Title: Patient adherence to and tolerability of self-administered interferon beta-1a using an electronic autoinjection device: a multicentre, open-label, phase IV study

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Author's response to reviews: see over
Dear Reviewers

Re: MS: 1125498122614170 – Patient adherence to and tolerability of self-administered interferon beta-1a using an electronic autoinjection device: a multicentre, open-label, phase IV study

On behalf of all authors, thank you for your valuable comments on how to improve the above submitted manuscript. We have worked to address these comments and hope that the revised manuscript is now acceptable for publication.

Best regards

Alessandra Lugaresi

Reviewer 1

The study assessed short-term adherence to, and tolerability of, IFN β-1a administered via electronic autoinjection device in patients with RRMS. This 12-week, multicentre, open-label, single-arm, observational, Phase IV study included 119 pts who self-administered IFN β-1a (titrated to 44 µg), subcutaneously (sc), three times weekly, via electronic autoinjection device. In general this is well written study that was conducted carefully. There are several issues, however that need to be addressed.

1. The authors should discuss in more detail their study design and whether potential alternative study designs were considered (long-term follow-up, placebo-controlled, comparison of autoinjector vs. no injector, etc).

We are planning to perform an extension study of patients included in the BRIDGE study, to assess long-term safety, tolerability and treatment persistence. However, we believe it is worth publishing the core study results, as a study of this duration still provides important information regarding short-term adherence. The potential to perform longer-term follow-up of this study population has been noted in the Discussion (see P19).

Regarding the study design, this was an observational, post-marketing study; therefore, it was not possible to include a placebo control arm. Furthermore, as it was a sponsored study, regulations in Italy dictated that we could not include patients undergoing different
treatments marketed by other pharmaceutical companies. As patients were switching from other treatments because of either a lack of efficacy or adverse effects, including poor local tolerability, the use of manual or conventional injecting devices was also not feasible. We recognize that the lack of a control group does not allow us to discriminate between the effects of the new device versus the new drug and this is now acknowledged in the Discussion (see P19).

2. The novelty of the study should be emphasized respect to the previous studies that used autoinjector with IFN β-1a. Why is this study worthy publishing and what adds to the literature that we did not learn from already published studies.

A previous study by Devonshire et al. on the same device (a prototype) has been published in BMC Neurology (2010;10:28), which differed from the current study in some important points. Firstly, the previous study did not assess adherence, as measured by the device log; therefore, our study provides new, valuable adherence data that was captured objectively. Secondly, the Devonshire study included a different patient population: patients already being treated with IFN β-1a sc administered using the conventional Rebiject™ injector; therefore, only the device, and not prior treatment, differed. The Devonshire paper is already referenced and we have performed a search of PubMed and found no recent articles reporting clinical trials of RebiSmart™ (search terms: “multiple sclerosis” AND “electronic injection device”). Comparison with the previous study and a note of what this study adds to the literature has been included in the Discussion (see pp 15 and 20).

The reviewers may be interested to know that in Italy, we thought it would be of interest to determine whether patients treated with other disease-modifying drugs may take advantage, when having indication to switch treatment, of the option of using an electronic device bearing some useful features. Compared with the injection devices available for use with other immunomodulators, the Rebismart™ device offers the possibility of regulating the speed of insertion and retracting the needle, as well as adjusting the depth of injection and needle gauge. The device also signals when the injection has been completed, and has a completely hidden needle, as in the case of the Betaject™ Comfort autoinjector for administering interferon beta-1b. As well as recording objective adherence data, the injection log can be used to remind the patient of the time of the last injection and, therefore, may prevent double-dosing or missed injections.
3. Were NAbs in previously treated pts with IFN-beta assessed and was adherence related to the NAbs? Did authors look at predictivity?

In the coordinating centre, NAbs were always monitored and no NAb-positive patients were included. Our study focussed on adherence, safety and tolerability, and not efficacy; further, as this was a short-term study, we believe that NAb status is unlikely to have had a significant impact on outcomes. We doubt that the use of a specific autoinjector is likely to have influenced the incidence of NAbs. The frequency of NAbs with the serum-free formulation of Rebif® (previously known as Rebif® New Formulation) has already been assessed in previous studies. We have, therefore, not amended the manuscript to discuss NAbs.

Reviewer 2

Reviewer 2 had no comments that required revision of the manuscript.