Abstract: Three interferons are marketed for the treatment of relapsing-remitting multiple sclerosis. In its pivotal trial, one of them demonstrated impressive efficacy as a once-weekly regimen, but later head-to-head studies and reviews questioned its superiority. Analysis of this pivotal trial in publications and health authority reviews has shown that its early termination might have caused attrition bias. Censored patients were different from those completing the study on magnetic resonance imaging parameters and benefited from placebo in terms of relapse rate. Early progression of disability and differences in follow-up duration could have favored the benefit observed for the progression of disability outcome. Only the raw data could be of help to confirm or refute doubts about this trial. Raw data should be made available to the scientific community.

Keywords: interferons, relapsing-remitting multiple sclerosis, efficacy

Journal of Central Nervous System Disease 2012:4 135–145
doi: 10.4137/JCNSD.S10150
This article is available from http://www.la-press.com.
© the author(s), publisher and licensee Libertas Academica Ltd.
This is an open access article. Unrestricted non-commercial use is permitted provided the original work is properly cited.
Background

Since 1995, three interferons have been marketed in Europe for the treatment of relapsing-remitting multiple sclerosis. These therapies include one interferon β-1b (IFNβ-1b) administered subcutaneously on alternate days (Betaseron®/Betaseron®/Extavia®) and two interferon β-1a products, ie, Avonex® (IFNβ-1a IM) administered once weekly by the intramuscular route and Rebif® (IFNβ-1a SC) administered three times weekly subcutaneously. Each of the three interferons was approved for the treatment of relapsing-remitting multiple sclerosis on the basis of one main, pivotal IFN β-1a Subcutaneously in Multiple Sclerosis) trial, and reviews of the initial trials and their main clinical outcomes are summarized in Table 1.

The first 2 years; however, the 2-year data includes progression sustained for 3 months. The three pivotal trials led to the approval of interferon in relapsing-remitting multiple sclerosis.

Description of the Trials

All three trials were randomized, multicenter, double-blind, placebo-controlled in design. The planned duration of the trials was 2 years for the PRISMS and MSCRG studies and 3 years for the IFNβ-1b Trial.
Analysis of Clinical Outcome Measures and MRI Data; Digging Deeper into the Data

Relapses

In PRISMS and the IFN β-1b Trial, the relapse rate reduction was slightly lower in year 2 than in year 1 (Table 1). In the MSCRG study, the relapse rate reduction was markedly higher for patients followed up for 2 years than for those followed up for one year (–32.2% versus –9.6%). According to the IFNβ-1a IM FDA summary used as the basis for regulatory approval, the sponsor suggested a lag time between initiation of treatment and onset of clinical benefit. This suggestion is not confirmed on more thorough analysis of the relapse rate (Table 2).

For analysis of MSCRG, three different cohorts of patients are considered: patients followed up for 2 years for analysis (n), patients followed up at year 2 for analysis (n), and year 2 patients for analysis/included (%).

Table 1. Patients, baseline characteristics and main results of the three pivotal trials.

| IFNβ-1a | IFNβ-1b | IFNβ-1a |
|---------|---------|---------|
| 30 (im) | 66 (sc) | 875 (sc) |
| 30 (im) | 66 (sc) | 132 (sc) |

Table 2. Data on relapse rate in Multiple Sclerosis Collaborative Research Group.

| Patients (n) | IFNβ-1a IM | IFNβ-1a IM |
|--------------|-------------|-------------|
| Placebo      | 132         | 150         |
| Placebo      | 45          | 65          |
| Placebo      | 87          | 85          |
| Placebo      | 87          | 85          |
| Placebo      | 143         | 158         |

Notes: *Not statistically significant; †P = 0.063 according to US Food and Drug Administration Center for Biologics Evaluation and Research analysis; ‡P = 0.04 according to the sponsor’s analysis; ††P = 0.063 according to FDA analysis; †‡P = 0.04 according to sponsor analysis.
Let us consider the annualized relapse rate of year 1 patients that would have evolved in the same proportion as did the one from year 1 to year 2 for patients followed up 2 years. The annualized relapse rates would be 0.83 for placebo: \([45 \times 0.8] + (45 \times 0.8 \times 0.78/1.01) + (87 \times 1.01) + (87 \times 0.78)\)/\((132 \times 2)\) and 0.75 for IFNβ-1a IM \([65 \times 1.03] + (65 \times 1.03 \times 0.54/0.72) + (85 \times 0.72) + (85 \times 0.54)\)/\((150 \times 2)\). The benefit on relapse would be −10.1%, corresponding logically to the results obtained for all patients during the first year of the study (−9.6%).

