BMJ - Decision on Manuscript ID BMJ.2015.027003
Body:
16-Jul-2015

Dear Mrs. Adrion

Manuscript ID BMJ.2015.027003 entitled "Betahistine therapy in patients with Menière's disease: Primary results of a long-term, multicentre, double-blind, randomized, placebo-controlled, dose-defining trial of efficacy and safety (BEMED trial)"

Thank you for sending us this paper and giving us the chance to consider your work, which we enjoyed reading.

Decision: We are pleased to say that we would like to publish it in the BMJ as long you are willing and able to revise it as we suggest in the report below from the manuscript meeting: we are provisionally offering acceptance but will make the final decision when we see the revised version.

Deadline: Because we are trying to facilitate timely publication of manuscripts submitted to BMJ, your revised manuscript should be submitted by one month from todays date. If it is not possible for you to submit your revision by this date, we may have to consider your paper as a new submission.

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Yours sincerely

Kristina Fišter
kfister@bmj.com,

** THE REPORT FROM THE MANUSCRIPT COMMITTEE MEETING, REVIEWERS' REPORTS, AND THE BMJ'S GENERAL REQUIREMENTS FOR RESEARCH PAPERS ARE AVAILABLE AT THE END OF THIS LETTER.**

First, however, please read these four important points about sending your revised paper back to us:

1. Deadline: Your revised manuscript should be returned within one month.

2. Online and print publication: All original research in The BMJ is published with open access. The full text online version of your article, if accepted after revision, will be the indexed citable version (full details are athttp://resources.bmj.com/bmj/about-bmj/the-bmjs-publishing-model), while the print and iPad BMJ will carry an abridged version of your article, usually a few weeks afterwards. This abridged version of the article is essentially an evidence abstract called BMJ pico, which we would like you to write using a template and then email it to papersadmin@bmj.com (there are more details below on how to write this using a template). Publication of research on bmj.com is definitive and is not simply interim "epublication ahead of print", so if you do not wish to abridge your article using BMJ pico, you will be able to opt for online only publication. Please let us know if you would prefer this option.
If/when your article is accepted we will invite you to submit a video abstract, lasting no longer than 4 minutes , and based on the information in your paper's BMJ pico evidence abstract. The content and focus of the video must relate directly to the study that has been accepted for publication by The BMJ, and should not stray beyond the data.

3. Open access publication fee: The BMJ is committed to keeping research articles Open Access (with Creative Commons licences and deposit of the full text content in PubMedCentral as well as fully Open Access on bmj.com). To support this we are now asking all authors to pay an Open Access fee of £3000 on acceptance of their paper. If we accept your article we will ask you to pay the Open Access publication fee; we do have a waiver policy for authors who cannot pay. Consideration of your paper is not related to whether you can or cannot pay the fee (the editors will be unaware of this), and you need do nothing now.

4. How to submit your revised article: Log into http://mc.manuscriptcentral.com/bmj and enter your Author Center, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision.

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You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer.

Once the revised manuscript is prepared, you can upload it and submit it through your Author Center. When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) and Committee in the space provided. You can use this space to document any changes you make to the original manuscript and to explain your responses. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

As well as submitting your revised manuscript, we also require a copy of the manuscript with changes highlighted. Please upload this as a supplemental file with file designation 'Revised Manuscript Marked copy'.

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

INFORMATION ON REVISING THE CONTENT AND FORMAT OF YOUR ARTICLE

Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript. Members of the committee were: Elizabeth Loder (chair), Gary Collins (statistics editor), editors - Alison Tonks, Rebecca Burch, Kristina Fišter, Jose Merino, Tiago Villanueva, Rubin Minhas, Wim Weber.

Decision: provisional acceptance

Detailed comments from the meeting:

The committee very much welcomed this well done trial of a commonly used drug, for which the evidence has been scarce.

