Author's response to reviews

Title: Tetrabenazine as Anti-Chorea Therapy in Huntington Disease: An Open-Label Continuation Study

Authors:

Samuel A. Frank (samuel.frank@bmc.org)
Huntington Study Group (shari.kinel@ctcc.rochester.edu)

Version: 2 Date: 14 July 2009

Author's response to reviews: see over
We thank the reviewers for their thoughtful and helpful comments. Their comments and concerns were divided into individual items and we have addressed them listed below.

**Reviewer 1 Comments to Address:**
Minor but essential issue is the uncertainty about the 26 patient lost for the study. They stopped! It is very informative to know the clinical characteristics of those who stopped and the reason, more precisely given, why they stopped. (Loss of efficacy?; otherwise?; center bound?)

There were 30 subjects who did not complete the protocol as intended. These subjects have been shown in the figure and explained in the text. The reasons for not completing the study are explained for all participants on page 8 in the tolerability section. There were some differences in baseline characteristics between those who completed and those who did not. Subjects who completed were more likely to be female, have higher CAG repeat length, and have a lower functional assessment score at baseline. There were no differences in race, affected parent, history of depression, chorea score, TFC, total motor score, age, years of education or duration of illness. This information has been included in the text.

A second point is that the numbers of those who were analyzed at the end are a little confusing: 42 or 45 patients (methods, results and figure). A point that seems easy to resolve.

There were 42 subjects that completed the 80 week protocol and attended the visit 1 week after stopping study medication. Three subjects completed 80 weeks of study treatment but did not return for the final visit. This information has been included in the figure and explained further in the text.

A really minor point is the lay-out and the lack of details in table (fi years at the point of the participants).

**If this is a critical point, please have the reviewer clarify which table and what details should be included.**

**Reviewer 2 Comments to Address:**
Minor essential revisions:
(1) Was any of the main side effects associated with treatments consisting of a specific class of medication?

There was no association between any adverse event and concomitant meds. This statement has been included in the tolerability section.

(2) Controlling for Parkinsonian side-effects by creating a "UHDRS-Parkinsonism-Score" is acknowledged. However, the selection of the sub-items could be challenged, e.g., tandem walking and gait. Negative effects of TBZ on the score may not be
detected if the anti-choreic effects are improving the score. Adding a more selective composite score, e.g. a sum of bradykinesia, rigidity may provide additional interesting clinical information.

The pre-specified analysis plan called for analyzing the specific UHDRS items as listed that can be associated with parkinsonism, including bradykinesia and rigidity. The reviewer has an excellent point of looking at a simpler list of individual items, but we included other UHDRS exam items that may also have been impacted due to the presence of parkinsonism. The steering committee for the trial identified these elements of the UHDRS as reflective of possible “parkinsonism” prospectively (before the first subject was consented); at this juncture, we elected to report this “parkinsonism” score on that basis, rather than retrospectively derive a new measure.

(3) Discussion: Why is increase of parkinsonism scores more likely due to disease progression than side effects of TBZ - please explain.

The length of time of study participation was about 2 years. In this amount of time, it is reasonable to expect that subjects will progress in their HD and develop more parkinsonism given their stage of disease and length of time with the illness. The change was small clinically (baseline score was 14.5 and mean change was 2.1 with SD of 4.3) but statistically significant. Had the effect been due to a pharmacological impact of tetrabenazine, we would have anticipated that it would have emerged more quickly.

Discretionary Revisions:
(1) Conclusion: "...as do the indications for suppressing chorea..." or "...as does the indication..."

This grammatical change was made.