The impact of the difference in follow-up duration between the different subsets of patients and treatment groups on the efficacy of IFNβ-1a IM in the prevention of relapse can also be evaluated using data from the FDA clinical review. These data comprise:

- a histogram of percentage of non-zero time at risk for patients progressing as per EDSS score and treatment group
- a histogram of percentage per year of non-zero time at risk for patients progressing as per EDSS score and treatment group
- a table of exacerbation rate and number of patients with non-zero time at risk as per EDSS score and treatment group.

The time at risk as per EDSS and treatment arm can be evaluated from the histogram bar measurements (Table 3). The benefit of IFNβ-1a IM on relapse rate increases from −11.5% to −17.2% when time at risk for each EDSS group is taken into account in the calculation showing the impact of follow-up duration on the outcome of relapse rate. Therefore, the time at risk is not equal to the duration on study, but this information is not available for each EDSS and treatment group in reviews by health authorities or in the published literature. The efficacy of IFNβ-1a IM in the prevention of relapse is thus probably nearer to −10%. Other figures: −32.2%, −18% and fortunately +29% do not correctly reflect the efficacy of IFNβ-1a IM in the randomized cohort.

**Progression of disability**

The IFNβ-1b Trial did not demonstrate a significant beneficial effect on sustained progression of disability and, according to the FDA analysis, the results of PRISMS were considered to be not significant for the 22 µg × 3/week regimen and significant for...
Table 3. Data according to EDSS and treatment group.\textsuperscript{17,18}

|                      | EDSS 1 | EDSS 1.5 | EDSS 2 | EDSS 2.5 | EDSS 3 | EDSS 3.5 | Total | Mean/patients | % change |
|----------------------|--------|----------|--------|----------|--------|----------|-------|---------------|----------|
| Number of patients with non-zero time at risk* | Placebo | 10       | 33     | 21       | 21     | 17       | 30    | 132           |          |
|                      | IFNβ-1a IM | 12       | 26     | 34       | 26     | 17       | 34    | 149           |          |
| Progressors (%)†     | Placebo | 20       | 21.2   | 28.6     | 33.3   | 29.4     | 30    |               |          |
|                      | IFNβ-1a IM | 16.7     | 19.2   | 20.6     | 15.4   | 5.9      | 14.7  |               |          |
| Progressors per year at risk (%)† | Placebo | 13.4     | 13.1   | 20.1     | 25.4   | 24.6     | 16.5  |               |          |
|                      | IFNβ-1a IM | 11.9     | 12.0   | 13.2     | 11.4   | 4.3      | 11.5  |               |          |
| Patients with EDSS increase (≥1 point) from week 0 to week 26* (n) | Placebo | 3        | 7      | 6        | 5      | 4        | 6     | 31            |          |
|                      | IFNβ-1a IM | 2        | 4      | 7        | 4      | 0        | 9     | 26            |          |
| Number of final progressors | Placebo | 2        | 2      | -1       | 1      | 4        | -3    | 5             |          |
|                      | IFNβ-1a IM | 2        | 5      | 4        | 1      | 5        | 24    |               |          |
| Mean time at risk (months) | Placebo | 17.9     | 19.4   | 17.1     | 15.7   | 14.3     | 21.9  | 18.2          |          |
|                      | IFNβ-1a IM | 16.9     | 19.3   | 18.7     | 16.2   | 16.6     | 15.4  | 17.2          |          |
| Mean annualized relapse rate* | Placebo | 0.397    | 0.638  | 0.834    | 0.717  | 0.992    | 0.98  | 0.76          |          |
|                      | IFNβ-1a IM | 0.412    | 0.716  | 0.62     | 0.584  | 0.727    | 0.93  | 0.66          | −12.50%  |
| Mean annualized relapse rate × number of patients per group | Placebo | 4.0      | 21.1   | 17.5     | 15.1   | 16.9     | 29.4  | 0.79          |          |
|                      | IFNβ-1a IM | 4.9      | 18.6   | 21.1     | 15.2   | 12.4     | 31.6  | 0.70          | −11.5%   |
| Mean annualized relapse rate × number of patients per group × mean time at risk (in years) | Placebo | 5.9      | 34.0   | 24.9     | 19.7   | 20.1     | 53.6  | 1.20          |          |
|                      | IFNβ-1a IM | 7.0      | 29.9   | 32.8     | 20.6   | 17.1     | 40.5  | 0.99          | −17.2%   |

