Neurana Pharmaceuticals Announces Top-Line Results from Tolperisone Phase 1 CNS Effects Study

- **Tolperisone was comparable to placebo on driving performance; cyclobenzaprine, market leading skeletal muscle relaxant, was significantly worse at all time points**
- **Tolperisone similar to placebo on three measures of sleepiness whereas cyclobenzaprine displayed significantly more sleepiness**

SAN DIEGO, Calif., December 8, 2020 -- Neurana Pharmaceuticals, a biotechnology company focused on the treatment of neuromuscular conditions, today announced positive top-line results from the Phase 1 central nervous effects (CNS) clinical study of tolperisone. The study, utilizing a validated driving test, confirmed that tolperisone does not impair driving performance. In addition, tolperisone does not appear to cause sleepiness, a side effect often associated with currently available skeletal muscle relaxants.

"This study is an important milestone for tolperisone and the evolution of muscle relaxants," shared Randall Kaye, MD, Chief Medical Officer of Neurana. "The study showed that volunteers taking tolperisone demonstrated no driving impairment with both the 200mg and 400mg doses used in the study. Alternatively, cyclobenzaprine, the positive control, displayed significantly worse driving impairment across all time points. In addition, utilizing three different validated measurements – the Karolinska Sleepiness Scale (KSS), the Epworth Sleepiness Scale (ESS), and treatment emergent adverse events (TEAEs) – tolperisone did not cause sleepiness compared to the positive control, cyclobenzaprine. We are very pleased with these results and the potential to offer patients a solution for their painful muscle spasms without interfering with their daily lives."

The Phase 1 CNS Effects Study was a randomized, 4-period, crossover study in 39 healthy volunteers designed to investigate the effects of tolperisone on multiple measures of driving performance, sleepiness and cognitive function. All volunteers received tolperisone 200 mg, tolperisone 400 mg (supratherapeutic dose), a positive control (cyclobenzaprine 10 mg), or placebo three times a day (TID) over 3 days of dosing per treatment period. The study employed a validated driving simulation trial design that is commonly utilized to assess driving impairment in CNS active medications. The primary endpoint for the study was Standard Deviation of Lateral Position (SDLP) which measures an individual's ability to maintain lane position.

For the primary endpoint of SDLP, the difference in least squared means compared to placebo, at both doses of tolperisone (200mg and 400mg) demonstrated non inferiority; however, on all three days, cyclobenzaprine exceeded the pre-established non inferiority margin (equivalent to a 0.05% blood alcohol content). Furthermore, cyclobenzaprine, as assessed by the least square means was clinically worse than placebo on Days 1 and 2.

In the study, tolperisone was well tolerated. Treatment emergent adverse events (TEAEs) for placebo, tolperisone 200mg, tolperisone 400mg, and cyclobenzaprine were: 19.4%, 5.6%, 15.8%, and 33.3%, respectively. The rates of somnolence as an adverse event (AE) for placebo, tolperisone 200mg, tolperisone 400mg, and cyclobenzaprine were: 2.8%, 0%, 5.3%, and 25.0%, respectively. TEAE's are summarized in the table below.

	Placebo (N=36)	**Tolperisone 200mg (N=36)**	**Tolperisone 400mg (N=38)**	**Cyclobenzaprine 10mg (N=36)**
Preferred Term	n (%)	n (%)	n (%)	n (%)
Any TEAE	7 (19.4)	2 (5.6)	6 (15.8)	12 (33.3)
Somnolence	1 (2.8)	0	2 (5.3)	9 (25.0)
Headache	1 (2.8)	0	5 (13.2)	0
Fatigue	1 (2.8)	0	0	2 (5.6)
Arthralgia	1 (2.8)	1 (2.8)	0	0
Nausea	1 (2.8)	1 (2.8)	0	0
Diarrhea	0	0	0	1 (2.8)
Lethargy	0	0	0	1 (2.8)
Paresthesia	0	0	0	1 (2.8)

Secondary endpoints assessed measures of sleepiness using the Epworth Sleepiness Scale (ESS). The ESS, administered only on Day 3, showed that volunteers taking tolperisone 200mg and 400mg TID had lower rates of daytime sleepiness compared to cyclobenzaprine, which demonstrated a significant increase in daytime sleepiness (p=0.03).

Gary Kay, Ph.D., President and Chief Scientific Officer of Cognitive Research Corporation, stated, "Developing a therapy that does not cause sleepiness is highly reminiscent of work done in the 1990's to transform the treatment paradigm from sedating antihistamines to antihistamines that were safe and effective without the sleepiness side effects. Tolperisone has the potential to offer a similar solution to patients. It is important for physicians and patients alike to have a skeletal muscle relaxant (SMR) that does not carry driving warnings and is effective without the sleepiness side effects observed with currently available SMRs."

Neurana will report full results from this Phase 1 study, including data assessing cognitive function impairment, at an upcoming medical conference.

About Neurana Pharmaceuticals, Inc.

Neurana Pharmaceuticals, Inc. is a privately held, clinical-stage, biotechnology company focused on the treatment of neuromuscular conditions, including acute, painful muscle spasms of the back. The company was founded in 2013 and is based in San Diego. Neurana's lead development compound is tolperisone, a novel, non-opioid, non-drowsy, non-cognitive impairing treatment, which the company is developing for the large population of patients who experience muscle spasms. In May 2018, Neurana completed a $60 million Series A financing

led by Sofinnova Ventures with participation from Longitude Capital, New Leaf Venture Partners and H.I.G. BioHealth Partners to fund the clinical development of tolperisone. For additional information, please visit www.neuranapharma.com.

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