Author’s response to reviews

Title: Results from the 5-year, phase IV RENEW (Registry to Evaluate Novantrone Effects in Worsening Multiple Sclerosis) Study

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Author’s response to reviews: see over
Dear BMC Neurology Editor:

Enclosed please find our revised manuscript entitled *Results from the 5-year, phase IV RENEW (Registry to Evaluate Novantrone Effects in Worsening Multiple Sclerosis) Study*.

We were encouraged by the positive comments from the two reviewers that this manuscript was acceptable for publication, pending minor suggested revisions. We have made all these revisions, and we thank the Journal for their thoughtful comments. We believe that the revisions have greatly enhanced the quality of this report.

We have enclosed the manuscript with changes shown in “track changes” mode. See specific comments and our response below. We hope that these requested changes result in speedy publication of this important study. Thank you.

**COMMENTS AND RESPONSES:**

- We feel that the quality of the written English needs to be improved.
  
  Improvements have been made to sentence structure and grammar.

- Are there any negative data on amenorrhea related to cumulative dose? 
  
  See edits made on page 10.

- The detailed description of AE (Result section) might be shortened by eliminating in the text how many of them were considered related or not related to therapy by the PI (data have been also reported in Table 5).
  
  See edits on page 10 +

- The same for the 12 deaths (data have been also reported in Table 7).
- I would cross out the paragraph related to the 12 deaths in the discussion.
  
  See edits on page 16.

- Since the patients received a mean of 6 infusions during the study period and the results showed that the cumulative dose of Mitoxantrone is the primary risk factor associated with cardiotoxicity (see Table 4, too), in the conclusion the authors should add a comment on the cumulative dose related toxicity (Renew data for cardiotoxicity and literature data for Leukemia), and a recommendation to use the lowest possible cumulative dose of Mitoxantrone. (“Stay on-label, but anyway try to use the lowest possible cumulative dose”).
  
  See edits on page 16.

Sincerely,

Victor M. Rivera, M.D., FAAN

, on behalf of the RENEW Study investigators.