Notes: *Figures obtained from the reference; †figures obtained from histogram bar measurements; other figures are calculated. Abbreviations: EDSS, Extended Disability Status Scale; IFN, interferon; IM, intramuscularly.
the 44 μg × 3/week. None of the three subcutaneous interferon arms could match the −37% benefit seen for IFNβ-1a IM in terms of reducing sustained progression of disability.

In the MSCRG study, 12 patients account for the difference in number of patients progressing in the placebo and IFNβ-1a IM arms. Eleven of these patients were in the year 2 cohort, favoring IFNβ-1a IM for reducing the risk of relapse and eight of these 11 patients started to progress during their first year on study. In the cohort of patients followed up for less than 2 years, seven patients on placebo and six patients on IFNβ-1a IM showed sustained progression. Five of seven patients on placebo and all patients on IFNβ-1a IM started to progress during year 1 (Table 3). The difference in increased benefit of IFNβ-1a IM on the outcome of relapse rate between the two cohorts seems to have also impacted the outcome of progression of disability. In the context of a trial of short duration with a 6-month delay in validation, early evolution of EDSS and follow-up duration are important parameters for validation of sustained progression.

Comparison of the numbers of patients progressing by at least one point at week 26 and the final numbers of patients who progressed as per EDSS in the different treatment arms indicates that most of the initial EDSS progression might have occurred during the first semester (Table 3). The numbers of patients who progressed in each EDSS and treatment group at week 26 and at the end of the study are often similar, except for the EDSS 3.5 group, suggesting an immediate difference between the two treatment arms which occurred during the first semester.

### Table 4. Number of patients who progressed according to treatment group, cohort, and year on study.4,16

|                    | First 52 weeks | Second 52 weeks | Total 104 weeks |
|--------------------|----------------|-----------------|-----------------|
| All patients using all data16 | 24             | 12              | 36              |
| Placebo            | 17             | 7               | 24              |
| IFNβ-1a IM         | 21             | 8               | 29              |
| Patients in study for ≥104 weeks:4 year 2 cohort | 19             | 10              | 29              |
| Placebo            | 11             | 7               | 18              |
| IFNβ-1a IM         | 6              | 0               | 6               |

**Abbreviation:** IFN, interferon.

In the EDSS 3.5 group, more patients on IFNβ-1a IM had progressed by week 26 (nine versus six), but at the end of the study, more patients on placebo had experienced sustained progression (five versus nine). The difference between the placebo and IFNβ-1a IM arms with regard to patients who progressed between week 26 and the final evaluation therefore changed from −3 to +4. All nine patients on placebo who progressed were from the year 2 cohort.18 EDSS 3.5 placebo group is the one with the longest time at risk, the EDSS 3.5 IFNβ-1a IM group, the one with the smallest.

Early EDSS evolution and differences in time at risk might account for the apparent efficacy of IFNβ-1a IM with regard to the outcome of disability progression. Unfortunately, without raw data, we cannot confirm that patients who started to progress between week 0 and week 26 are those with sustained progression at the end of the study or that the difference in time at risk favored the IFNβ-1a IM arm in terms of the disability outcome.

