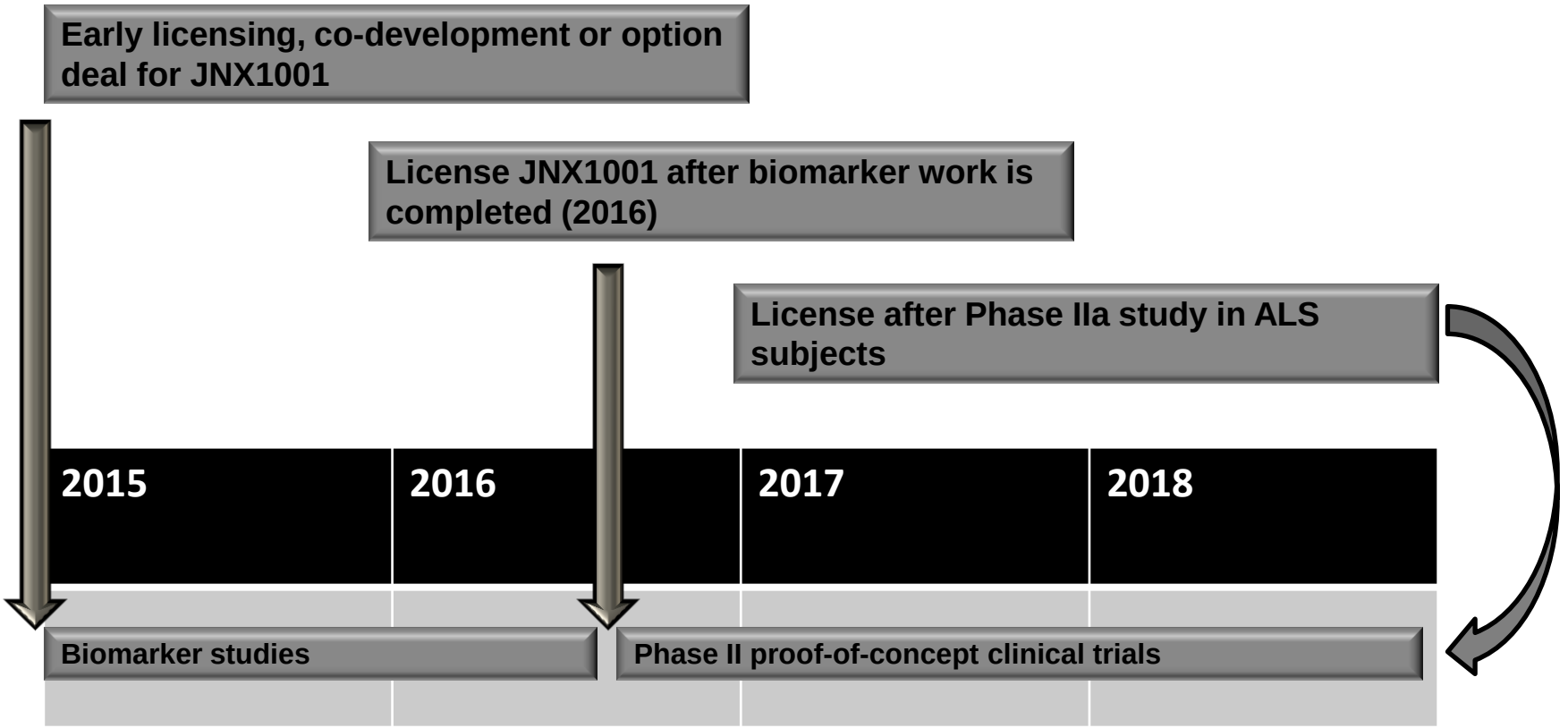
- **Five Phase I studies**
  - up to 28 days in duration
  - food effect study
  - comparative safety & PK in healthy volunteers and patients with Parkinson's disease (PD)
- **12 week, Phase II** safety study in patients with mild Alzheimer's disease
- **28 week, Phase II** dose ranging study in patients with early stage Parkinson's disease
- Once-daily dosing with good safety profile demonstrated

Next stages of development

- Good package already available
  - Open IND for ALS
  - Orphan disease designation in ALS in US and EU
  - GMP manufacturing complete
  - Phase I studies complete
- Clinical target engagement – Ongoing (2015 – 2016)
  - Define peripheral biomarker of drug effect in mouse ALS models
  - Define variability of biomarkers in patient-derived tissue
- Phase IIa clinical trial (2016 – 2019)
  - Randomised, placebo-controlled double-blind study
    - 52 weeks, approx. 80 subjects randomised 1:1 (placebo:JNX1001)
  - Demonstration of target engagement/drug effect
  - Preliminary efficacy investigated using rate of decline in ALSFRS-R

Licensing opportunity

- Multiple licensing opportunities for JNX1001



- Licensing opportunities available on other Junaxo products