Safety and Efficacy Summary for GM6

Highlights of GM604 safety and efficacy in treating ALS and PD patients where statistical significance or strong trend have been achieved

Normally no one expects statistical significance in data from a small sample size Phase 2A trial. Most trials have a hard time even finding a positive trend. GM6 is so potent that there were multiple endpoints that achieved statistical significance in the ALS phase 2A trial and in the Individual patient Compassionate Use Study, not only in clinical data and results, but also in correlating biomarker data and results.

Safety and Efficacy	Study
1. Safety and tolerability	GM604 is a 6 amino acid endogenous peptide. It is very safe and tolerable as shown in Phase 1 (32 subjects) and ALS Phase 2A (12 subjects). The number of adverse events (AEs) and serious adverse events (SAEs) are comparable to placebo, with no reported drug-related clinically (SEs).
2. Trophic Effect	Axon regeneration in rats with 8 mm gap in severed sciatic nerve, $p<0.001$
3. Tropic Effect	Neurons preferentially projected correctly to motor nerves instead of cutaneous nerve, $p<0.001$
4. Endogenous neuroprotection at fetal development	MNTF expression detected in human placenta peaking at week 9
5. Protection against toxic factors in CSF of CNS diseases patients	The human patient neuron survival percentages (compared to baseline): ALS (175%)
6. Neuroprotection	13 studies with in vitro and in animal models showed GM6 has neuroprotection efficacy in ALS, PD, and stroke models, $p<0.001$
7. PCR Study: GM6 modulates multiple CNS target genes	PCR study of GM6 with SHSY5Y cells (neuroblastoma cells) and microglia showed GM6 modulates (up or down) the expression (by up to two fold or more) of many ALS related genes identified by the scientific community, such as SOD1, TDP-43, FUS, Cystatin-C, tau. and Parkinson Disease related genes such as BDNF.
8. ALS Biomarker: plasma total tau, reduced	ALS Phase 2A trial, plasma total tau lower than placebo at week 6 ($p=0.0369$)
9. ALS Biomarker: ALS Biomarker: plasma SOD1, reduced	ALS Phase 2A trial, plasma SOD1 percentage change is lower than placebo at week 2, $p=0.0550$
10. ALS Biomarker: plasma TDP-43, reduced	ALS Phase 2A trial, the slope in plasma TDP-43 through week 12 in treated patient group (-3.513 pg/mL/wk) is lower than the placebo patient group (0.493 pg/mL/wk), $p=0.0078$. The mean percentage change in TDP43 of the treated GALS001 patient group was -34% and the mean of percentage change in the placebo patient group was +6% at 12 weeks.
11. ALS Biomarker: plasma TDP-43, reduced in both Phase 2A GM604 treated patients and GALS-C patient	In the GALS-C trial, the plasma TDP43 baseline level was 144.54 pg/ml. This value was as high as those of all the definite ALS patients in the phase 2A trial, who had a mean of 138.88 pg/ml at baseline. The normal range of TDP 43 in plasma is 0-50 pg/ml. At the end of two weeks of treatment (6 doses) the value in the compassionate patient was 92.59 pg/ml and at the end of 12 weeks it was 52.53 pg/ml. The percentage change in TDP43 from baseline in the compassionate patient was thus -63% in 12 weeks.
12. ALS Biomarker: CSF total tau, reduced in Phase 2A GM604 treated patients, but increased in GALS-C patient	The normal range of Tau in CSF of healthy subjects is100-350 pg/mL. In ALS Phase 2A trial, CSF Tau levels at baseline were at the high end of normal or higher than normal. After a 6-dose treatment in 2 weeks, the GM604 treated group had their CSF tau levels lowered while the placebo group had CSF tau levels that increased showing continued disease progression. In the Compassionate use case, the patient was already at a very advanced stage of the disease, and so the CSF Tau level at baseline was 60.55 pg/mL, well below the normal range. After 6 doses treatment in 2 weeks, the patient's CSF Tau level was 63.33 pg/mL, an increase of 4.59%, closer to the normal range.
13. ALS Biomarker: CSF Cystatin C, increased in Phase 2A GM604 treated patients and in GALS-C patient	The normal range of Cystatin C in the spinal fluid of healthy subjects is 3.0-8.0 ug/ml. In the Phase 2A trial we found that the Cystatin C levels in both the treated and placebo groups were at the low end of the normal range. Treatment with GM604 raised Cystatin C levels in the treatment group, but the placebo group showed decreasing CSF Cystatin C levels. In the compassionate use patient, his baseline value was 1.97 ug/mL, well below the normal range. After 2 weeks of treatment, the level was 2.35 ug/ml, an increase of 19% towards the normal range.