### MRI data

MRI outcomes demonstrated a significant benefit from interferon in the IFNβ-1b Trial and PRISMS, but were less impressive in the MSCRG trial, especially for T2-weighted lesion volume. In the MSCRG study, analysis of MRI characteristics at baseline shows differences between the year 1, year 2, and year 1 only cohorts. Mean gadolinium and T2 lesion volumes for patients who were on study for only one year can be calculated from the available baseline data for year 1 and year 2 patients as per treatment group, mean gadolinium lesion volume, mean T2 lesion volume, and number of patients with MRI results (Table 5).

For the subsets of patients, those on placebo had a higher mean T2 lesion volume than patients on IFNβ-1a IM (+25%, +26%, and +23% for patients followed up at one year, 2 years, and one year only, respectively). Compared with the IFNβ-1a IM group, the median T2 lesion volume in the placebo group was 1.29 higher for the year 1 cohort and 1.54 higher for the year 2 cohort.16 Patients followed up for 2 years had a higher mean T2 lesion volume than patients followed up for one year only (+34% for IFNβ-1a IM and +32% for placebo).

Patients on IFNβ-1a IM and those on placebo followed up for 2 years had a similar gadolinium lesion volume (253 mm³ versus 252 mm³), but patients on
Beta interferons efficacy in relapsing remitting multiple sclerosis

Table 5. Baseline magnetic resonance imaging data for the Multiple Sclerosis Collaborative Research Group study.5

|                  | Mean Gd lesion volume (mm³) | Δ | Mean T2 lesion volume (mm³) | Δ | Patients (n) |
|------------------|-----------------------------|---|-----------------------------|---|--------------|
|                  | Placebo | IFN* | Placebo | IFN* | Placebo | IFN* |
| Year 1 cohort    | 249     | 220  | 29      | 15703  | 12454  | 3249  |
| Year 2 cohort    | 252     | 253  | −1      | 16963  | 13817  | 3346  |
| Year 1 only (calculated) | 242 | 159  | 83      | 12648  | 10298  | 2350  |
| Δ Year 2–year 1 only | 10   | 94   |         | 4315   | 3319   | 33    |

Abbreviation: Gd, gadolinium.
Note: *IFN = interferon β-1a IM.

IFNβ-1a IM followed up for only one year had a lower mean gadolinium lesion volume compared with either IFNβ-1a IM patients followed up for 2 years (159 mm³ versus 253 mm³) or placebo patients followed up for year 1 only (159 mm³ versus 242 mm³).

The baseline MRI data confirm that patients followed up for one year only are different from those followed for 2 years. The baseline MRI data also suggest that the placebo and IFNβ-1a IM arms in the year 2 and year 1 only cohorts might have different profiles, but the small patient numbers limit the power of statistical testing of such a possibility.

Discussion

Of the three registration trials, the MSCRG seems to be the odd one out. The significant benefits of IFNβ-1a IM reported for relapse rate (−32%) and progression of disability (−37%) have been drawn from two different cohorts, ie, a year 2 cohort for relapse rate and an all-patient cohort for progression of disability. Neither figure is significant when drawn from the opposing cohort, even if a 5% threshold is used.18,20

The MSCRG does not provide us with an accurate evaluation of the benefit of IFNβ-1a IM on relapse rate except during year 1, ie, −10% calculated from the randomized cohort. Other figures for the efficacy of IFNβ-1a IM in reducing the relapse rate, such as −32.2% for patients who complete 2 years of treatment and −18%4 (−17.4% P = 0.063)17 for intent-to-treat analysis and fortunately +29% for patients followed up for one year only, should be interpreted with caution.

The difference in outcome for relapse rate between the year 1 cohort and the year 2 cohort is not linked to a lag time between initiation of treatment and onset of clinical benefit, and is more probably linked to differences between the two subsets of patients, ie, the year 1 and year 2 patient cohorts and/or between the treatment groups in these different cohorts.

The published comparisons of baseline characteristics for the placebo and IFNβ-1a IM arms per accrual period (4 of 6.5 months each)4 do not exclude the possibility of a difference between the year 1 only patients and those followed up for 2 years. Patients followed up for one year only might be the last patients included or early dropouts among the patients recruited, and none of the four periods analyzed would include just the year 1 only patients.

