Reviewer’s report

Title: Feasibility of a randomized single-blind cross-over trial to assess the effects of the second generation slow-release dopamine agonists pramipexole and ropinirole on cued-recall memory in idiopathic mild or moderate Parkinson's disease without cognitive impairment.

Version: 0 Date: 08 Mar 2017

Reviewer: Susanna Dodd

Reviewer's report:

The authors have presented a comprehensive description of the conduct and research of a well-conducted trial. There are a number of minor comments:

1) The authors have provided a good description of the treatment patterns (discontinuations, switches and trial drop out). However it is not immediately clear how the 18% missing data rate was calculated: my estimation of missing data is based on completion rates (16/22 = 73%, ie missing data rate of 27%) but perhaps the authors can clarify here?

2) Can I ask why the ON/OFF assessments were made prior to the 6 week stabilization period on each IMP (lines 5-7 on p11 it states "The ON-medication and OFF-medication sessions for each drug should have taken place during a 7-day window, on separate days separated by at least 3 days and followed by a 6 week stabilization period on each IMP")? If my understanding is correct, the ON/OFF assessments should take place after the stabilization treatment period?

There are a few more important comments arising from the complexities introduced by the use of a crossover design:

3) I notice that results are split according to the pre-randomisation treatment. Did the authors consider the impact of carryover effect (from pre-randomisation treatment) - and perhaps whether a future phase III trial may benefit from a washout period prior to administration of the first treatment, in order to remove the potential effect of pre-randomisation treatments?

4) The use of a crossover design assumes that there is no "period effect" (which would occur if patients become more comfortable, for example (or more unsettled) during the course of the trial which in turn affected their outcome) in order to ensure that the two treatment periods are comparable. Might it be worth the authors discussing the whether such a period effect is likely in this clinical area?

5) The advantage of using a crossover design is to permit within-patient differences (of the treatment effects from the two treatment periods) to be used rather than between-patient differences (which would be available from a parallel group design), which reduces the
variability of the data and therefore increases power. Therefore, assuming that this pilot study aims to inform the sample size calculation of a future crossover trial, the authors need to provide an estimate of the SD of the within-patient differences (of the two ON/OFF treatment effects); however, this information has not been presented in the manuscript - instead, the authors have provided the individual SDs (of the ON/OFF differences) for each treatment period separately.

As such, the projected sample sizes (in Table 4) are NOT accurate for a future crossover trial, as they have been calculated under the assumption that the SDs reflect the within-patient differences between the two treatment effects. The authors need to calculate the within-patient between-treatment SDs before calculating projected sample sizes.

6) If the authors feel that some features of the crossover trial (e.g. the washout period) may be a barrier to recruitment (as evidenced by the low consent rate), they may want to suggest that a future trial should instead be based on a simpler parallel group design. In this case, the reported SD estimate (0.18) would be appropriate for the projected sample size calculations for a two-arm trial (ie the sample size projections in Table 4 would need to be amended to reflect results based on a two-group hypothesis test).

7) When discussing the trial results (at the top of p16), authors should stress the fact that the results are imprecise (as demonstrated by wide CIs which include 0) and therefore, even though the individual estimates of decrement in cued recall may be above or below 0, these could be chance findings rather than reflecting an indication of positive/negative treatment effects.

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