

Pyridostigmine bromide versus Fludrocortisone in the treatment of orthostatic hypotension in Parkinson`s disease – reply

Sebastian R. Schreglmann, MD^{1,2}, Fabian Büchele, MD¹, Georg Kägi, MD², Christian R. Baumann, MD¹

¹Department of Neurology, University Hospital Zurich, Frauenklinikstrasse 26, CH-8091 Zurich, Switzerland

²Department of Neurology, Kantonsspital St. Gallen, Rorschacherstrasse 95, CH-9007 St. Gallen, Switzerland

Sebastian R. Schreglmann, MD

current address: Sobell Department of Motor Neuroscience and Movement Disorders

University College London (UCL), Institute of Neurology

London, United Kingdom

tel: +44(0)20 344 88604

fax: +44(0)20 344 88642

email: skgtsrs@ucl.ac.uk

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Dear Editors,

We thank Rita Moiron Simões, Ana Castro Caldas and Joaquim Ferreira for their constructive comment on our publication “Pyridostigmine bromide versus fludrocortisone in the treatment of orthostatic hypotension in Parkinson’s disease – a randomized controlled trial“. We fully agree that there are important considerations regarding the planning of orphan disease interventional trials, and we acknowledge methodological limitations of our study. However, we would like to draw the attention towards issues our respected colleagues did not debate.

As correctly pointed out by the three authors, proven efficacy is mandatory for an “active control” to be included in a controlled trial. Given the scarcity of trials for this indication, we deemed it acceptable to choose a drug that showed efficacy in previous trials that were not controlled [1] or showed efficacy in at least subjective outcome parameters [2]. Moreover, fludrocortisone is considered a mainstay therapeutic agent in this indication by the field and is used frequently, despite the lack of level I evidence [3].

Please let us also provide the non-inferiority outcome analysis, which was excluded from the manuscript because of space restrictions: the between-group difference (Pyridostigmine bromide in comparison to Fludrocortisone) in the mean diastolic blood pressure drop during Schellong test in both *intention to treat* (-12.41; 95% confidence interval: -28.19 to 3.38) as well as *per-protocol* analysis [4] (-10.09; 95% confidence interval: -25.88 to 5.69) exceeded the non-inferiority margin M of 6.61 (50% of the mean reduction in diastolic blood pressure drop during Schellong under Fludrocortisone: 13.24 ± 11.27) – see Figure 1. Albeit the small trial size, given this very lenient M , we feel confident to conclude that Pyridostigmine bromide in all likelihood is inferior to Fludrocortisone in the treatment of OH in PD.

As indeed the analysis presented in the final paper reflects a head-to-head cross-over trial, results are displayed as *intention-to-treat*. We therefore accept the criticism that the final presentation of data does not fully reflect the initial trial plan. We also agree that the addition of a placebo-arm would have certainly added greatly to the validity of our findings. In retrospect, we agree therefore that the initial design as a non-inferiority trial was over-zealous and a comparative trial would have been superior to the design chosen. As treatment data for

this indication however is scarce, and as our data provide evidence for the efficacy of Fludrocortisone, we decided to present the data in this way. Even more so, we would like to argue that the comparison between an interventional drug with an active comparator in a randomized, double-blind head-to-head design constitutes a controlled trial, yielding valid results.

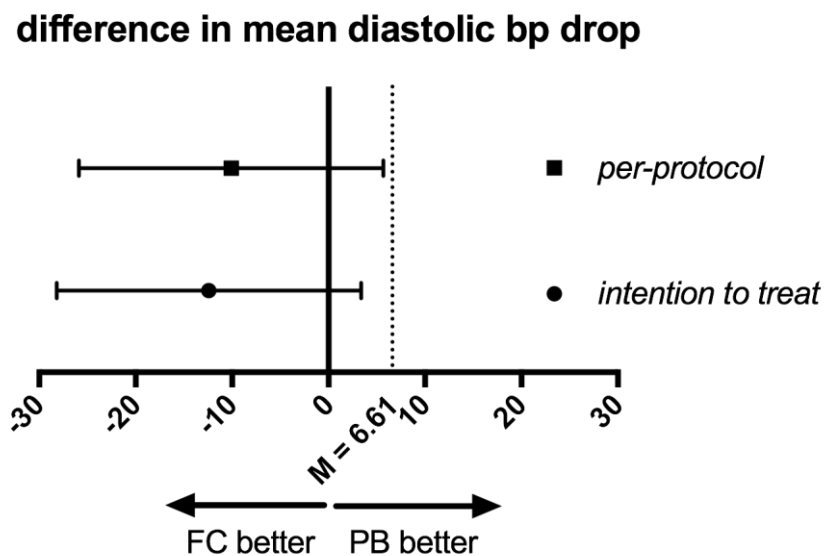


Figure 1: Estimates of the difference in mean diastolic blood pressure drop (mean and 95% confidence intervals). 95% Confidence intervals for both per protocol and intention to treat analyses do not cross the non-inferiority margin M , rendering Pyridostigmine bromide inferior to Fludrocortisone at the pre-defined $M=50\%$

When planning a single centre interventional trial in orphan disease indications, alongside choosing a suitable trial design, feasibility is of paramount importance in order to reach viable conclusions. During the conduction of this particular trial we were faced with the difficult trade-off between well-defined, homogeneous trial groups and too restrictive in-/exclusion criteria in order to reach reasonable numbers of participants. From our own experience, a cross-over design therefore should not be taken as a means to reach significant results with less participants at the expense of longer trial duration per participant. Instead, collaboration between centres with sufficient numbers of participants is most likely the only solution to tackle low statistical power.

As indicated by our respected colleagues and others [5], non-inferiority trials, their design, statistical analysis and interpretation, should be viewed with the degree of caution commanded by their underlying complexity.

Kind regards,

S. R. Schreglmann, F. Büchele, G. Kägi and C. R. Baumann

on behalf of the study authors

1. Hoehn MM. Levodopa-induced postural hypotension. Treatment with fludrocortisone. *Arch Neurol.* 1975 Jan;32(1):50–1.
2. Schoffer KL, Henderson RD, O'Maley K, O'Sullivan JD. Nonpharmacological treatment, fludrocortisone, and domperidone for orthostatic hypotension in Parkinson's disease. *Mov Disord.* 2007 Aug 15;22(11):1543–9.
3. Wu CK, Hohler AD. Management of orthostatic hypotension in patients with Parkinson's disease. *Pract Neurol.* BMJ Publishing Group Ltd; 2015 Apr;15(2):100–4.
4. Shah PB. Intention-to-treat and per-protocol analysis. *CMAJ.* 2011 Apr 5;183(6):696–6.
5. Head SJ, Kaul S, Bogers AJC, Kappetein AP. Non-inferiority study design: lessons to be learned from cardiovascular trials. *Eur Heart J.* 2012 Jun;33(11):1318–24.