ALSUntangled No. 34: GM604

The ALSUntangled Group*

ALSUntangled Update 34

ALSUntangled reviews potential therapies on behalf of patients with ALS (PALS). Here we provide our opinion on GM604 (sometimes called GM6), a compound owned by Genervon Biopharmaceuticals, for which we have had more than 950 requests (1).

Overview

GM604 is a synthetic six-amino acid peptide fragment of a larger protein growth factor called motoneurontrophic factor (2).

Mechanism(s)

Genervon makes several claims on its website (3) regarding possible mechanisms of GM604 without any supporting data or references. Multiple members of ALSUntangled contacted Genervon by phone and emails in the hope of establishing a dialogue that would allow us to eventually better understand this and several other issues described below; unfortunately, our requests were either never answered (4) or were answered along with the following statement, which prevents us from sharing: ‘This email is sent on behalf of Genervon Biopharmaceuticals, LLC. It may be privileged and contains confidential information intended only for the use of the recipient(s) named above. Use by anyone else is strictly prohibited’ (5).

PubMed searches of GM6 and GM604 identified only a single possibly relevant publication (2). In this study, GM604 or vehicle were administered to mice following an experimentally induced stroke and reperfusion. Treatment with GM604 was associated with lower markers of inflammation and apoptosis, reduced stroke size, and improved behavioral outcomes relative to treatment with vehicle. It is not clear that recovery from stroke bears any similarity to neuroprotection in ALS, so this paper cannot be relied upon to provide foundation for a relevant ALS mechanism. This study was funded by Genervon, and one of the authors of this paper is a member of the Genervon leadership team (6), which creates a potential conflict of interest.

There may be other unpublished mechanistic data on GM604. The paper on GM604 (2) states ‘Studies with the synthesized GM6 also demonstrated similar trophic effects in a transected femoral nerve rat model. In a zebrafish bioassay, GM6 protected the organism from L-2-hydroxyglutaric acid (LGA), induced oxidative stress and apoptosis in the CNS, and reduced apoptosis by 85% in the midbrain’. However, the only references we can find to support this work are patent applications. Based on all this, ALSUntangled assigns a TOE ‘Mechanism’ grade of D.

It should be noted here that various other neurotrophic factors have been tested in ALS, including IGF1 (7), CNTF (8) and BDNF (9).


Note: this paper represents a consensus of those weighing in. Every investigator in this group does not necessarily share the opinions expressed in this paper.
and were largely ineffective. Trophic factors have also been tested for a variety of other neurodegenerative diseases, including Parkinson’s and Alzheimer’s, without clear benefit to date. A challenge for many of these prior studies has been demonstrating that the neurotrophic factor has hit its target within the CNS.

**Pre-clinical data**

Genervon claims to have positive pre-clinical data on GM604 in ALS models. Its website (3) says ‘GM604 also proved to be quite effective in the disease modification of ALS in ALS animals with mutant SOD1. It led to an improved clinical score in SOD1 mice (p < 0.001 for all groups compared to control). Moreover, GM604 delayed the onset of ALS symptoms by 27%, extended life by 30% and delayed the median clinical score deterioration time in ALS mice by 41%’. It further states ‘GM604 dramatically increased the survival life span by 500% (six-fold from 7–14 weeks to 55–65 weeks) and increased preservation of motor neurons by 160% (2.6-fold) in a wobbler mouse model for motor neuron diseases such as ALS’. Important design issues necessary to interpret ALS animal studies are not provided in these website statements (10). No references are provided. PubMed search identifies no published peer-reviewed papers that support these claims. Based on all on this, ALSUntangled assigns a TOE ‘Pre-clinical’ grade of D. Even if these data are eventually published and determined to be scientifically sound, there is no guarantee that they will translate into humans (11).

**Data in PALS**

**Cases**

Genervon’s website describes six patients who were treated with GM604 via compassionate use programs (12,13). These patients received different numbers of GM604 treatments. It is not clear how many patients have been treated via these programs, exactly how these patients were selected, or whether any objective validated ALS outcomes are being systematically gathered during treatment. Genervon describes improvements in subjective, non-validated measures such as swallow volume (12), energy and mood (13). Improvements in fasciculation frequency are described in two patients (13); fasciculation frequency is not a useful ALS outcome measure, as it does not correlate with strength or progression rate (14). ALSFRS-R scores during treatment are described for only one of the patients (13); these improved by 1 point over two months, a change that is not uncommon in the natural history of ALS (15). ALSUntangled attempted to independently validate the reported diagnoses and benefits in these patients, as we have done for every treatment we review; unfortunately, we were told they had signed confidentiality agreements and thus could not share any information with us (16). Searches on PatientsLikeMe and Google identified no other reports. Based on all this, ALSUntangled assigns a TOE ‘Cases’ grade of D.