The difference between the two cohorts and the absence of information on their baseline characteristics beg the question of whether the 172 (87 placebo and 85 IFNβ-1a IM) patients in the year 2 cohort are actually the first 172 patients enrolled in this trial. This point is crucial to analysis of the trial.21

There was a considerable imbalance in treatment assignment between the two treatment arms, leading to inclusion of 143 patients on placebo and 158 patients on IFNβ-1a IM. This imbalance was even greater for patients included in the analysis of the primary endpoint, ie, 132 patients on placebo and 151 patients on IFNβ-1a IM.15 This imbalance is not apparent for the 172 patients followed up for 2 years, (87 on placebo and 85 on IFNβ-1a IM). Between weeks 78 and 104, 24 patients on placebo and 38 patients on IFNβ-1a IM attending the week 78 visit did not attend the week 104 visit.4 This implies that either the imbalance in treatment assignment occurred almost exclusively during this 6-month period or that censoring linked to study termination does not correspond to the recruitment schedule, with the consequence that the year 2 cohort is not representative of the first 172 patients included. If such an imbalance in assignment did actually occur during this 6-month period, it remains to be explained how randomization provided two cohorts
with such different responses to the study treatment, ie, the year 2 cohort benefiting from IFNβ-1a IM and the year 1 only cohort benefiting from placebo.

If the year 2 cohort is not a direct consequence of the recruitment schedule, evaluation on any cohort, randomized or year 2 cohort is doubtful. The absence of a significant difference in baseline characteristics between the placebo and IFNβ-1a IM patients resulting from the small study population would not allow consideration of any of the cohorts as valid for statistical purposes. Only raw data could provide us with the answer to this question.

Furthermore, baseline comparison of randomized patients in a truncated trial does not give any information on whether follow-up of patients is similar in the two treatment groups with regard to any prognostic factor or disease categorization. For example, staying time at each EDSS score decreases from EDSS 1 to EDSS 5. A difference in follow-up duration between the two treatment groups in the upper range of EDSS would increase the likelihood of more patients progressing than in the lower range of EDSS. In the MSCRG study, patients on placebo in the year 2 cohort had the highest mean and median T2 lesion volumes and were probably in the upper part of the cohort had the highest mean and median T2 lesion volumes and were probably in the upper part of the EDSS range, with their EDSS at entry to the study volumes and were probably in the upper part of the EDSS range, with their EDSS at entry to the study volumes and were probably in the upper part of the EDSS range, with their EDSS at entry to the study volumes and were probably in the upper part of the EDSS range, with their EDSS at entry to the study being weakly but significantly correlated with T2 lesion volume. The extra time at risk for the placebo group with EDSS 3.5 thus predisposes to bias, and this cannot be seen in the published baseline patient characteristics for the MSCRG study. Once again, only raw data could be of help to confirm or refute the possible impact of a difference in follow-up duration on the outcome for disability.

Early differences between disease evolution in the placebo and treatment arms can be seen in the survival curves, which diverge during the first months of the study. This early gap is seen in the disability progression survival curves for the MSCRG study. Unintentional unblinding is suspected, and possibly linked to the flu-like syndrome which can occur during the 48 hours after IFNβ-1a IM injection, a side effect known to patients via the patient information sheet required as part of the informed consent procedure.

Early divergence of the survival curves was also seen in CHAMPS (the Controlled High Risk Avonex Multiple Sclerosis Study) especially in the subgroup with spinal cord syndrome. In CHAMPS, almost 60% of the difference in the number of patients developing clinically definite multiple sclerosis between the two arms occurred during the first 4 months of the study and one third during the first month. This disability outcome is thus very sensitive to the evolution of a few patients and progression or non-progression, sustained or not, for each single patient will depend on early evolution possibly linked to unintentional unblinding and time on study linked to censoring.

The above hypotheses are based on calculations of mean time at risk and characteristics for the different subsets of patients. These confirm differences between the year 1 only and the year 2 cohorts which differences induced a better “mean” condition for a positive trial through attrition bias. Unfortunately, time on study, ranking of enrollment, evolution of EDSS, and date of censoring cannot be deduced on a patient basis from the published literature or the reviews available from health authorities.

