Author's response to reviews

Title: Patient-rated suitability of a novel electronic device for self-injection of subcutaneous interferon beta-1a in relapsing multiple sclerosis: an international, single-arm, multicentre, Phase IIIb study

Authors:

Virginia Devonshire (vdev@shaw.ca)
Txomin Arbizu (unitatem@bellvitgehospital.cat)
Björn Borre (bjorn.borre@neurokliniken.se)
Michael Lang (lang@neurologie-ulm.de)
Alessandra Lugaresi (a.lugaresi@unich.it)
Barry Singer (bnvsinger@earthlink.com)
Elisabetta Verdun di Cantogno (elisabetta.verdun@merckserono.net)
Peter Cornelisse (peter.cornelisse@merckserono.net)

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Response to reviewers

Reviewer 1 (Dr Freedman)

The study is described as a phase IIIb, which usually examines efficacy, though the stated goal of this study is "feasibility" which makes it almost a pilot study looking to move towards a true efficacy study which might compare the new Rebismart with the previous injector in terms of adherence issues as well as perhaps drug delivery. This study does neither and as such should really not be tagged anything more than a phase IV observational study.

As the outcomes are just those of patients' subjective opinion of the device there is little objective evidence such as drug levels, biomarkers or even laboratory changes that would indicate that drug delivery is more efficacious, consistent and attains the desired therapeutic goals. A true phase IIIb study might also randomize patients to the old vs. new device and rate such important adherence factors such as ISRs, pain etc. or a much harder endpoint of simply those still using the device after a set amount of time.

It is odd that patients are asked to assess the new device after only a minimum of 6 weeks on the original one. Reality though was that most patients took the original for nearly a year.

The authors thank Dr Freedman for his query regarding the classification of this trial. However, as the multidose cartridge had not been approved at the time of the study inception, this study could not be listed as a Phase IV observational study. In addition, the trial is currently listed on clinicaltrials.gov as a Phase III study. Therefore, no change can be made to the manuscript in this regard.

Probably figures 2 and 4 are all that are required.
Figure 1 has been removed as suggested; however Figure 3 has been retained as this gives additional information regarding the different features that was not included in the text, and which the authors consider to be of relevance and interest to the reader. Additional text has been added (‘ratings for each feature are shown in Figure 2’) to highlight the added value of this figure above the text.

The observations are valid and probably warrant a true phase III study to demonstrate whether the device may well be superior than current delivery systems in terms of adherence or some other outcome, but the authors should state this.

An addition has been made to the text on page 20 as requested, as shown below:

‘In addition, it may be interesting to compare treatment adherence and disease outcomes in patients using the new device and in those using other delivery methods.’

Reviewer 2 (Dr Jaber)

This study reports higher occurrence of ISRs (especially pain of injection) vs. previous studies using a different device or manual injection. The discussion meant to explain this difference is not supported by data, and requires further clarification. Among other factors, it would be useful to compare "refrigerating" practices during the previous studies.

Unfortunately, detailed information on the refrigeration and pre-injection preparations by study participants was not captured in this study, so a formal comparison with practices in other studies is not possible. However, as noted in the text, at the time of this trial the multidose cartridge required refrigeration and would have taken longer to come to room temperature than previous sc IFN beta-1a devices Therefore, patients would need to change their injection practice to accommodate the need to warm the greater volume of drug prior to injection, which may have affected the incidence of ISRs. In response to the reviewer’s
query in this regard, we have added some additional text and rewording has been done on page 17 to clarify that the issue further, as shown below:

‘It is possible that patients familiar with the single-dose syringe may have underestimated the time needed to warm the larger volume of drug in the multi-dose cartridge within the device to room temperature…… However, as detailed information on injection preparation was not formally collected, we cannot confirm that injection of cold drug contributed to the relatively high incidence of ISRs seen in this study.’

There is no data or description showing how this device supports treatment adherence.

The authors agree that, at this time, we do not have data to demonstrate that the device supports treatment adherence; this has been further clarified in the text (page 20). This issue is also addressed in response to the comment from Dr Freedman (see above).

‘Dosing history data can also be downloaded, linked to electronic patient records and reviewed by physicians, and thus may promote an open dialogue between patient and neurologist regarding treatment adherence, although this was not assessed in this study.’

In summary, over the study period, Rebismart has been assessed as at most equivalent to already existing device, with a higher incidence of ISRs (specially pain): could you please comment on the benefit to patient vs. existing device?

Benefits over the existing injection devices are discussed in the final paragraph on page 19 - this section has been reworded for clarity, as shown below:

‘In addition to shielding the needle from view and improved convenience, which are benefits common to all currently available injection devices, the new electronic injection device has
several specific additional features that may further benefit patients. The ability to adjust injection comfort settings may encourage patients to experiment with new settings and customise these to their personal preferences. This function may enable patients to continue therapy where they may previously have chosen to stop treatment. Additionally, over 90% of patients considered confirmation of successful injection to be useful in providing reassurance that they had administered their injections correctly. The multidose cartridge contains one week’s worth of medication, so reducing the frequency of device loading. The novel dosing log informs the patient that an injection is due and serves as a reminder of treatment history, which may be particularly useful to patients with cognitive impairment. The log also enables adherence to MS treatment to be recorded accurately and objectively for the first time. In contrast, all previous measures of adherence have relied on subjective, often retrospective, patient reporting, which can give inaccurate results.'