Reviewer’s report

Title: Switching patients with acromegaly from octreotide to pasireotide improves biochemical control: crossover extension to a randomized, double-blind, Phase III study

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Reviewer: M Druce

Reviewer's report:

This is a well-written and clear paper that is drawn from a previously published randomised controlled trial (Colao, JCEM 2014)

As this is an extension study, the format, description etc parallel the core study and all aspects are clearly outlined and explained

The background and methods are clear and similar to previous studies - they also parallel a similar study carried out by the C2402 study group (PAOLA)

The section on statistical analysis is a little surprising - it is clear from the description of the study that it was designed as a 'bolt-on' via protocol extension, but it is odd that the study was not 'designed' to demonstrate statistical differences between groups and this makes it unclear therefore what it WAS designed for. The authors do not therefore offer any statistical interpretation and this comes across as rather odd. Is it because the sample sizes are too small (in which case please state and explain why) or for some other reason. Could no statistical tests be reasonably applied even if the results are negative?

The protocol amendment is clearly described but quite confusing to visualise - perhaps a patient flow diagram might help? Actually I see that there is one among the figures (figure 1) but this is not referenced in the section titled 'protocol amendment' so it is not clear if the nuances outlined in the amendment are clearly detailed in the flow chart? In addition of course the way that this occurred does leave the study open to potential bias - while there is not a particular reason to suppose any specific bias beyond the fact that some of the patients received their drug unblinded, the issue of potential bias should be explicitly addressed in the discussion.
Likewise the results are for the most part clearly described. The one confusing section relates to the biochemical response and this relates to the variability at baseline, where inadequate control may refer to elevated GH OR elevated IGF1 OR both. I wonder if this might be most simply clarified by adding a t=0 / baseline to each of the sections in table 2.

The remainder of the results are clearly explained and parallel those from the core study. Under adverse events / safety and tolerability, it is assumed that the figures refer to the cumulative incidence of the effects outlined across core and extension study but could this be confirmed in the text?

Overall it is a well-executed study with results clearly and fairly outlined and 'supportive' of existing data - however the absence of statistical power or any application of numerical testing is a significant limitation that while fairly and clearly reported needs to be better addressed, otherwise the data provided have very limited value indeed.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.
Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.
Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.
Yes

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