These results on the MSCRG study, if confirmed by analysis of the raw data, imply that the efficacy of IFNβ-1a IM is not similar to that of the other interferons. They imply that analysis of responders to interferon or the efficacy of interferon should probably separate IFNβ-1a IM data from those obtained with the approved regimens for IFNβ-1a SC and IFNβ-1b. Further, we may need to consider products compared with IFNβ-1a IM and other interferons differently. However, these results do not imply that IFNβ-1a IM might not benefit some patients.

IFNβ-1a IM biosimilars might not be able to demonstrate a significant clinical effect. Manufacturers of biosimilars will prefer copying the more effective products to lower the costs of a placebo-controlled clinical trial, with the consequence that less efficient biologic products will more often remain “biosimilar-free”, be more heavily promoted, and thus probably more widely prescribed.

Further analysis should be done on the MSCRG and on raw data, as already requested by Filippini et al, to confirm or refute doubts and uncertainties concerning the outcomes. Gathering raw data from clinical trials and analyzing patient characteristics and evolution could also help to understand better the evolution of the disease, the impact of treatments, and enable comparison of trials and more comprehensive meta-analysis.
Unfortunately, raw data from clinical trials are not often available. Good and less good reasons, such as confidentiality, ownership of data, lack of permission of patients, and commercial interests continue to restrict their publication, but solutions to some obstacles reasons have been proposed. Advantages of publication of raw data are numerous, and evaluation of interferons in relapsing-remitting multiple sclerosis provides us with a good example of its potential benefit.

The European Medicine Agency was unable to retrieve the IFNβ-1a IM marketing authorization file from its archives upon request. A complaint has been lodged with the European ombudsman, but 18 months after the initial request made, raw data are still unavailable.

Conclusion
Evaluation of agents used to treat in multiple sclerosis is challenging. This evaluation points out some problems in the evaluation of IFNβ-1a IM in multiple sclerosis. The efficacy of IFNβ-1a IM in multiple sclerosis could have been overestimated by an attrition bias linked to early trial termination. However, this possibility warrants further analysis using raw data. Unfortunately, raw data from clinical trials are still very difficult to obtain from the pharmaceutical industry and health authorities. Availability of raw data would not only help, as in the present case, in the reanalysis of clinical trials, but would also provide the scientific community with a huge amount of information on pathology, patient characteristics, and evolution of disease, as well as enabling comprehensive meta-analysis.

Acknowledgements
The author extends his thanks to the manuscript editors for their constructive contributions towards improving this paper.

Author Contributions
Conceived and designed the experiments: AC. Analyzed the data: AC. Wrote the first draft of the manuscript: AC. Contributed to the writing of the manuscript: AC. Agree with manuscript results and conclusions: AC. Jointly developed the structure and arguments for the paper: AC. Made critical revisions and approved final version: AC. All authors reviewed and approved of the final manuscript.

Funding
Author(s) disclose no funding sources.

Competing Interests
AC worked for Serono from 1994 to 2000. AC invited to two dinners and one lunch by Serono in Dusseldorf during ECTRIMS 2009 (participation, hotel and travel paid by AC).

