Genervon Announces ALS and PD Phase 2a Trial Results

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PASADENA, Calif.--(BUSINESS WIRE)--Genervon Biopharmaceuticals LLC (“Genervon”) today announced that it has completed the analysis of its Phase 2a double blinded, randomized, placebo controlled clinical trials of Amyotrophic Lateral Sclerosis (“ALS”) (NCT01854294) and Parkinson’s disease (“PD”) (NCT 01850381) for its drug candidate GM6 (also known as GM604 in the ALS trial and GM608 in the PD trial). Genervon has received both fast track and orphan drug designations for GM 604 in the treatment of ALS. Genervon has submitted the results of these trials to the FDA for guidance on how to make GM6 available as a therapeutic ALS and PD drug.

Genervon ALS and PD Trials: The two trials were designed to determine whether a six-dose treatment of GM6 would begin the process of disease modification. Genervon was told not to expect any statistically significant drug effects because of the small number of patients in both trials, but was delighted to find that both clinical and biomarker data in the ALS and the PD trials reported statistically significant results.

These results suggest that GM6 has a disease-modifying effect, indicating that a six-dose treatment of GM6 begins the disease modification process. Genervon is particularly excited about the trials’ biomarker data, given that biomarkers are highly sensitive to changes in the underlying disease processes and are useful in predicting drug efficacy. In addition, biomarker measures are usually immune to the “placebo effect.”

New Multi-Target Development Paradigm: In the 1990s, Genervon realized that the many failures of clinical trials for central nervous system (“CNS”) diseases can be attributed to the fact that the classic drug development paradigm – designing single-target drugs – simply cannot account for the multifactorial nature of these complex diseases.

Instead, Genervon’s drug development strategy was to find the endogenous regulator(s) that control the development and function of the nervous system by modulating the expression of multiple genes through different pathways, thus bringing homeostasis and health to the biological systems. Through this approach, Genervon discovered GM6, a form of the embryonic/fetal stage motor neuron trophic factor that is the master regulator of the human nervous system.

Discovery of a Multi-Target Regulatory Peptide: During early in vitro trials, GM6 was shown to protect neurons against soluble inflammatory factors in human cerebrospinal fluid from patients with various CNS diseases. GM6 also modulated a large number of ALS-related genes in both DNA microarrays and PCR arrays, indicating that these genes may be targeted by GM6.

Potential benefits of GM6 include reduced inflammation and apoptosis, increased expression of kinesins and dynactins to improve axonal transport efficiency, modulation of undesirable gene expressions, reduction of toxic protein aggregates, attenuation of ALS and PD disease progression, improvement in clinical outcomes,


and reduction of disability caused by neurological deficit.

**Safety and Tolerability:** GM6 is a small, endogenous regulatory peptide that has been shown to be safe and tolerable in intravenous injection of six doses of 320 mg each over a two-week period. The Phase 1 and Phase 2a trials showed no clinically significant shift in ECG readings, neurological indicators, hematology, or clinical chemistry as a result of GM6 intravenous dosing. There were no reported deaths or withdrawals due to Adverse Events (AE) or any reported clinically Serious Adverse Events (SAE) related to GM6.

**ALS and PD Phase 2a Trials Result Analyses:**

**ALS Biomarker Data:** GM604 modulated one target biomarker (SOD1 Plasma and CSF), two efficacy biomarkers (Total TAU Plasma, Complement c3 CSF), two target/efficacy biomarkers (TDP43 Plasma and Cystatin C CSF), and one prognostic biomarker (pNFH CSF). The following multiple biomarkers have statistical significance or strong trend:

1. Total TAU plasma percentage change reduction from baseline to week 7 when compared between GM604 treated and placebo groups, p value =0.0369. Total Tau is mainly expressed in neurons of the CNS and is crucial in axonal maintenance and transport; it is a major component of abnormal intraneuronal aggregates in many CNS disorders, including Alzheimer.

2. Reduction of TDP 43 plasma slope from baseline to week 12 when compared between GM604 treated and placebo groups, p value =0.0078. TDP 43 is a major diseased protein of ALS and other CNS disorders such as Alzheimer.

3. SOD1 plasma percentage change at week 2 also showed a significant reduction trend when compared between GM604 treated and placebo groups, p=0.0550. A single mutant copy of this gene is sufficient to cause ALS in 90% of sporadic ALS patients.

4. And the slope for GM604 treated patients for SOD1 CSF was reduced by -1.875 through week 6 whiles the placebo group increased by 15.226 (increase indicates disease progression).

**ALS Clinical Data:** The clinical data ALSFRS-R and FVC scores:

1. GM604 significantly reduced the decline in ALSFRS-R versus the historical control, p=0.0047. 7 out of 8 treated patients had their ALS disease progression slowed or stopped at week 12 after initial six doses of GM604.

2. 5 out of 7 treated patients had their forced air capacity (FVC) disease progression slowed down or reversed at week 12 when comparing with historical placebo. At week 12 FVC of mean value of placebo group is -11.5% (lower capacity is not good) and mean value of treated group is -4.7%.

**ALS Compassionate Use:** An ALS patient was first diagnosed with the disease in Q1 2005 and by Q3 2008 was quadriplegic and on a ventilator. After a six-dose treatment of GM604 under an approved single patient compassionate-use IND, the patient's swallowing volume increased in two weeks to 20cc from a baseline of 10cc. Five weeks after treatment, the patient consumed 240cc of water in 20-25cc bursts without leakage.

**PD Biomarker Data:** Changes in targeted neuroprotective and inflammatory biomarkers suggested drug efficacy and disease modification in the treated patients group, while the placebo group demonstrated the opposite trend.

1. GM608 significantly increased the neuroprotective biomarker BDNF at week 2 when compared between GM604 treated and placebo groups, p value =0.035. BDNF has potent effects on survival and morphology of dopaminergic neurons; its loss could contribute to death of these cells in PD.
2.) GM608 dramatically lowered the levels of the inflammatory biomarker MMP9 at week 2 to -14.88% (lower is better) while the biomarker in the placebo group increased to +1.31%, an indication of disease progression. MMP9 gene is associated with the risk of PD.

**PD Clinical Data:** The clinical data score used United Parkinson’s Disease Rating Scale (UPDRS):

1.) Comparing the UPDRS of the treated PD patients by GM608 at week 12 and historical placebo PD patients is statistically significant, p=0.0085.

2.) Changes in 4 out of the 8 secondary clinical outcome measures (UPDRS ADL, Schwab & England, Hoehn & Yahr and MOCA) at week 2 (visit 6) were statistically significant at the one-tailed 10% level.

**About Genervon:** Genervon is a privately held, clinical-stage biopharmaceutical company in California developing breakthrough multi-target biological drugs to address the world’s critical unmet medical needs in CNS disorders.

**Contacts**
Genervon Biopharmaceuticals LLC
Dorothy Ko, 323-721-5500
Chief Operating Officer
info@genervon.com
www.genervon.com