First and foremost, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

* The outcomes in the tables look different from the outcomes listed in the methods. For example the primary outcome is given in the text as " the individual attack rate standardized on a 30 day period", but it seems to be given as "decay rate" in table 3. Secondary outcomes start with " the median duration and median severity of evaluated Menière attacks during months 7 to 9 within the 9-month treatment period". That outcome seems not to be given in table 4.

* We expect all outcomes to be reported in the order and as defined at the registration website. If there are any discrepancies these need to be explained and justified, in the response to reviewers and editorial comments as well as in the manuscript. This goes for the primary outcome as well as all secondary outcomes.

* Can you say a bit more about this drug and its presumed mechanism, and also say whether it or something similar is used in other countries in the world, such as the US?

* P-values in table 1 should be removed. There is no need to 'test' for balance - this is a randomised controlled trial.

* +/- should be removed throughout with standard deviations given in brackets.

* Page 17. The main result you report (first) is the mean attack rate over the nine 30-day time intervals for the placebo group. This isn't really an outcome per se, (as no treatment comparisons are being made), but rather a description of what is happening in one arm (placebo) of the trial. We thought the main outcomes are the rate ratios over the 90 day period at the end of the treatment period.

* The sample size calculation is nicely detailed but complex, and it would benefit from a re-writing to make it clear what (and why) you are doing.

* There is missing data for many of the secondary outcomes (table 4) and a complete case was carried out. Why not impute? It was indicated in the methods (page 15) that you would impute for secondary outcomes.

* Attack severity and duration (secondary outcomes) reported on page 20, should for clarity and completeness be reported in Table 4 with the other outcomes. Only p-values are reported in the text for these outcomes without and quantification of severity or duration.

IMPORTANT
When you revise and return your manuscript, please take note of all the following points about revising your article. Even if an item, such as a competing interests statement, was present and correct in the original draft of your paper, please check that it has not slipped out during revision.

a. In your response to the reviewers and committee please provide, point by point, your replies to the comments made by the reviewers and the editors, and please explain how you have dealt with them in the paper. It may not be possible to respond in detail to all these points in the paper itself, so please do so in the box provided

b. If your article is accepted it will then be edited, proofed, and - after your approval - published on bmj.com with open access. This open access Online First article will not be a pre-print. It will represent the full, citable, publication of that article. The citation will be year, volume, elocator (a unique identifier for that article): eg BMJ 2008;337:a145 — and this is what will appear immediately in Medline, PubMed, and other bibliographical indexes. We will give this citation in print and online, and you will need to use it when you cite your article.

c. Please write an abridged version of the article for the print and iPad BMJ using the appropriate BMJ pico template for your study's design. Please be reassured that it doesn't take long to complete this. When your BMJ pico is ready please email it to papersadmin@bmjgroup.com.The templates for you to download are at
http://resources.bmj.com/bmj/authors/bmj-pico

d. Please include these items in the revised manuscript to comply with BMJ style:

Title: this should include the study design eg "systematic review and meta-analysis"

Abstract
structured abstract including key summary statistics, as explained below (also see
http://resources.bmj.com/bmj/authors/types-of-article/research)
for every clinical trial - and for any other registered study - the study registration number and name of register – in the last line of the structured abstract.

Introduction
this should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now

Methods:
for an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the manuscript urls to openly accessible websites where these materials can be found
Results
please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines http://www.equator-network.org/reporting-guidelines/sampl/

summary statistics to clarify your message. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:

For a clinical trial:
• Absolute event rates among experimental and control groups
• RRR (relative risk reduction)
• NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000)

one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers eg STATA, but please say in the text which version you used
for articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system
Discussion
please write the discussion section of your paper in a structured way, to minimise the risk of careful explanation giving way to polemic.Please follow this structure:
statement of principal findings of the study
strengths and weaknesses of the study
strengths and weaknesses in relation to other studies, discussing important differences in results and what your study adds. Whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses (eg Cochrane reviews)
meaning of the study: possible explanations and implications for clinicians and policymakers and other researchers; how your study could promote better decisions
unanswered questions and future research