Disclosures and Ethics
As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

References
1. The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis: I. clinical results of a multicenter, randomized, double blind, placebo controlled trial. Neurology. 1993;43:655–61.
2. Paty DW, Li DKB; UBC MS/MRI Study Group, IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in remitting and relapsing multiple sclerosis: II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology. 1993;43:662–67.
3. The IFNB Multiple Sclerosis Study Group and the University of British Columbia. Interferon beta-1b in the treatment of multiple sclerosis. Final outcome of the randomized controlled trial. Neurology. 1995;45:1277–85.
4. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in exacerbating remitting multiple sclerosis. Ann Neurol. 1996;39:285–94.
5. Simon JH, Jacobs LD, Campion M, et al. Magnetic resonance studies of intramuscular interferon beta-1a for relapsing multiple sclerosis. Ann Neurol. 1996;43:79–87.
6. Rudick RA, Goodkin DE, Jacobs LD, et al. Impact of interferon beta-1a on neurologic disability in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group. Neurology. 1997;49:358–63.
7. PRISMS Study Group. Randomized double-blind placebo controlled study of interferon beta-1a in relapsing-remitting multiple sclerosis. Lancet. 1998;352:1498–504.
8. Li DK, Paty DW; UBC MS/MRI Analysis Research Group, PRISMS Study Group. Magnetic resonance imaging results of the PRISMS trial: a randomized, double-blind, placebo controlled study of interferon-beta1a in relapsing-remitting multiple sclerosis. Prevention of relapses and disability by interferon-beta1a subcutaneously in multiple sclerosis. Ann Neurol. 1999;46:197–206.
9. US Securities and Exchange Commission. Biogen and BiogenIdec. Available from: http://www.sec.gov/cgi-bin/browse-edgar?company=biogen&match=&CIK=&filename=&State=&Country=&SIC=&owner=exclude&Find=Find&Companies&action=getcompany. Accessed on May 1, 2012.

10. Durelli L, Verdun E, Barbero P, et al. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomized multicentre study (INCOMIN). Lancet. 2002;359:1453–60.

11. Panitch H, Goodin DS, Francis G, et al. Randomized, comparative study of interferon beta-1a treatment regimens in MS: the EVIDENCE Trial. Neurology. 2002;59:1496–506.

12. Filippini G, Munari L, Incorvaia B, et al. Interferons in relapsing remitting multiple sclerosis: a systematic review. Lancet. 2003;361:545–52.

13. Goodin DS, Frohman EM, Garmany GP, et al. Disease-modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Neurology. 2002;58:169–78.

14. Rice G, Ebers G. Interferons in the treatment of multiple sclerosis: do they prevent the progression of the disease? Arch Neurol. 1998;55:1578–83.

15. Goodin DS. Disease-modifying therapy in multiple sclerosis: update and clinical implications. Neurology. 2008;71 Suppl 3:S8–13.

16. US Food and Drug Administration. Interferon beta-1a product approval information—licensing action—Avonex®. Available from: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm080458.htm. Accessed on May 1, 2012.

17. US Food and Drug Administration. Clinical review of PLA-95-0979 Biogen-Inc Interferon Beta-1a.

18. US Food and Drug Administration. Statistical Review PLA-95-0979 Biogen-Inc Interferon Beta-1a.

19. US Food and Drug Administration. Interferon beta-1a product approval information—licensing action—Rebif: Medical Officer’s Clinical Review and Statistical Review and Available from: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm080737.htm. Accessed on May 1, 2012.

20. Palace J. New and old treatments for multiple sclerosis. Neurologia. 1998;13:162–5.

21. Piantadosi S. Proper interpretation and analysis of censored events and studies that contain them. Multi Scler. 2005;11:624–5.

22. Weinsenker BG, Rice GPA, Noseworthy JH, Carriere W, Baskerville J, Ebers GC. The natural history of multiple sclerosis: a geographically based study 4. Applications to planning and interpretation of clinical therapeutic trials. Brain. 1991;114:1057–67.

23. Jacobs LD, Beck RW, Simon JH, et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. N Engl J Med. 2000;343:898–904.

24. Beck RW, Chandler DL, Cole SR, et al. Interferon beta-1a for early multiple sclerosis: CHAMPS trial subgroup analyses. Ann Neurol. 2002;51:481–90.

25. Filippini G, Munari L, Incorvaia B, et al. Interferons in relapsing remitting multiple sclerosis (letter). Lancet. 2003;361:1824–5.

26. Hrynashkiewicz I, Norton ML, Vickers AJ, Altman DG. Preparing raw clinical data for publication: guidance for journal editors, authors, and peer reviewers. Trials. 2010;11:9.

27. Gotzsche PC. Why we need easy access to all data from all clinical trials and how to accomplish it. Trials. 2011;12:249.
Supplementary Data

1. US Food and Drug Administration. Clinical review of PLA-95-0979 Biogen-Inc Interferon Beta-1a.
2. US Food and Drug Administration. Statistical Review PLA-95-0979 Biogen-Inc Interferon Beta-1a.