14. ALS Biomarker: CSF SOD1, reduced in Phase 2A GM604 treated patients, but increased in GALS-C patient	The normal range of SOD1 in the spinal fluid of healthy individuals is 50-200 ng/ml. All the Phase 2A ALS patients at baseline had CSF SOD1 levels at the high end of the normal range. The SOD1 levels in treated patients decrease through week 6, while in the placebo patients, it increased. In the Compassionate Use patient, his SOD1 level at baseline was 27.22 ng/mL, which is below normal. After two weeks of treatment, his level was 30.996 ng/mL, an increase of 13.84%, and closer to the normal range.
15. Homeostasis Theory	Most biomarkers (SOD1, Tau, and TDP-43) for ALS patients in Phase 2A were above the normal range and the treatment with GM604 down regulated their expression levels. In the advanced stage ALS patient, his CSF SOD1 and Tau were below normal at baseline. Treatment up regulated both. This surprising observation indicated that GM604 can modulate the same biomarker in both the up and down regulation directions. This phenomenon is very unique, and is the hallmark of homeostasis.
16. Clinical Trials Biomarker Data is consistent with In Vitro PCR Data	In the PCR study, SOD1 was reduced more than two fold at 4 hr, TDP43 was reduced more than two fold at 48 hr, and Cystatin C was increased more than two fold at 12 hr. The observed effects of GM604 on SOD1, cystatin C and TDP-43 are consistent with its neuroprotective properties reported in previous Genervon in vitro studies, and suggests that GM604 modulates numerous genes towards a more homeostatic expression level in treated patients.
17.Clinical Trials SOD1 Biomarker Data is consistent with in vivo ALS mice (SOD1) data	The observed effects of GM604 on SOD1 are consistent with the neuroprotective properties of GM604 reported in a previous Genervon in vivo SOD1 transgenic ALS animal model study. ALS mice (SOD1, stodk#G93A Jackson Lab) were treated with IV injections of GM604 daily until the animal died. Two different doses (1 mg/kg and 5 mg/kg) were applied. Endpoints were age of disease onset, age of death and behavioral deficit which included tests on Rota-rod, grip strength, tail test, and clinical evaluation. A dose dependent effect was found, with the 5 mg/kg dose group showing a 27% increase in age of onset ($p<0.001$), a 30% increase in age at death ($p<0.001$), a 41% increase in rota-rod performance ($p<0.001$), a 41% increase in grip strength, and a 53% increase in clinical score ($p<0.001$).
18. Clinical data: ALSFRS-R treated vs historical placebo	In the ALS Phase 2A trial, GM604 significantly reduced the decline in ALSFRS-R in treated patients compared to the rate of decline of a historical placebo control ($p=0.0047$).
19. Clinical data: ALSFRS-R before and after treatment	To measure the change in disease progression before and after the start of treatment, the ALSFRS-R results were analyzed using a mixed model analysis. The ALSFRS-R score was imputed as 48 at the date of onset. The least square equations are: In the placebo group: Before treatment: predicted ALSFRS-R = 34.62 -0.037*Day After treatment: predicted ALSFRS-R = 34.61 - 0.034*Day In treated group Before treatment: predicted ALSFRS-R = 36.30 - 0.046*Day After treatment: predicted ALSFRS-R = 36.28 - 0.032*Day. Note: the slope for the placebo group changes minimally before (-0.037/day) and after (-0.034/day) treatment. Though not significant, the slope for the treated group changes noticeably before and after treatment going from -0.046/day before treatment to -0.032/day after treatment. It appears that the GM604 treatment was slowing the disease progression..
20. Clinical data: FVC slowed	In the ALS Phase 2A trial, GM604 treatment reduced the decline in FVC in ALL treated patients at both sites from screening to week 12 with statistical significance favoring the treated group. The mean change in FVC from screening to week 12 for the placebo group was -17.5, while the change in the treated group it was -5.6, $p=0.0476$. The mean of percentage change in FVC from screening to week 12 for the placebo group was -22.61 % while for GM604 treated group it was -5.6%, $p=0.0359$.
21. Clinical Observation result of end stage ALS patient Compassionate use case: Improvement in speech, swallow, and mouth suction	After a six-dose treatment of GM604, the clinical observation results of the GALS-C patient revealed small but significant improvements from baseline to week 12. At week 2, the patient's speech video definitely showed clearer articulation than baseline. Two Weeks after the final dose, patient's swallow volume had increased by 150%-200% to 25cc-30cc. Oral fluid consumption reported by the patient was improved, measuring 250cc total in 25cc increments without leakage. Mouth suction as measured by water column height increased from 5-8cm to 10-15cm with both 1/8 and 1/4 inch drinking straws. Speech, swallowing, and suction were used as the primary metrics based on the theory that the motor neurons servicing the tongue and lips, being some of the shortest, would show improvements first. During the trial, no adverse side effects were noted.