PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cause of death in MS: Long-term follow-up of a randomised cohort, 21-years after the start of the pivotal IFNB-1b study
AUTHORS	Goodin, Douglas ; Ebers, George; Cutter, Gary; Cook, Stuart; O'Donnell, Timmothy; Reder, A; Kremenchutzky, Marcelo; Oger, Joel; Rametta, Mark; Beckmann, Karola; Knappertz, Volker

VERSION 1 - REVIEW

REVIEWER	Kjell-Morten Myhr, MD, PhD, Professor in Neurology The Norwegian Multiple Sclerosis competence centre, Department of Neurology Haukeland University Hospital Bergen, Norway KM Myhr has no competing interests related to this manuscript
REVIEW RETURNED	22-Aug-2012

GENERAL COMMENTS	This is a very interesting study reporting the cause-of-death (COD) and describing the probable relationship between deaths and the underlying MS in the cohort of relapsing-remitting (RR) MS patients who had previously participated in the pivotal RCT of interferon beta (IFNβ)-1b for MS. The authors predefined rules to classify the underlying COD into one of nine COD-categories, and used a pre-defined decision algorithm to determine the relationship of death to MS. Although much of the results have been previously reported in Neurology, I think that this new approach aiming at determine the relationship of death to MS is worth publishing. The manuscript, however, could preferably be more focused on the "primary" objective and shortened. Some questions and comments/suggestions to the authors: Although the pre-defined decision algorithm is used to determine the relationship of death to MS, the authors should discuss the decision why death in cases with EDSS equal or higher than 7.0 should be “Always MS-Related”. Young MS-patients with high disability (EDSS equal or higher than 7.0) may certainly also die from cardiovascular/cerebrovascular diseases, cancers etc, independent of MS. General comments/suggestion: The manuscript should be more focused on the objectives of the study: reporting the cause-of-death (COD) and its relationship to MS. This is also the novelty of this manuscript.

	The authors may reduce the general description of survival and mortality analysis, and also details from the “Neurology-paper” could be reduced. I suggest that “Introduction” could be substantially shortened – especially from the second paragraph on page 4 (line 25) to the last paragraph on page 5 (line 36). The “Discussion” should also be more focused on the cause-of-death (COD) and its relationship to MS. Therefore the first paragraph of the “Discussion” on page 14, line 32 to page 15, line 14 could be substantially reduced. Similarly also the second paragraph on page 16 (line 18) to the third paragraph on page 17 (line 39) could be substantially reduced.

REVIEWER	Henrik Brønnum-Hansen Department of Public Health University of Copenhagen Denmark No competing interests
REVIEW RETURNED	03-Sep-2012

THE STUDY	The research question integrate two purposes that should be more clearly separated Overall study design: Sample too small No statistical analysis or tests
GENERAL COMMENTS	The paper presents a sub-study of a survival study published in 2012 (ref 18) and describes the distribution of causes of death (COD) among 81 MS patients originally enrolled in the RCT of IFNβ-1b. The sub-study had two purposes, (1) to determine the COD for MS patients and to assess the relationship to MS (2) to establish if the excess mortality among placebo randomised patients was mainly MS-related. The results that might come from scrutinizing the first purpose have limited value because of scarce data. It would have been better if the two research questions were investigated separately and independently from pharmaceutical companies. The first sentence in the abstract conclusion seems to refer to the result of the survival study published in Neurology 2012 (ref 18). In the section “Establishing cause of death” the authors state that “Two of these three members (SC and TO) were completely independent from the 21Y-LTF” (page 8, line 5). What is meant by “completely”? Were they or were they not independent from the 21Y-LTF? What is the role in the committee of a neurologist representative from Bayer? “No specific statistical analysis ... were undertaken” (page 10, line 34) Nevertheless, “Statistical analysis were performed under the direction of GC and KB” (page 22, line 40). How is this to be understood? The first column in table 1 has the heading “Always MS-related”. In

	the text only the relationship “MS-related” is used. I assume that “MS-related” does not include “Probably MS-related”. Regarding purpose 1, the assumption, that suicide is “always MS-related” is questionable. Furthermore, one could hypothesize that elevated suicide risk might be related to disease-modifying therapy because the medication might cause depression. The authors argue, that “Also typically of younger MS populations, the observed suicide rate was quite high (page 15, line 26). But according to a Danish study (jnnp 2006) excess suicide rate seems to increase again some 20 years after diagnosis probably because patients typically experience the most serious consequences after long term disease. The present study has not enough power to confirm this result. Regarding purpose 2, the distribution of COD changes with length of follow-up as illustrated in ref 23 (Figure 6). I wonder what the conclusion would have been if end of follow-up was after 15 years since RCT enrolment or – in a future update of the trial – 30 years since RCT enrolment. The main problem with the scarce data is the lack of power to allow for performing a proper survival analysis. After all, I wonder if the conclusion from the data is that IFNβ-1b reduces the risk of pulmonary infections among MS patients.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

Although the pre-defined decision algorithm is used to determine the relationship of death to MS, the authors should discuss the decision why death in cases with EDSS equal or higher than 7.0 should be “Always MS-Related”. Young MS-patients with high disability (EDSS equal or higher than 7.0) may certainly also die from cardiovascular/cerebrovascular diseases, cancers etc, independent of MS.

