Reviewer's report

**Title:** Evaluation of the muscle strength and motor ability in type II and III spinal muscle atrophy children treated with valproic acid

**Version:** 1  **Date:** 31 March 2010

**Reviewer:** Brunhilde Wirth

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Major revisions:

1.) The authors should specify explicitly that not including a control group is a major limitation of their results. It is impossible to differentiate between a potential effect of the drug treatment and the natural history of the disease. Despite suffering from a progressive neurodegenerative disease, individual patients with SMA II/III may well show short term improvements of their motor status. In addition, 3 out of 9 SMA III patients in this study were diagnosed at age 12 months or younger, which is very early for SMA III. If they were enrolled in the study relatively soon after diagnosis, this means that they may well have shown motor function improvements even if untreated. Unfortunately, the age at enrollment is only given as mean and as range in Table 2.

2.) The conclusion “Treatment of patients with VPA is a potential alternative to alleviate the progression of the disease” should therefore be phrased “Treatment of SMA patients with VPA may be a potential alternative to alleviate the progression of the disease”, since no proof of therapeutic efficacy can be extracted from this uncontrolled study.

3.) The characterization of the patients should - for comparison with future studies – include the individual numbers of SMN2 gene copies for each patient. It would be desirable to reanalyse the data from Table 3 according to SMN2 copy number and according to SMA type II versus III. If this is not possible, it should be made clear that this is a limitation of the present study.

Minor essential revisions:

1.) **ABSTRACT:** Methods: “were treated with VA” should be spelled “were treated with VPA” since VPA is the abbreviation for Valproic Acid used in the remaining text body.

2.) **BACKGROUND:** 1st paragraph, 1st line: “autosome” should be spelled “autosomal”.

3.) **BACKGROUND:** 1st paragraph, 3rd last sentence: “In SMA III patients the initial manifestations usually occurs after ten months of age …” should be changed to “…18 months of age” which is the accepted definition.

4.) **BACKGROUND:** 3rd paragraph, 3rd line: “phenilbutirate” should be spelled “phenylbutyrate”.

5.) **BACKGROUND:** 3rd paragraph, 2nd last sentence: “However, phase III
clinical trials have not had their results disclosed yet…” . There have as yet not been initiated any phase III clinical trials for SMA. Which trial the authors have in mind?

6.) METHODS; 2nd line: “Hammersmith function motor scale” should be changed into “Hammersmith functional motor scale”.

7.) RESULTS: The authors should provide information on the VPA serum concentrations that were achieved at 20 mg/kg/d.

8.) DISCUSSION; 1st paragraph, last word: “… withdraw [17].” should be spelled “withdrawal [17].”.

9.) DISCUSSION, 2nd paragraph, last sentence: “… treatment, in contrast ..” should be spelled “… treatment, in contrast ..”


11.) TABLE 1; 4th column from the left “Age at diagnosis”: the unit should be given as “(years unless specified otherwise)”.

12.) TABLE 2; what does” Q1-Q3” stand for?

13.) TABLE 3; legend: “ HMAS e Barthel index” should be spelled “HMAS and Barthel index”. The p values are given inconsistently, sometimes with as 0.xxx, sometimes as 0,xxx and sometimes as 0xxx.

14.) TABLE 4; p-values: it is not obvious how these values were obtained.

Discretionary Revisions

1.) Reference 10 (Yamashito et al.) is a case report and as such not the strongest evidence in favour of a genotype-phenotype correlation in SMA. A systematic study such as

Feldkötter M et al., Quantitative analyses of SMN1 and SMN2 based on real-time lightCycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. Am J Hum Genet. 2002;70:358-68.

or

Wirth B et al., Mildly affected patients with spinal muscular atrophy are partially protected by an increased SMN2 copy number. Hum Genet. 2006 May;119(4):422-8.

should be quoted instead.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

YES ; amongst others www.fsma.org, www.initiative-sma.de

Yes, I am involved in the CARNIVAL I trial (NCT00661453)