Footnotes and statements

What this paper adds/what is already known box (as described at http://resources.bmj.com/bmj/authors/types-of-article/research)

ID of ethics committee approval and name of the ethics committee/IRB; or a statement that approval was not required (see http://resources.bmj.com/bmj/authors/editorial-policies/guidelines) and a statement that participants gave informed consent before taking part

a statement that any identifiable patients have provided their signed consent to publication. Please submit, as a supplemental file, the signed BMJ patient consent form giving consent to publication in The BMJ of any information about identifiable individual patients. Publication of any personal information about a patient in The BMJ, for example in a case report or clinical photograph, will normally require the signed consent of the patient.

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signed patient consent form(s), if the article gives enough personal information about any patient(s): this sometimes occurs even in research papers - for example in a table giving demographic and clinical information about a small subgroup in a trial or observational study, or in quotes/tables in a qualitative study - (see http://resources.bmj.com/bmj/authors/editorial-policies/copy_of_patient-confidentiality)

a data sharing statement declaring what further information and data you are willing to make available, over and above the results reported in the paper. Suggested wording: "Data sharing: technical appendix, statistical code, and dataset [state whether any patient level data have been anonymised] are available at this repository or website OR from the corresponding author at ". If there are no such further data available, please use this wording: "Data sharing: no additional data available". For papers reporting the main results of trials of drugs or devices we require that the authors state, at a minimum, that the relevant anonymised patient level data are available on reasonable request from the authors
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a statement describing the role of the study sponsor(s), if any, in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication
assurance, in the cover letter, that a clinical trial funded by a pharmaceutical or other commercial company follows the guidelines on good publication practice (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements)
inclusion in the list of contributors the name(s) any professional medical writer(s), specifying in the formal funding statement for the article who paid the writer. Writers and authors must have access to relevant data while writing articles.

Patient centred research
for studies that are relevant to patients we expect authors to report in their articles the extent of their study's patient-centredness, as highlighted by these questions:
did you involve patients/service users/carers/lay people in the design of this study? Please state whether you did, and give details (Methods section)
was the development and/or selection of outcome measures informed by patients' priorities and experiences? Please give details (Methods section)
were patients/service users/carers/lay people involved in developing plans for participant recruitment and study conduct? If so, please specify how (Methods section)
have you planned to disseminate the results of the study to participants? If so how will this be done? (Describe in brief footnote)
are patients thanked in the contributorship statement or acknowledgements?
for articles reporting randomised controlled trials: did you assess the burden of the intervention on patients' quality of life and health? If so, what evaluation method did you use, and what did you find? (Methods and Results sections)

REFEREE COMMENTS

Reviewer: 1

Recommendation:

Comments:
This is a well constructed multicenter randomized blinded trial assessing the effects of low and high dose betahistine versus placebo on multiple outcome measures in patients with definite Meniere's Disease (MD) as defined by AAO and Barany criteria. The methods are clear and the analysis and results are well described. I have only a few requests of the suthors to conside for clarificationr:

1.Please state the duration of MD prior to enrollment for each treatment group. It would be desirbale to see a balanced duration of symptoms of MD in each group prior to enrollment such that one group did not have a proportionately earlier or later stage MD when starting the trial.

2.How did the authors screen for retrocochlear disease in their subjects (MRI, ABR)? There are cases of small intracanalicular or even intralabyrinthine schwannomas that mimic MD and routine clinical care for all patients with asymmetric hearing loss is the consideration of retrocochlear or intracochlearlesions.

3.How was "postural vertigo" differentiated from BPPV in your analysis? There is an increased incidicne of BPPV in MD and I would assume these posiitonal attacks would be excluded if they are cuased by canalithiasis.