We now discuss these issues on p. 8. This impacted only three patients (evenly divided among the treatment arms) and excluding didn’t alter the analysis.

General comments/suggestion:

The manuscript should be more focused on the objectives of the study: reporting the cause-of-death (COD) and its relationship to MS. This is also the novelty of this manuscript.
The authors may reduce the general description of survival and mortality analysis, and also details from the “Neurology-paper” could be reduced.
I suggest that “Introduction” could be substantially shortened – especially from the second paragraph on page 4 (line 25) to the last paragraph on page 5 (line 36).
The “Discussion” should also be more focused on the cause-of-death (COD) and its relationship to MS. Therefore the first paragraph of the “Discussion” on page 14, line 32 to page 15, line 14 could be substantially reduced. Similarly also the second paragraph on page 16 (line 18) to the third paragraph on page 17 (line 39) could be substantially reduced.

As suggested, we have substantially reduced the Introduction and the Discussion to make it more focused

Reviewer #2

Overall study design: Sample too small
This was a LTF of a defined population who participated in the original RCT.

No statistical analysis or tests
Only descriptive statistics were possible.

The paper presents a sub-study of a survival study published in 2012 (ref 18) and describes the distribution of causes of death (COD) among 81 MS patients originally enrolled in the RCT of IFNβ-1b. The sub-study had two purposes, (1) to determine the COD for MS patients and to assess the relationship to MS (2) to establish if the excess mortality among placebo randomised patients was mainly MS-related.
We agree that the trial is not a population-based study that can provide a good answer to the first question. That was not the intent. Rather, as the reviewer points out, this is an LTF following an RCT, which can answer the second. We have clarified this in the text (p. 4)

The results that might come from scrutinizing the first purpose have limited value because of scarce data. It would have been better if the two research questions were investigated separately and independently from pharmaceutical companies.
The pharmaceutical company sponsored the original RCT and its follow-up. However, the data was analyzed by an independent academic statistician and the measured outcome (death) was unambiguous.

The first sentence in the abstract conclusion seems to refer to the result of the survival study published in Neurology 2012 (ref 18).
This is correct.

In the section “Establishing cause of death” the authors state that “Two of these three members (SC and TO) were completely independent from the 21Y-LTF” (page 8, line 5). What is meant by “completely”? Were they or were they not independent from the 21Y-LTF? What is the role in the committee of a neurologist representative from Bayer?
“No specific statistical analysis ... were undertaken” (page 10, line 34) Nevertheless, “Statistical analysis were performed under the direction of GC and KB” (page 22, line 40). How is this to be understood?
We have clarified the meaning of “completely independent”, which meant that they didn’t participate in the 21 year LTF (p.6). VK oversaw the deliberations and we have njow stated this (p. 6). Only descriptive statistics were undertaken. We have clarified this (p. 9).

The first column in table 1 has the heading “Always MS-related”. In the text only the relationship “MS-related” is used. I assume that “MS-related” does not include “Probably MS-related”.
The a priori rules are what are specified in the Table. The committee adjudicated whether each death was MS-related. We have now clarified this (p. 8).

Regarding purpose 1 (overall study design: sample too small), the assumption, that suicide is “always MS-related” is questionable. Furthermore, one could hypothesize that elevated suicide risk might be related to disease-modifying therapy because the medication might cause depression. The authors argue, that “Also typically of younger MS populations, the observed suicide rate was quite high (page 15, line 26). But according to a Danish study (jnnp 2006) excess suicide rate seems to increase again some 20 years after diagnosis probably because patients typically experience the most serious consequences after long term disease. The present study has not enough power to confirm this result.
We agree that this is not a population-based study and can’t really address question #1. As the reviewer points out, the issue of suicides is controversial. We made the decision to consider them

MS-related was made a priori. Regardless, however, this didn't affect our analysis because the suicides were evenly divided between groups. We have now clarified this (p. 8).

Regarding purpose 2 (no statistical analysis or tests), the distribution of COD changes with length of follow-up as illustrated in ref 23 (Figure 6). I wonder what the conclusion would have been if end of follow-up was after 15 years since RCT enrolment or – in a future update of the trial – 30 years since RCT enrolment.
As has been repeatedly found in the literature, the cause of death in MS patients changes as a person ages. Early after diagnosis, MS-related causes predominate, whereas later on the usual causes of death in the elderly become more prominent. All we are reporting is that we found excessive mortality in patients randomized to placebo and that this excessive mortality (after 21 years) was attributable to MS-related causes.

The main problem with the scarce data is the lack of power to allow for performing a proper survival analysis. After all, I wonder if the conclusion from the data is that IFNβ-1b reduces the risk of pulmonary infections among MS patients.
This was an ITT and patients were only on placebo for and average of 3 years. We doubt that IFNβ-1b taken for 3 years reduces pulmonary infections 21 years later.

VERSION 2 – REVIEW

REVIEWER	Kjell-Morten Myhr, MD, PhD, Professor in Neurology The Norwegian Multiple Sclerosis competence centre, Department of Neurology Haukeland University Hospital Bergen, Norway KM Myhr has no competing interests related to this manuscript
REVIEW RETURNED	15-Oct-2012

- **The reviewer completed the checklist but made no further comments.**