**Trial**

Genervon sponsored one small, brief, randomized, double-blind, placebo-controlled pilot trial of GM604 in PALS (17). Eight patients received GM604 for two weeks, four patients received placebo for two weeks, and these patients were followed for a total of 12 weeks. Outcomes included clinical measures (ALSFRS-R, FVC, timed get up and go (TUG), muscle strength, mortality), candidate biomarkers, and safety and tolerability (17). This study started in August 2013, and was completed in April 2014 (17,18). To date, the only publicly available source of results from this trial that we are aware of is the Genervon website. There is a potential for bias and conflict of interest when the company that owns a drug reviews, interprets and reports on its efficacy and safety data.

With regard to ALSFRS-R, the website states (19) ‘seven out of the eight treated patients had their ALS disease progression slowed or stopped by week 12’. The website does not appear to describe what happened in the eighth treated patient nor in the placebo treated patients in this same analysis. Since ALSFRS-R plateaus (periods where this measure of disease seems to slow or stop) are not uncommon, especially over short intervals (15), it is not clear to us that this is evidence of treatment benefit. In an assay comparing imputed ALSFRS-R changes before and after treatment, the website states that there was no statistically significant difference between their two treatment groups (20). The website does report a statistically significant difference in ALSFRS-R slope between GM604 treated patients and the placebo group of the ceftriaxone trial (21). However, when using historical controls, it is critical to match according to demographic and disease-related variables that predict progression (22). The GM604 and ceftriaxone trials had different entry criteria (17,23) including some that are known to influence the rate of disease progression such as body mass index (24). Since it is not clear whether these groups were appropriately matched, these data are presently uninterpretable in our opinion.

With regard to FVC, the Genervon website states (20) ‘The mean change in FVC from screening to week 12 for the placebo group was –17.5, while the change in the treated group was –5.6, p = 0.0476. The mean percentage change in FVC from screening to week 12 for the placebo group was –22.61% while for the GM604 treated group it was –5.6%, p = 0.0359’. As highlighted previously (25),
measure the candidate biomarker in each biofluid, with results supporting further use of the candidate biomarker in subsequent and larger clinical trials. The results indicate the ability to detect the candidate biomarkers in patient biofluid samples and support continued drug development in larger clinical trials. The biomarker data from this small trial do not indicate drug effectiveness in the patients, as the time-course of drug treatment is short, with no long-term outcome measures or long-term biomarker measurements. Any small changes in biomarker levels in the CSF or blood between groups may reflect the small sample size of the treatment and placebo groups as well as the short duration of this study. Larger clinical trials with longer drug treatment should be performed to test the efficacy of GM604, using biomarkers to assist in determining the ability of the drug to target particular pathways. Without these larger clinical trials, it remains unclear if GM604 alters biomarker levels during disease course, or what these alterations might mean with regard to clinical efficacy.’

In addition to all the above issues and problems, Genervon’s pilot trial of GM604 fails to comply with consensus guidelines for the design and implementation of clinical trials in ALS due to its very short duration and lack of information release for peer review (35). Based on all this, ALSUntangled assigns a TOE ‘Trials’ grade of U.

**Risks and costs**

Genervon’s website reports that GM604 ‘is very safe and tolerable as shown in phase I (32 subjects), ALS phase IIA (12 subjects), PD phase IIA (six subjects) and Stroke (28 of 36 subjects, as yet unblinded) trials. The number of adverse events (AEs) and serious adverse events (SAEs) are comparable to placebo, with no reported drug-related clinically (SEs)’ (20). However, as mentioned above, we have been unable to review any of these data independently or even question patients who took GM604 in the trial or in the compassionate use program. This level of secrecy is unusual in our experience. Based on this, ALSUntangled assigns a TOE ‘Safety’ grade of U.

GM604 has been offered to patients in compassionate use programs outside the United States at a cost of $94,500 per six-dose treatment (16).

**Conclusions**

At this time ALSUntangled finds no independently verifiable data supporting the efficacy or even the safety of GM604 in patients with ALS. We believe that independent peer review and replication are fundamentals of good science (36,37). Accordingly, we share the FDA’s April 2015 opinion that the data on GM604 in ALS should be released now for
independent peer review (38). If these preliminary data are confirmed to be positive, statistics on the false-positive rate of small trials (29,30) and consensus ALS trial guidelines (35) dictate that they be replicated in a larger, longer duration study before GM604 is deemed effective or even safe for patients with ALS.

ALSUntangled generally supports the use of expanded access programs during ALS drug development. We believe that these should be reserved for treatments that have at least some independently verifiable safety data. In our opinion, that is not the case with GM604, so we feel that expanded access is premature at this time. When we can independently verify safety data, we hope to see a GM604 group expanded access program that has transparent entry criteria, systematic objective outcome measures, full disclosure of results, and, as suggested by the FDA, allows for a sponsor’s cost recovery but not for profit (39).

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References

4. Emails from ALSUntangled to info@genervon.com, and ewang@genervon.com 12/15/15 and 12/21/15, and telephone call from ALSUntangled to Dorothy Ko at Genervon, 12/21/15.
5. Other emails from clinicians who are ALSUntangled members to info@genervon.com, or ewang@genervon.com.
16. Emails between ALSUntangled and various patients and families fighting ALS.