4.How complete were the daily diaries for vertigo reporting? Did the patients report their symptoms regularly each day or wait and fill in daya at a time? In my experience with diary studies, it is important that the subjects enter data on a regular basis.

5.How were missing data points handled? For instance, if a subject skipped five days in a month in their diary, were these days counted as "failures=vertigo" or just not analyzed. Missing data points is always a struggle in large trias likethis one and the proper management of messing data is critical. Please expand in the manscript how these missing data were handled.

Additional Questions:
Please enter your name: Joel A Goebel, MD

Job Title: Professor and Vice Chairman

Institution: Washington University Department of Otolarynoglogy, Saint Louis,MO USA

Reimbursement for attending a symposium?: Yes

A fee for speaking?: Yes

A fee for organising education?: Yes

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: Yes

Have you in the past five years been employed by an organisation that may
in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way
gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: I have no direct competing interests with the topico fhtis paper or the authors. I do lecture and conduct research on various vestibular topics unrelated to this project.

Reviewer: 2

Recommendation:

Comments:
This is an excellent randomized controlled study investigating the efficacy of beta-histine at low and high dose against placebo fro the management of vertigo and other symptoms of definite Meniere's disease.

It is a very well structured study and acts as a very important contribution to this area of clinical treatment. Such a well-constructed and rigorous trial has been long awaited.

Meniere's disease is relatively uncommon (as highlighted in our recent BMJ review) but it is a well known condition in general practice and the article is likely to have an important bearing on the management of these patients.

The study design, participants, methods, results, interpretations and references are beyond criticism.

I strongly recommend the article to the BMJ

Additional Questions:
Please enter your name: Jonathan Harcourt

Job Title: Consultant ENT Surgeon

Institution: Charing Cross Hospital

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may
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Do you hold any stocks or shares in an organisation that may in any way
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If you have any competing interests (please see BMJ policy) please declare them here:

Reviewer: 3

Recommendation:

Comments:
The manuscript is a randomized placebo-controlled double-blind 3 arm Phase III clinical trial for the prophylactic treatment of vestibular episodes in Meniere's disease. The intervention consisted of two dosages of betahistine-dihydrochloride [high dose (HD): 3 x 48 mg per day, (N=74); approved standard dose (LD): 2x 24 mg per day, (N=73)] and placebo (PL) (N=74) over a period of 9 months. The results show no significant differences among the three groups.
Since betahistine is the most prescribed drug to treat MD in Europe, the result of this clinical trial should be published and they will have a significant impact on current clinical practice.
The RCT has been carefully designed, including power calculation and no apparent bias is observed to this reviewer.
There are some minor questions to solve:
1. Patients with MD have a high prevalence of migraine. Vestibular migraine may overlap with MD is some cases. How did the author consider migraine and vestibular symptoms? Was migraine one of the exclusion criteria? If so, it should be stated. If this was not the case, this information should be added on Table 1. The most common adverse effect was headache and it would be interesting to know if patients reporting betahistine-associated headache had in fact a previous history of migraine.
2. Patients with MD also have a higher comorbidity of autoimmune diseases (Gazquez 2011; Tyrell 2014) On Page 7: in the exclusion criteria, complex diseases that might confound treatment assessment were included. Autoimmune background is probably involved in a subset of patients with MD. Did the authors exclude patients with systemic autoimmune disorders such as rheumatoid arthritis or SLE? This should be also included in the exclusion criteria.
3. Table 1 does not include the age of onset of the disease on each group. This could be a potential bias in case of differences among groups.

Additional Questions:
Please enter your name: Jose Antonio Lopez-Escamez MD, PhD

Job Title: PI Otology and Neurotology Group CTS495

Institution: Centre for Genomic and Oncology Research Genyo, University of Granada

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: Research Grants from Instituto de Salud Carlos III PI13-1242 and Meniere's Society, UK.

END
Date Sent:
16-Jul-2015